HAYDARPAŞA NUMUNE MEDICAL JOURNAL

DOI: 10.14744/hnhj.2022.99810
Haydarpasa Numune Med J 2023;63(1):89–93

ORIGINAL ARTICLE

Is There a Relationship Between Omalizumab Treatment and the Development of Thromboembolic Events in Asthmatics?

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Abstract

Introduction: Omalizumab is indicated for the treatment of uncontrolled moderate and severe allergic asthma. The long-term real-life studies showed that it may result in an increase in thromboembolic events (TEs). This single-center study was planned to evaluate whether the use of omalizumab was related to the development of thromboembolism and change in peripheral blood thrombocyte counts.

Methods: Adult patients with moderate and severe asthma treated with (study group) and without omalizumab (control group) for at least 12 months were evaluated retrospectively. Data for demographic and clinical characteristics, duration of omalizumab treatment, number of thrombocytes before and after omalizumab, and development of TE were examined and compared between the two groups.

Results: A total of 168 patients, 73 were treated with omalizumab (13/73 male (17.8%), the mean age was 56.63±12.41 years), and 95 were treated without omalizumab (30/95 male (31.6%), the mean age was 50.71±16.34 years) were included in the study. The median (25–75th percentile) omalizumab treatment duration was 52 (36–78.5) months. None of the controls but two (2.7%) of the cases in the study group developed thromboembolism (p=0.187). The mean number of thrombocytes was similar before and after the treatment (276575.34±47869.59 vs. 294356.16±72351.26, p=0.087).

Discussion and Conclusion: Although there were sporadic cases with TE following omalizumab treatment in the study, it was not related to a significantly increased thromboembolism risk.

Keywords: Asthma; omalizumab; thrombocyte; thromboembolism.

Omalizumab treatment is indicated for the treatment of uncontrolled moderate and severe allergic asthma patients. It was reported to be effective in improving disease control in moderate and severe allergic asthma patients[1-3]. The drug was reported to be safe in several studies,[2,4-6] but long-term real-life studies showed that it may increase thromboembolic events (TEs)[7]. This single-center study was planned to evaluate whether the use of omalizumab changes the peripheral blood thrombocyte count, and/or it was related to thromboembolic complications.

Materials and Methods

This retrospective observational study included adult patients with moderate and severe allergic asthma that were treated according to GINA guideline[8] with and without omalizumab at least for 12 months and admitted to Ümraniye Training and Research Hospital pulmonology outpatient clinic between January 1, 2010, and January 1, 2022. The study was approved by the Local Ethics Committee. Demographic and, clinical data, development of TE, and

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Submitted Date (Başvuru Tarihi): 30.05.2022 **Revised Date (Revize Tarihi):** 19.06.2022 **Accepted Date (Kabul Tarihi):** 26.07.2022

pulmonary function test (PFT) parameters at the time of diagnosis (Forced expiratory volume in the first second [FEV1] liter and %, Forced vital capacity [FVC] liter, and %, FEV1/FVC), and number of thrombocytes on the last routine follow-up visit were collected from the hospital's medical files. The patients were divided into two groups as omalizumab group (who received omalizumab treatment) and the control group (who were treated without omalizumab or mepolizumab). Demographic and clinical characteristics including age, gender, comorbidities, asthma severity and duration, smoking status, and development of TE were examined and compared between the two groups. In the omalizumab group, the thrombocyte counts before and after omalizumab treatment were also compared.

The patients with a body mass index (BMI) over 30 kg/m^2, history of the hematological disease, malignancy, previous thromboembolic disease (deep vein thrombosis, pulmonary embolism [PE], cerebrovascular event [CVE]), TE developed following Coronavirus disease 2019 (COVID-19), cardiac disease (atrial fibrillation, arrhythmias, coronary artery disease, and cardiac failure), hyperlipidemia and those who were treated with omalizumab for <12 months, and the patient lacking the examined data were excluded from the study.

Statistical Analysis

Patient data collected in the study were analyzed with the IBM Statistical Package for the Social Sciences (SPSS) for Windows 23.0 package program (SPSS, Chicago, IL, USA). The descriptive values of categorical and continuous data were presented in frequency and percentage, and mean±standard deviation or median (25th and 75th percentile range), respectively. The comparison of categorical data between the two groups was made with the Pearson Chi-square test or Fisher-Freeman-Halton exact test. The comparison of numerical data between the two groups was made with the Mann–Whitney U-test. The Wilcoxon sign-rank test was used for the comparison of parameters before and after the treatment. The results were considered statistically significant when p-value was <0.05.

Results

Eighty-four patients treated with omalizumab were evaluated retrospectively. Two who had previous CVE history, one who developed CVE following COVID-19, five who had a BMI>30/m^2, and three who did not apply for follow-up visits regularly and lacked detailed medical history were excluded and the study was done with a total of 73 omalizumab cases and 95 controls.

In the omalizumab group, 13/73 were male (17.8%), 60/73 were female (82.2%), and the mean age was 56.63±12.41 years. The mean BMI was 25.86±2.61 kg/m^2. There were 28 (38.4%) patients with allergic rhinitis (AR), 17 (23.3%) patients with hypertension (HT), and 14 (19.2%) patients with diabetes mellitus (DM). 62/73 (84.9%) were non-smokers and 11/73 (15.1%) were ex-smokers. The mean smoking amount was 14.89±8.31 packages years. 11/73 (15.1%) had moderate, and 62/73 (84.9%) had severe asthma. The mean asthma duration was 15.37±6.87 years and the median (25th and 75th percentile) omalizumab treatment duration was 52 (36–78.5) months. The median (25th and 75th percentile) monthly omalizumab dose was 300 (300–450) mg. The mean PFT parameters were as follows: FEV1:1.52±0.43L, FEV1%:49.22±12, FVC:1.96±0.53 L, FVC%:56.42±11.54, and FEV1/FVC:77.09±8.84%.

In the control group, 30/95 were male (31.6%), 65/95 were female (68.4%), and the mean age was 50.71±16.34 years. The mean BMI was 25.86±2.50 kg/m^2. There were 22 patients with AR (23.2%), 17 patients with HT (17.9%), and nine patients with DM (9.5%). 78/95 (82.1%) were non-smokers and 17/95 (17.9%) were ex-smokers. The mean smoking amount was 15.56±7.32 packages years. Thirty-one patients (32.6%) had moderate, and 64 (67.4%) had severe asthma. The mean asthma duration was 12.62±3.53 years. The mean PFT parameters were as follows: FEV1: 1.83±0.73L, FEV1%:54.62±13.29, FVC:2.09±0.84 L, FVC%:52.92±13.67, and FEV1/FVC:88.43±11.6%.

The comparison of demographic, clinical, and PFT results of the two groups is given in Tables 1 and 2. In the omalizumab

Table 1. Demographic, clinical data, and development of venous thromboembolism in two groups

	Omalizumab group n (%)	Control group n (%)	p
Sex			
Female	60 (82.2)	65 (68.4)	0.043
Male	13 (17.8)	30 (31.6)	
Comorbidities			
Allergic rhinitis	28 (38.4)	22 (23.2)	0.033
Hypertension	17 (23.3)	17 (17.9)	0.388
Diabetes Mellitus	14 (19.2)	9 (9.5)	0.07
Smoking status			
Nonsmoker	62 (84.9)	78 (82.1)	0.9
Exsmoker	11 (15.1)	17 (17.9)	0.78
Asthma grade			
Moderate	12 (16.9)	31 (32.6)	0.009
Severe	59 (83.1)	64 (67.4)	
Venous thromboembolism	2 (2.7)	0 (0)	0.187

Table 2. Age, clinical data, and pulmonary function test parameters of two groups

	Omalizumab group Mean±SD or median (25^{th}-75^{th} percentile)	Control group Mean±SD or median (25^{th}-75^{th} percentile)	p
Age (years)	56.63±12.41	50.71±16.34	0.004
BMI (kg/m^2)	25.86±2.61	25.86±2.5	0.983
Asthma duration (years)	15.37±6.87	12.62±3.53	0.001
Duration of omalizumab treatment (months)**	52 (36-78.5)	-	-
Treatment dose (mg/month)**	300 (300-450)	-	-
Smoking (package years)	14.89±8.31	15.56±7.32	0.8
FEV1 (L)	1.52±0.43	1.83±0.73	0.003
FEV1 %	49.22±12	54.62±13.29	0.004
FVC (L)	1.96±0.53	2.09±0.84	0.534
FVC %	56.42±11.54	52.92±13.67	0.049
FEV1/FVC (%)	77.09±8.84	88.43±11.6	0.001

SD: Standard deviation; **: Data that were abnormally distributed; BMI: Body mass index; FEV1:Forced expiratory volume in the first second; FVC: Forced vital capacity.

group, the cases were older (p=0.004), females were more frequent (p=0.043), and the median duration of asthma was longer (p=0.001), more patients had AR (p=0.033), and severe asthma (p=0.009). There were no cases that developed TE in the control group, while two cases (2.7%) developed venous thromboembolism (VTE) in the omalizumab group, but the difference was not significant (p=0.187). The mean FVC% was higher (p=0.049), while the mean FEV1, FEV1%, and FEV1/FVC ratio (p=0.003, p=0.004, and p=0.001, respectively) were significantly lower in the study group.

The mean number of thrombocytes was similar before and after the treatment (276575.34±47869.59 vs. 294356.16±72351.26 and, p=0.087). Among the 73 cases, two developed thrombocytosis (platelet count was >450×10^9/L), one was a 45 years old non-smoker man without any comorbidities, and the other was a 65 years old non-smoker woman with DM. Both cases were consulted at a hematology clinic and, treated with hydroxyurea; the male discontinued the omalizumab treatment at the 16^{th} month, but the thrombocytosis persisted, and the female continued to receive omalizumab because when she quit the treatment she suffered from severe asthma attacks.

Two females developed VTE. The first case was a 65 years old diabetic woman who had developed thrombocytosis following the omalizumab treatment mentioned above. She developed CVE in the 10^{th} year of the treatment. The other patient who developed pulmonary thromboembolism was a 65 years old non-smoker female with moderate asthma, who had no comorbidities and normal thrombocyte count and developed unprovoked PE in the 3^{rd} year of treatment.

Discussion

Omalizumab is a monoclonal anti-IgE antibody that was reported to be effective in improving disease control and quality of life, decreasing asthma attacks, hospitalization, and systemic corticosteroid need in uncontrolled moderate and severe allergic asthma patients[1-3]. The most common adverse events reported with omalizumab use were headache, fatigue, and injection site reaction; anaphylaxis and VTE were also reported in a few cases[4,9]. In most studies, the frequency of the adverse effects was reported to be similar between omalizumab and placebo and it was used safely and, widely for the treatment of not only allergic asthma but also chronic urticaria and AR[2,5]. VTE was reported as a rare adverse effect of omalizumab in the literature but a real-life study including 5007 patients revealed a higher rate of cardiovascular and CVEs in the omalizumab versus the non-omalizumab cohort with a hazard ratio of 1.32 and, it was expressed that an increase in risk for thromboembolism related to omalizumab treatment cannot be excluded[7]. It was suggested that this increase might be related to increased systemic inflammation in severe asthma and also to exposure to chronic systemic corticosteroids[7,10].

In the study, only two cases developed TE following omalizumab treatment, both were 65 years old non-smoker females, one with moderate asthma and no comorbidities, the other with severe asthma, DM, and essential thrombocytosis. The sample size of the study was small but still, this result may be striking to show the risk of thromboembolism related to the omalizumab use. In the EXCELS

study, 201/5007 (4%) cardiovascular and CVEs and 49/5007 (0.97%) PE were reported in omalizumab-treated asthma patients who were significantly more frequent than in the non-omalizumab group. In our study, the frequency of CVE and PE was 1.35%, but there was no significant difference between the control and omalizumab groups probably due to the small sample size.

The role of high platelet count in the occurrence of VTE was shown in several studies in patients with malignancy and a cutoff level of 350×10^9/L was reported to be related to an increased risk of developing VTE during hospitalization[11-14]. Furthermore, a population-based study evaluating over 25000 subjects aged 25–96 years revealed that an increased mean platelet volume was identified as a predictor for VTE, in particular VTE of unprovoked origin[15]. These findings support that the cases with an increased number of thrombocytes may be at increased risk for VTE.

There are few studies evaluating the effect of omalizumab on peripheral blood cell counts. Acer et al.[16] reported that there was a significant increase in mean platelet volume with omalizumab treatment in chronic urticaria patients. In another study, it was reported that omalizumab did not alter the hematological parameters except for an increase in basophil counts in chronic urticaria patients[17].

There were a few limitations of the study. First, as this was a single-center study, the sample size was small. Second, although the patients with risk factors for developing VTE were excluded, there may be undetected underlying thrombophilia.

As a result of this study, although there were sporadic cases of TE following omalizumab treatment, it may not be related to a significantly increased risk for thromboembolism. Further multicentral studies should be performed to enlighten this issue.

Ethics Committee Approval: Ethics committee approval was obtained in the study (University of Health Sciences, Umraniye Training and Research Hospital, Turkey. Approval date and number: April 21, 2022 and, B10.1.TKH.4.34.H.GP.0.01).

Peer-review: Externally peer-reviewed.

Conflict of Interest: None declared.

Financial Disclosure: The authors declared that this study received no financial support.

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