Research Article / Araştırma Makalesi

Omalizumab for the Treatment of Bullous Pemphigoid: A Single Center Experience

Büllöz Pemfigoid Tedavisinde Omalizumab: Tek Merkez Deneyimi

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Özet: Büllöz pemfigoid yaşlı popülasyonda en sık görülen ve birçok komorbiditenin eşlik ettiği büllöz dermatozdur. İmmünoglobulin-E (Ig-E) antikorları hastalığın patogenezinde önemli bir rol oynadığından, Ig-E'yi hedef alan omalizumab etkili ve güvenli bir profil göstermektedir. Bu çalışmada büllöz pemfigoid hastalarda omalizumabın etkinlik ve güvenilirliğini değerlendirmeyi amaçladık. Çalışmaya büllöz pemfigoid tanısıyla en az 3 ay omalizumab tedavisi alan 19 hasta dahil edildi. Hastaların tamamında en az bir eşlik eden hastalık mevcuttu; en sık görüleni hipertansiyon (%79.0) ve tip 2 diyabet (%68.4) idi. Ortalama omalizumab tedavi sayısı 7.0±2.9 idi. Omalizumab tedavisi ile hastaların 11 (%57.9) 'inde tam yanıt, 8 (%42.1)'inde kısmi yanıt elde edildi. Tam yanıt alınan tüm hastalarda başlangıç sistemik steroid dozu azaltılabildi. Tüm hastalar omalizumabı yan etki olmaksızın tolere etti. Sonuç olarak omalizumab ileri yaş ve çoklu komorbiditeleri olan hastalarda sistemik kortikosteroid ihtiyacını azaltan etkili ve güvenli bir tedavi seçeneğidir. Omalizumabın büllöz pemfigoid tedavisinde etkinliğini değerlendirmek için daha büyük ölçekli ve prospektif çalışmalara ihtiyaç vardır.
Anahtar Kelimeler: Omalizumab, büllöz pemfigoid, immunoglobulin-E

Abstract: Bullous pemphigoid is the most common bullous dermatosis seen in elderly population and accompanied by many comorbidities. Since immunoglobuline-E (Ig-E) antibodies play an important role in the pathogenesis of the disease, omalizumab targeting Ig-E proposes an effective and safe profile. In this study, we aimed to evaluate the efficacy and safety of omalizumab in bullous pemphigoid patients. Nineteen patients who received omalizumab treatment for at least 3 months with the diagnosis of bullous pemphigoid were included in the study. All patients had at least 1 comorbid condition, the most common being hypertension (79.0%) and type 2 diabetes mellitus (68.4%). The mean number of omalizumab treatments was 7.0±2.9. With omalizumab treatment, complete response was achieved in 11 (57.9%) of the patients and partial response was achieved in 8 (42.1%). The initial systemic steroid dose could be reduced in all patients with a complete response. All patients tolerated omalizumab without side-effects. In conclusion, omalizumab is an effective and safe treatment option that reduces the need for systemic corticosteroids in patients with older age and multiple comorbidities. Further large-scale and prospective studies are needed to evaluate the efficacy of omalizumab in the treatment of bullous pemphigoid.
Keywords: Omalizumab, bullous pemphigoid, immunoglobulin-E

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1. Introduction

Bullous pemphigoid (BP) is the most common subepidermal autoimmune bullous skin disease generally affects elderly population. It is characterized by the formation of immunoglobuline-G (Ig-G) antibody and/or complement C3 against hemidesmosomal antigens BP180 and BP230. The clinical manifestations of BP include eczematous or urticarial plaques with tense blisters predominantly in flexures of limbs and abdomen. With mechanical friction, bullous lesions may turn into erosions and crusts before healing. Patients also typically experience severe pruritus. Oral mucosal involvement can be seen in nearly 20% of the patients and approximately 50% of the patients are accompanied by neurological diseases (1, 2).

Topical and/or systemic corticosteroids remain the first line treatment for BP. They are generally used together with steroid sparing agents like azathiopurine, mycophenolate mofetile, dapsone, methotrexate, tetracyclines furthermore intravenous immunoglobulins and rituximab are also reported to be effective in resistant cases. However, in elderly patients, the side effects of systemic corticosteroids and immunosuppressive agents limit their use in the long-term period (2, 3).

Recent studies documented that mast cells, eosinophils and immunoglobuline-E (Ig-E) antibodies targeting BP180 or BP230 have a role in the pathogenesis of BP. Over 75% of untreated BP patients have elevated circulating Ig-E levels and serum eosinophilia has been documented in patients (4, 5). Omalizumab a human monoclonal anti-Ig-E antibody that has been also showed promising results in BP patients. Considering the multiple comorbid conditions accompanying the disease, omalizumab treatment has become an effective and safe option in numerous BP patients (3, 6). In this study, we aimed to evaluate the efficacy and safety of omalizumab in the treatment of BP.

2. Materials and Methods

We evaluated BP patients who received omalizumab in our dermatology department between 2020-2023 retrospectively. The diagnosis was confirmed in all patients by routine histopathology and direct immunofluorescence. Omalizumab was administered subcutaneously at a dose of 300 mg every 4 weeks in all patients. Response to treatment was evaluated in patients who received omalizumab for at least 3 months. Sociodemographic features (age and gender) of the patients, duration of disease, accompanying comorbidities, clinical findings, previous treatments, omalizumab administration doses and concominant treatments were recorded from the follow-up forms.

Patients in whom systemic corticosteroids has been discontinued or used in minimal doses (≤16 mg/day methylprednisolone) along with omalizumab treatment were considered to have a complete clinical response (7). Patients in whom the systemic steroid dose could be reduced to half of the initial dose or who developed new lesions within 3 months were considered as partial clinical response. The study protocol was approved by Eskişehir Osmangazi University Ethics Committee.

Statistical Analysis

SPSS 22.0 software was used for data analysis. Continuous quantitative data were expressed as mean or median according to the normality analysis. Besides, qualitative data were expressed as n (%).

3. Results

A total of 19 patients were included in the study. Eleven (58%) of the patients were female. Mean age of the patients was 77.6±9.1 years (range=55-90) and the mean duration of disease was 22.9±12.9 months. All of our patients had generalized classical disease. Hyperglycemia due to chronic systemic steroid use was observed in 2 (10.5%) patients and cataract (5.2%) was observed in 1 patient. All of the patients have accompanying systemic disease. Hypertension and type 2 diabetes mellitus were the most common comorbidities detected in 15 (79.0%) and 13 (68.4%) of the patients, respectively. Before omalizumab treatment, all patients received

topical steroids, 10 (52.6%) received systemic steroids, and 5 (26.3%) received doxycycline treatment (Table-1). The mean duration of disease prior to initiation of omalizumab was 10.3±7.9 months. Prior to omalizumab treatment, elevated eosinophil levels were found to be high in 13 (68.4%) of the patients. Baseline total serum Ig-E level was available in 4 (21%) of the patients and in all cases was above 100 IU/ml before omalizumab treatment.

The mean number of omalizumab treatments received by patients was 7.0 ± 2.9. While 2 (10.6%) of the patients received omalizumab monotherapy, 10 (52.6%) patients methylprednisolone, 4 (21.0%) patients doxycycline and 1 (5.3%) patient methylprednisolone and doxycycline. The systemic corticosteroid dose could be reduced in 5 (26.3%) of 19 patients after a mean of 9 sessions. With omalizumab treatment, complete response was achieved in 11 (57.9%) of the patients after a median duration of 8 months and partial response was achieved in 8 (42.1%) of the patients after a median duration of 6.5 months (Table-2). Of the 4 patients with elevated initial Ig-E levels, 3 (75%) patients had achieved complete response and 1 (25%) patient had partial response.

The patients were followed up for approximately 3-12 months since the initiation of omalizumab treatment. While 3 (27.2%) of the patients with complete response were receiving omalizumab monotherapy, 4 (36.3%) were additionally receiving systemic steroid and 4 (36.3%) were receiving topical steroid treatment. Initial systemic corticosteroid dose could be reduced in all of the patients who had a complete response in the 3rd month of omalizumab treatment. The mean number of omalizumab treatments in patients who achieved complete response was 6.4 ± 2.8. The systemic corticosteroid dose was increased due to the flare-up in 5 (62.5%) of the patients with partial response. Of the 3 (37.5%) patients with partial response, omalizumab treatment was discontinued due to their own request and the patients were lost to follow-up. No omalizumab-related side effects were observed in any of the patients.

Table 1. Demographic and clinical data

Sex	
-Female	11 (58.0%)
-Male	8 (42.0%)
Age	
-Mean ± SD	77.6 ± 9.1
Mean duration of disease ± SS (months)	22.9 ± 12.9
Oral mucosal involvement	7 (36.9%)
Serum eosinophilia	13 (68.4%)
Comorbidities (%)	
Cardiovascular disorders	
-Hypertension	15 (79.0%)
-Coronary artery disease	4 (21.0%)
Endocrine-metabolic disorders	
-Type 2 diabetes mellitus	13 (68.4%)
- Hypothyroidism	2 (10.5%)
-Chronic renal failure	2 (10.5%)
Neurological disorders, n (%)	
-Alzheimer disease-dementia	3 (15.8%)
-Stroke	3 (15.8%)
Previous treatments, n (%)	
-Topical corticosteroids	19 (100%)

-Systemic corticosteroids (metylprednisolone)	10 (52.6%)
-Doxycycline	5 (26.3%)

SD: Standart Deviation

Table 2. Treatment features and response to treatment

Mean omalizumab administrations	7.0 ± 2.9
Treatment received	
-Omalizumab in monotherapy	2 (10.6%)
-Omalizumab with metylprednisolone	10 (52.6%)
-Omalizumab with doxycycline	4 (21.0%)
-Omalizumab with metylprednisolone and doxycycline	1 (5.3%)
Clinical response	
-Complete response	11 (57.9%)
-Partial response	8 (42.1%)

SD: Standart Deviation

4. Discussion

BP is an autoimmune blistering disease mainly affects the elderly population and its incidence is increasing worldwide. Mortality rates in the first year of the disease vary between 12-40%. The chronic course of the disease and accompanying comorbidities significantly reduce the quality of life. Systemic corticosteroids and immunosuppressants comprise the main step of the treatment. However, the main goal of treatment is to reduce skin manifestations of disease and recurrences in the elderly population, as well as reduce side effects due to medications (8-10).

Based on the studies documented the pathogenic role of Ig-E antibodies targeting the NC16A fragment of the BP180 protein in early BP lesions, omalizumab is recognized as an alternative agent in the treatment of the disease (11-13). It is suggested that omalizumab downregulates Ig-E receptors and prevents Ig-E from binding to its receptor, thereby inhibiting the activation of mast cells that is increased in bullous pemphigoid lesions (3, 6).

Since BP affects the vulnerable elderly population, there is a trend to favor safer medications such as omalizumab over systemic immunosuppressive agents. Considering the chronic course of the disease and accompanying comorbidities in elderly patients, the main advantage of the omalizumab treatment is its corticosteroid-sparing effect (3, 14). In our study, mean age of the patients with BP was 77.6 and mean the duration of disease was 22.9±12.9 months. Additionally, 3 (15.7%) patients had experienced adverse events (hyperglycemia: 2, cataract:1) due to the systemic corticosteroids before omalizumab. Lonowski et al. evaluated 11 BP patients treated with omalizumab. They reported that the mean age of the patients was 78 years and the median duration of disease prior to initiation of omalizumab was 6.8 months. Although the mean age of the patients in Lonowski et al.'s study was similar to our study, due to the side effects such as prednisone-related bone fractures and osteoporosis occurred in 7 (63.6%) of 11 patients, omalizumab may have been started earlier in this study (15).

In a recently systematic review, Aguanno et al. had summarized a total of 56 patients (median age=72.1) treated with omalizumab for BP. The most common accompanying comorbidities were reported hypertension (41.2%) and type 2 diabetes mellitus (32.4%), respectively. When the patients' previous treatments were examined, it was revealed that 43 (91.1%) of the patients used systemic corticosteroids, 23 (51.1%) used systemic antibiotics, and 20 (44.4%) used potent topical steroids (3). In our study, the most common comorbidities were similarly determined to be hypertension (79%) and type 2 diabetes mellitus (68.4%). However, in our study, it was revealed that our patients used a lower

(52.6%) rate of systemic steroids prior to omalizumab. This may be due to the older age compared to their study and the presence of comorbidities such as hypertension and diabetes mellitus of our patients.

Fairley et al. reported the first case of BP treated with omalizumab who was under poor control and developed side effects due to systemic corticosteroids. The patient was administered 300 mg omalizumab in every 2 weeks and after 1 week of treatment the patient reported a decrease in pruritus and more than 40% regression in the number of the blisters. Since then, a number of case series of BP treated with omalizumab have been reported and its efficacy has been well documented (7, 14-20).

Due to off-label use of omalizumab in the treatment of BP, the optimal dosing regimen has not yet been determined. Additionally, treatment intervals and clinical efficacy criteria vary between studies. However, it is suggested that rather than increasing the frequency of omalizumab administrations for clinical efficacy, more than five doses are recommended to achieve an over 70% complete response rate (3, 6). In a multicenter French study with the largest patient group to date, Chebani et al. evaluated 100 BP patients. In this study, complete response was achieved in 49% of patients with omalizumab monotherapy, but the overall complete response rate was reported in 77% of the patients. Moreover, in this study, only 35% of the patients received treatment with 300 mg/4 weeks, and 61% received doses higher than 300 mg/4 weeks (21). This suggests that omalizumab treatment response rates may be dose dependent.

In the most recently systematic review, Ling et al. evaluated the efficacy of omalizumab in the treatment of 83 BP patients and reported a 67.5% (52 patients) complete response rate and a 23.3% (18 patients) partial response rate. In this study, complete response was determined as 80% of the lesions regressed at least 2 months after treatment cessation (6). Although efficacy criteria are not comparable between this systematic review and our study, 11 (57.9%) of our patients were achieved the complete response and partial response was achieved in 8 (42.1%) patients. Incel Uysal et al. evaluated the clinical response of 11 BP patients with 300 mg/4 week omalizumab treatment. They found that 6 (55%) patients achieved complete clinical response with topical and systemic steroids. They could reduce the systemic corticosteroid dose to minimal doses in 5 (45%) of the patients after 7 injections (7). In our study, although complete response rates were similar to their study, the systemic corticosteroid dose could be reduced in 5 (26%) of our patients with a median of 9 injections. In the study conducted by Lonowski et al., although diagnostic criteria are not clearly stated, they reported that 6 (54.5%) of 11 patients treated with omalizumab had complete clearance after a median duration of 4.4 months on omalizumab. Additionally, in all 10 patients using prednisone prior to omalizumab, the prednisone dose could reduced during follow-up and systemic steroids were completely discontinued in 5 (50%) of the patients (15). In our study, similar complete response rate was obtained after a median duration of 8 months on omalizumab. The differences in response rates in various studies may be explained by the patients' characteristics, the effect of additional treatments and the number of omalizumab administrations.

Regarding as a response predictor of omalizumab, laboratory findings including serum eosinophil and Ig-E levels are generally suggested. It is well known that higher serum eosinophil and Ig-E levels are decreased after initiation of omalizumab (22-25). However, it is also documented that no statistically significant difference was detected between these laboratory parameters and response rates (3). In our study, more than half (68.4%) of our patients had serum eosinophilia. Additionally, baseline total serum Ig-E levels were available in 4 (21%) of the patients and in all cases Ig-E levels were above 100 IU/ml before omalizumab treatment.

The limitations of our study are its retrospective design from a single-center and the small sample size of patients. Besides the lack of long-term follow-up results, evaluating the specific efficacy related to omalizumab

has been difficult, as high number of patients used concomitant treatments with omalizumab treatment.

In conclusion, omalizumab appears to be an effective and safe treatment option for patients with BP. In our study, more than 50% of our patients achieved complete response without any side effect. Omalizumab is also an important alternative treatment with its corticosteroid-sparing effect, especially in elderly patients with multiple comorbidities. Further prospective and randomized controlled trials are needed to elucidate our results.

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Ethics

Ethics Committee Approval: This study was approved by the Ethics Committee of the Eskişehir Osmangazi University (Decision no: 47, Date: 20.06.2023).

Informed Consent: The authors declared that it was not considered necessary to get consent from the patients because the study was a retrospective data analysis.

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