



Our clinical experience with the use of omalizumab in the treatment of bullous pemphigoid

Büllöz pemfigoid tedavisinde omalizumab kullanımı üzerine klinik deneyimlerimiz

Pinar Incel Uysal, Basak Yalcin, Ayse Oktem

Ankara Numune Training and Research Hospital, Department of Dermatology, Ankara, Turkey

Abstract

Background and Design: In the era of biological therapies, omalizumab (OMZ), a monoclonal antibody which inhibits IgE, has been postulated to be effective in the treatment of bullous pemphigoid (BP). We report our clinical experience with the use of OMZ in the treatment of BP.

Materials and Methods: Retrospective data analyses of eleven patients were performed.

Results: Seven patients receiving OMZ treatment demonstrated clinical improvements. Three patients terminated treatment because of intermittent co-morbidities. None of the patients had any significant adverse events.

Conclusion: OMZ may be a promising corticosteroid-sparing treatment option for moderate to severe BP patients. Future randomized controlled trials are indicated to evaluate the efficacy of OMZ in the treatment of BP.

Keywords: Bullous pemphigoid, immunotherapy, omalizumab

Öz

Amaç: Biyolojik tedaviler döneminde, IgE'yi inhibe eden monoklonal antikor olan omalizumabın (OMZ), büllöz pemfigoidin (BP) tedavisi için etkili olduğu kabul edilmiştir. Bu çalışma BP tedavisinde OMZ kullanımına ilişkin klinik deneyimlerimizi değerlendirmektedir.

Gereç ve Yöntem: On bir hastanın retrospektif verilerinin analizi gerçekleştirilmiştir.

Bulgular: OMZ tedavisiyle 7 hasta klinik düzelmeye gösterdi. Üç hastada araya giren komorbiditeler nedeni ile tedavi kesilmiştir. Hastalarımızdan hiçbirinde dikkate değer advers olay izlenmemiştir.

Sonuç: OMZ, orta-şiddetli BP'ler için umut vaat eden bir kortikosteroidten koruyucu tedavi opsiyonu olabilir. Gelecekte, OMZ tedavisinin BP tedavisindeki etkinliğini değerlendiren randomize kontrollü çalışmalara ihtiyaç vardır.

Anahtar Kelimeler: Büllöz pemfigoid, immünoterapi, omalizumab

Introduction

Bullous pemphigoid (BP) is the most common acquired autoimmune bullous disease with an incidence varying between 7 and 43 cases per million per year in different European countries¹⁻⁴. Recent studies have highlighted the increased incidence of the disease³. Autoantibodies against two hemidesmosomal proteins -BP180 (type XVII collagen) and BP230- leading to dermoepidermal separation play an important role in the pathogenesis of BP. The patients

typically develop pruritic urticarial lesions and tense, mostly clear blisters on both erythematous inflammatory skin and normal appearing skin.

The disease primarily affects elderly population in the late 70s with a significant mortality and morbidity^{3,5}. Mortality of the disease depends on the age of the patient, severity of the involvement and, above all, high-dose and long-term corticosteroid and immunosuppressive therapy^{6,7}. These patients tend to have significant age dependent co-morbidities. In addition, its association with neurological

Address for Correspondence/Yazışma Adresi: Dr. Pinar Incel Uysal, Ankara Numune Training and Research Hospital, Department of Dermatology, Ankara, Turkey Phone.: +90 312 508 56 43 E-mail: pinarincel@hotmail.com **Received/Geliş Tarihi:** 24.02.2017 **Accepted/Kabul Tarihi:** 11.08.2017

ORCID ID: orcid.org/0000-0002-4540-6560



diseases including stroke, Parkinson's disease, multiple sclerosis and pulmonary embolism, has also been shown^{8,9}.

Numerous therapeutic options are available and several guidelines have been published to assess the optimal method according to comorbidities^{7,10,11}. Therefore, despite the fact that topical and systemic corticosteroids are still the mainstay of the therapy, in this high-risk population, the main goal of the treatment is to use the lowest dose corticosteroids as soon as possible. For this purpose, corticosteroid-sparing agents including, dapsone, tetracycline, cyclosporine, methotrexate, azathioprine and mycophenolate mofetil are commonly used. Furthermore, in therapy-resistant cases, intravenous immunoglobulins, cyclophosphamide, rituximab, plasmapheresis and immunoadsorption may be used^{7,12}.

Omalizumab (OMZ), which is a monoclonal anti-IgE antibody, decreases the expression of IgE receptor on immune cells, prevents the binding of IgE to its receptor and thus, neutralizes the effect of IgE on mast cells and basophiles^{13,14}. Elevated levels of circulating IgE in the majority of untreated BP patients and IgE autoantibodies predominantly targeting the same extracellular non-collagenous 16A (NC16A) domain have been demonstrated¹⁵⁻¹⁷. Over the recent years, based on the experimental work demonstrating the critical role for IgE in the pathomechanism of BP, inhibition of IgE/IgE receptor interaction have become a promising option for the treatment of the condition¹⁸⁻²¹. For this purpose, we reviewed the records of 11 patients with BP who were treated with OMZ.

Materials and Methods

Records of patients diagnosed with BP and treated with OMZ in our department between January 2015 and November 2016 were retrieved from our clinical databases. A total of 11 patients who received treatment with OMZ included in this study. All patients had

classical clinical disease and diagnosis of BP was confirmed by routine histology and direct immunofluorescence. For each patient included in the study, demographic and clinicopathological information, previous therapies, co-morbidities and treatment-related side effects were recorded from medical charts. Patients who stopped to develop new lesions during OMZ therapy and topical corticosteroids or tapering of systemic corticosteroids to minimal therapy or to discontinuation were considered with complete clinical response. The study was conducted according to the ethics principles expressed in the Declaration of Helsinki and approved by the Medical Ethics Committee of the Ankara Numune Training and Research Hospital, Ankara, Turkey (Protocol number: E-16-1168).

Results

Five (54%) patients were women and six (46%) were men. The mean age of the patients was 78 years (range 58-86, median 81 years). All of our patients with BP had typical lesions with pruritic urticarial plaques, vesicles and bullae. Nine of them (81%) had classical generalized disease and four (36%) patients had also oral mucosa involvement. All patients had serious co-morbidities. Hypertension, diabetes mellitus, and osteoporosis were the most common co-morbid diseases (Table 1). Prior to initiation of OMZ therapy, elevated eosinophils and IgE were detected in five and four of the cases, respectively. Six patients had no response to previous BP therapies. None of them had been previously treated with OMZ therapy. The average length of time from onset of the disease to OMZ therapy was 13 months. OMZ was introduced as corticosteroid-sparing treatment in 5 (45%) patients. The patients were receiving prednisone (40-60 mg/day) and methylprednisolone (12-40 mg/day) at considerable amount of variation. Two patients had been treated with long-term systemic corticosteroid and immunosuppressive therapy before introducing OMZ. In these patients,

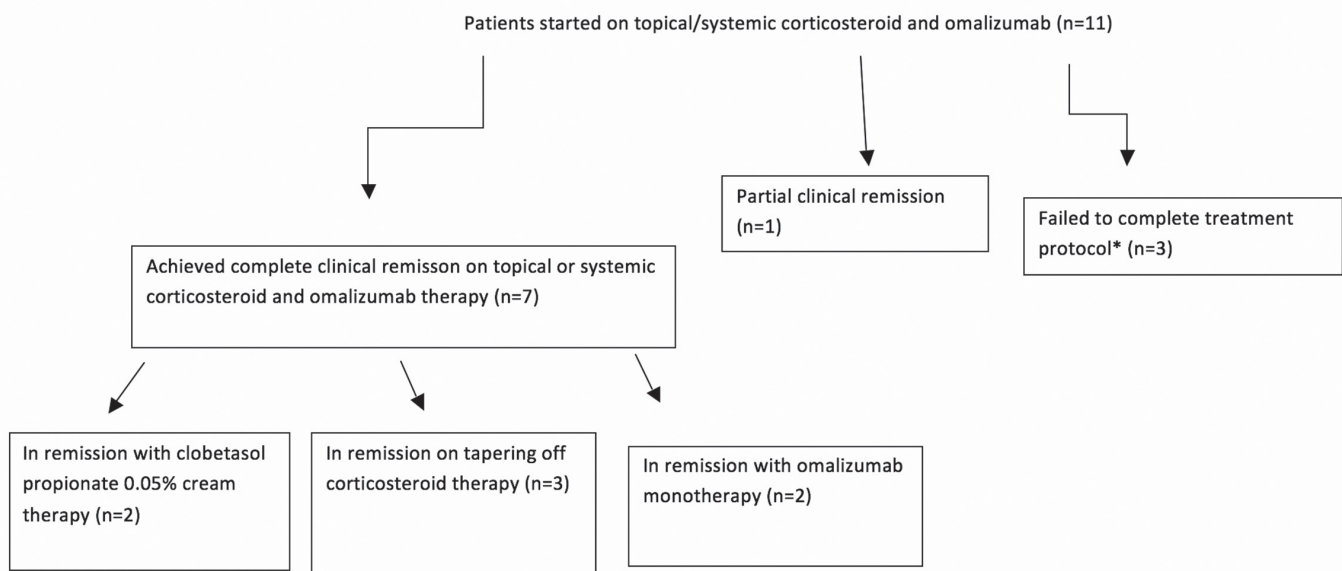


Figure 1. Diagram of patients with the diagnoses of bullous pemphigoid. One patient was in remission while tapering off corticosteroid therapy but because of elevation of liver enzymes omalizumab therapy was discontinued. One patient died because of myocardial infarction during intermittent period after the first dose omalizumab. One patient had mild thrombocytopenia and had myocardial infarction after 9-dose cycle thereafter discontinued therapy

Table 1. Case series

Patient	Gender	Age and disease duration	Co-morbidities	Treatment protocol	Clinical response	Eosinophil counts*	Total OMZ cycle/response cycle	Side effects [‡]	Final dose
1	Female	77 y, 48 months	Coronary heart disease, hypertension, diabetes mellitus type 2, Parkinson's disease	Methylprednisolone 12 mg/day AZT 100 mg/day 300 mg OMZ SC q4 wk	Complete	Not elevated 1.1%, 0.1x10 ³ /μL	21/9	-	Methylprednisolone 4 mg/day AZT 50 mg/day 300 mg OMZ SC q5 wk
2	Female	81 y, 14 months	Hypertension, arrhythmia, asthma, osteoporosis	Methylprednisolone 40 mg/day AZT 50 mg/day 300 mg OMZ SC q2 wk	Partial	Elevated 6%, 0.7x10 ³ /μL	40/20	-	Methylprednisolone 4 mg/day 300 mg OMZ SC q3 wk
3	Male	74 y, 2 months	Hypertension, benign prostate hyperplasia, chronic obstructive pulmonary disease, diabetes mellitus type 2	Clobetasole propionate 0.05% cream 300 mg OMZ SC q2 wk	Complete	Elevated 13%, 1x10 ³ /μL	16/12	-	300 mg OMZ SC q4 wk
4	Male	86 y, 9 months	Benign prostate hyperplasia, senile cataract	Prednisolone 40 mg/day 300 mg OMZ SC q2 wk	Complete	Not elevated 0.4%, 0.1x10 ³ /μL	10/5	-	300 mg OMZ SC q8 wk
5	Female	84 y, 1 month	Diabetes mellitus type 2, hypertension	Prednisolone 40 mg/day 300 mg OMZ SC q4 wk	N/A	Elevated 18.4%, 1.4x10 ³ /μL	1/-	Elevated liver enzymes	OMZ therapy was discontinued prednisolone 20 mg/day
6	Male	79 y, 1 month	Alzheimer disease, Chronic obstructive pulmonary disease, hypertension, Parkinson's disease	Clobetasole propionate 0.05% cream 300 mg OMZ SC q4 wk	N/A	Elevated 7.4%, 1.4x10 ³ /μL	1/-	MI	Failed to complete treatment and follow-up protocol
7	Male	83 y, 12 months	Hypertension, benign prostate hyperplasia	Prednisolone 60 mg/day 300 mg OMZ SC q2 wk	N/A	Not elevated 0.8%, 0.1x10 ³ /μL	9/6	Trombocytopenia (67x10 ³ /microliter) MI	Failed to complete treatment and follow-up protocol
8	Female	86 y, 1 month	Hypertension, romatoid arthritis, osteoporosis	Clobetasole propionate 0.05% cream 300 mg OMZ SC q2 wk	Complete	Elevated 29.6%, 3.8x10 ³ /μL	9/4	-	Topical steroid 300 mg OMZ SC q4 wk
9	Male	58 y, 1 month	Chronic hepatitis B	Clobetasole propionate 0.05% cream 300 mg OMZ SC q2 wk	Complete	Not elevated 1%, 0.1x10 ³ /μL	11/3	-	Topical steroid 300 mg OMZ SC q4 wk
10	Male	81 y, 18 month	Chronic obstructive pulmonary disease, cataract, hypothyroidism osteoporosis	Prednisolone 40 mg/day 300 mg OMZ SC q2 wk	Complete	Elevated 11.6% 0.9x10 ³	11/2	-	Prednisolone 2.5 mg/day 300 mg OMZ SC q4 wk
11	Female	77 y, 36 months	Diabetes mellitus type 2, hypertension, glaucoma, coronary heart disease, osteoporosis	Methylprednisolone 32 mg/day 300 mg OMZ SC q4 wk	N/A	Not elevated 4.6%, 0.2x10 ³ /μL	3/-	-	Failed to complete treatment and follow-up protocol

[‡]None of these reactions were attributable to OMZ therapy. AZT: Azothiopurine, N/A: Not applicable, OMZ: Omalizumab, Q: Every, SC: Subcutaneous injection, y: Years, wk: Week, MI: Myocardial infarction

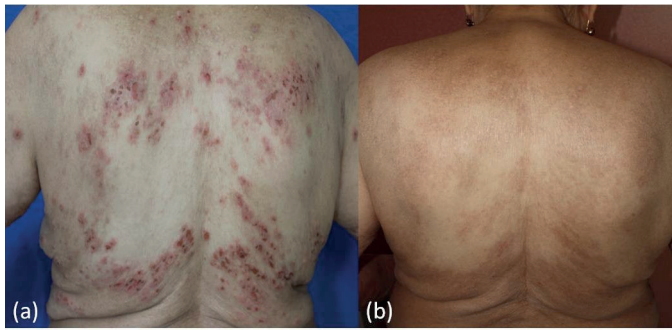


Figure 2. Clinical appearance of the patient number 2 at initial presentation (a) and after 20 cycles of omalizumab therapy (b)

tapering of corticosteroid therapy could not be performed because of development of new lesions and itchy sense. Four patients (36%) received OMZ in combination with topical corticosteroid as first line therapy. Based on the reported studies in the literature, OMZ was started at 300 mg subcutaneously in all patients with two- or four-week intervals. Patients with generalized bullous and urticarial lesions, dense itchy sense, eosinophilia or topical corticosteroid treatment plan were chosen for OMZ treatment biweekly. Four patients who had significant co-morbidities accompanying thrombosis, including uncontrolled hypertension, were treated every 4 weeks. None of our patients had adverse reactions. At the time of disease control, tapering of systemic corticosteroid was started. The mean follow-up time after remission was 19 weeks (range 6-48). The adverse events in patients 5, 6, 7 were not directly related to OMZ therapy (Figure 1).

Clinical response was evaluable in 7 (64%) patients (Figure 1). One patient interrupted treatment due to myocardial infarction (MI) and another patient died because of MI three weeks after the first-cycle OMZ therapy. We discontinued OMZ therapy in one patient due to elevated liver enzymes (alanine aminotransferase 106 IU/L, aspartate aminotransferase 60 IU/L, gamma-glutamyl transferase 419 IU/L, alkaline phosphatase 125 IU/L). Patient number eleven showed poor therapeutic adherence and discontinued OMZ on her own. Complete disease control was achieved in six patients (Table 1) and two of them are in remission on OMZ monotherapy. The average duration of OMZ therapy to achieve control disease was 19 weeks and approximately 7-cycle OMZ therapy. After being treated with OMZ, 7 patients (64%) had dramatic relief of pruritus. OMZ was initiated in a patient with intractable pruritus (patient 1) who had worsening of itching while tapering of corticosteroid. Two weeks after the first OMZ dose, improvement of the symptoms was observed. Relief of dense itching was achieved by 8-cycle OMZ in another patient (patient 2) who was considered as having partial clinical response because of new blister formation and exacerbation of pruritus with further tapering of her methylprednisolone to 4 mg alternate day therapy. She is on therapy with methylprednisolone 4 mg/day, azathiopurine 50 mg/day, 300 mg OMZ every three weeks (Table 1, Figure 2a, 2b).

The mean follow-up time after remission was 19 weeks (range 6-48). Complete clinical response was observed in 6 (55%) patients and OMZ therapy was effective as steroid sparing agent in 5 (45%) of them (Table 1). We could reduce systemic corticosteroid to minimal daily doses after 7 injections of OMZ over 5 months on average. In one patient (patient 4), corticosteroids were tapered after the initiation of therapy with OMZ and the patient has remained disease-free for the

past 40 weeks. Four patients (patients 3, 6, 8, 9) with mild disease activity received OMZ in combination with topical steroid therapy and 3 (75%) of them achieved remission (Table 1).

Discussion

BP is a manageable bullous disease and general treatment goal is to use the lowest dose of corticosteroid therapy in the shortest possible period of time. Based on the studies that have identified IgE antibodies targeting NC16A domain of BP180 protein (BPAG2, collagen XVII) and developing knowledge of pathogenetic role of these antibodies for reproducing early phase BP lesions, a new therapeutic option for BP becomes evident^{16,22,23}.

All of our patients with BP had generalized classical disease and significant co-morbidities. In our series, therapy with OMZ had marked therapeutic and steroid-sparing effect rates of about 64% and 45%, respectively. Seven of the patients are currently on OMZ therapy and in follow-up period. Notably, three of our severe BP patients were successfully treated with topical corticosteroid and OMZ therapy. In contrast with asthma studies revealing higher frequency of hypersensitivity reactions, we did not observe any reactions. Elevated liver enzymes and thrombocytopenia were temporary laboratory findings and they were associated with other medications that have been used for other purposes. It is also worth considering that in our series, two patients had MI during the interval period of OMZ therapy, in one causing death. It has been suggested that OMZ inhibits activation of extrinsic pathway of tissue factor and lowers d-dimer level by blocking free IgE, consequently, shows effects similar to heparin²⁴. On the other hand, recently, in an observational study, it has been mentioned that OMZ treatment has a higher incidence of cardiovascular and cerebrovascular events²⁵. We assume that these thrombotic events were associated with age related co-morbidities in our patient. Even though there is no definitive relationship between anti-IgE therapies and prothrombotic state, we believe this aspect needs to be clarified in future reports.

Conclusion

To our knowledge, this is the largest series of patients treated with OMZ reported to date. Considering the published data, OMZ have been found to be successful and lack of side effects in small case series and a few case reports^{18,19,21,26,27}. Moreover, there have been reports suggesting steroid-sparing effect of OMZ²⁷. According to the Oxford Center for Evidence-based Medicine Levels of Evidence Grades of Recommendation criteria, OMZ for BP has been mentioned with conflicting evidence. However, we believe that taking into account these data with the observed results of efficacy and safety of OMZ make sense to prioritize its use as a corticosteroid-sparing agent in elderly patients²⁸. Although it is not possible to make strong conclusions based on our retrospective study design and lack of long-term follow-up results, therapy of BP with OMZ alone or in combination with topical/oral corticosteroids may be a valuable alternative in the elderly patients with moderate to severe BP. When other first-line corticosteroid sparing agents are contraindicated or have failed, OMZ may act as them. Future prospective studies with larger sample and longer follow-up period will lead to better understanding of the exact role of OMZ in the treatment of BP.

Ethics

Ethics Committee Approval: The study was approved by the Local Ethics Committee of Ankara Numune Training and Research Hospital (Protocol number: E-16-1168).

Informed Consent: Consent form was filled out by all participants.

Peer-review: Externally peer-reviewed.

Authorship Contributions

Surgical and Medical Practices: P.İ.U., B.Y., Concept: P.İ.U., Design: P.İ.U., B.Y., Data Collection or Processing: P.İ.U., A.O., Analysis or Interpretation: P.İ.U., A.O., Literature Search: P.İ.U., Writing: P.İ.U.

Conflict of Interest: No conflict of interest was declared by the authors.

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

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