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Dupilumab for atopic dermatitis treatment: A single-center retrospective study

Atopik dermatit tedavisinde dupilumab: Tek merkezli retrospektif çalışma

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Abstract

Background and Design: Atopic dermatitis (AD) is a common chronic, recurrent, and itchy inflammatory skin disease. Various therapeutic agents are available, but severe side effects may limit their usage. Recently, dupilumab, a human monoclonal antibody that targets the interleukin-4 (IL-4) receptor alpha subunit of heterodimeric IL-4 and IL-13 receptors, is approved and might be used in patients with resistant AD, with the permission of the Ministry of Health.
Materials and Methods: This study aimed to retrospectively evaluate the clinical characteristics of patients and dupilumab treatment responses in our center. This study included patients with AD who were unresponsive to conventional treatments and treated with dupilumab. Sociodemographic, laboratory data, previous treatments, and responses along with disease severity scores [eczema area and severity index (EASI)] before and after dupilumab were evaluated through the electronic files of patients.
Results: A total of 21 patients (13 males and 8 females) between June 2019 and March 2021 were identified. The mean age of patients was 40.57±15.21 years. The mean duration of dupilumab treatment was 6.59±5.88 months. The mean EASI score at the beginning of dupilumab was 15.35±8.03, whereas 4.6±2.9 after treatment. A 70-100% improvement was found in approximately 75% of the patients. No side effects were observed that required treatment discontinuation or dose changes.
Conclusion: Our study has the highest number of reported patients in our country, which revealed that dupilumab is highly effective and safe for conventional treatment-resistant AD.
Keywords: Atopic dermatitis, dupilumab, treatment

Öz

Amaç: Atopik dermatit (AD) sık görülen kronik, tekrarlayıcı, kaşıntılı, inflamatuvar bir deri hastalığıdır. Tedavisinde çeşitli tedavi ajanları bulunsa da bu ajanların ciddi yan etkileri kullanımlarını sınırlamaktadır. Son zamanlarda, interlökin-4 (IL-4) ve IL-13 reseptörlerinin IL-4 reseptör alfa alt birimini hedefleyen heterodimerik bir insan monoklonal antikoru olan dupilumab onay almıştır ve dirençli AD'li hastalarda Sağlık Bakanlığı izni ile kullanılabilmektedir.
Gereç ve Yöntem: Bu çalışmada hastalarımızın klinik özelliklerini ve dupilumab tedavi yanıtlarını retrospektif olarak değerlendirmeyi amaçladık. Konvansiyonel tedavilere yanıt vermeyen ve dupilumab başlanan AD'li hastalar çalışmaya dahil edildi. Hastaların sosyodemografik ve laboratuvar verileri, önceki tedavileri ve dupilumab tedavi öncesi ve sonrasındaki hastalık şiddet skorları [egzama alan ve şiddet indeksi (EAŞİ)] ve tedavi yanıtları değerlendirildi.
Bulgular: Haziran 2019 ile Mart 2021 arasında takip edilen toplam 21 hasta (13 erkek, 8 kadın) saptandı. Hastaların ortalama yaşı 40,57±15,21 yıldı. Ortalama dupilumab tedavi süresi 6,59±5,88 aydı. Dupilumab başlangıcındaki ortalama EAŞİ skoru 15,35±8,03 iken, tedavi sonrası ortalama EAŞİ skoru 4,6±2,9 olarak saptandı. Hastaların yaklaşık %75'inde %70-100 aralığında bir iyileşme saptandı. Tedavinin kesilmesini veya doz değişikliğini gerektiren hiçbir yan etki gözlenmedi.
Sonuç: Ülkemizden bildirilen en yüksek hasta sayısına sahip olan çalışmamızda, dupilumabın geleneksel tedavilere dirençli AD'de oldukça etkili ve güvenli bir seçenek olduğu saptanmıştır.
Anahtar Kelimeler: Atopik dermatit, dupilumab, tedavi

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Introduction

Atopic dermatitis (AD) is a chronic, recurrent, and itchy inflammatory skin disease, with a prevalence that changes from 4% to 10% among adults in the United States and Europe[1-3]. The incidence of AD has been increasing, especially in developed countries. Lifelong incidence is also increasing worldwide. The two basic and intertwined mechanisms for AD pathogenesis include structural and functional abnormalities and inflammation of the skin. Increased expression of cytokines [interleukin-4 (IL-4), IL-5, and IL-13] that are secreted by T-helper 2 cells play an important role in its inflammatory pathogenesis[4,5].

AD treatment mainly aimed to suppress acute attacks and symptoms, as well as long-term disease control. The epidermis and epidermal barrier play an important role in disease pathogenesis, thus topical agents have an important place in the treatment. The main topical therapeutic options include emollients and anti-inflammatory agents, such as topical corticosteroids (CS) and calcineurin inhibitors[6]. Systemic therapies are necessary for patients with moderate-to-severe conditions, in whom the disease cannot be fully controlled with topical treatments. Systemic CS and cyclosporine (CsA) are the most used and effective treatments for AD, along with others, including methotrexate (MTX), mycophenolic acids, and azathioprine (AZA). However, serious side effects may develop, which limits the use of these agents. Thus, these treatments should be used at the lowest doses, which control the disease, and maintenance should be done with the lowest possible doses.

Recently, dupilumab, a monoclonal antibody that is directed against the alpha subunit of the heterodimeric IL-4 and IL-13 receptors, became the first biologic that is available for the treatment of inadequately controlled moderate-to-severe AD in adults. It blocks the signaling of AD-relevant cytokines and reduces Th2-mediated inflammation[6]. It was first approved by FDA in 2017 for adult patients with moderate-to-severe AD that is inadequately controlled with topical therapies or when those therapies are unadvisable, and later on was extended to pediatric patients aged 6 years and above[7]. It has also received marketing approval by the European Medicines Agency for the treatment of moderate-to-severe AD in adolescent and adult patients who are candidates for systemic therapy (accessed: September 4, 2021; https://www.ema.europa.eu/en/medicines/human/EPAR/dupixent#authorisation-details-section) Under the insurance system in Turkey, dupilumab is indicated only in adult patients with moderate-to-severe AD who are resistant to systemic CS and CsA and/or who cannot use these agents because of their serious side effects (https://www.mevzuat.gov.tr/mevzuat?MevzuatNo=17229&MevzuatTur=9&MevzuatTertip=5). Retrospective analysis and real-life experience of dupilumab treatment in AD have been increasingly investigated in recent years.

This study aimed to retrospectively evaluate the clinical characteristics and treatment responses of patients with AD who were treated with dupilumab in our unit and present the real-life data of our center.

Materials and Methods

This study included patients with AD who were treated with dupilumab and had at least two documented follow-up visits at the department of dermatology and venereology between June 2019 and March 2021. This study was approved by the Akdeniz University Faculty of Medicine Clinical Research Ethics Committee, with permission from the Ministry of Health (approval number: 660, date: 26.08.2020). Informed consent was obtained. A retrospective review of electronic medical records was conducted regarding sociodemographic characteristics, laboratory data, concomitant diseases, history of allergy, previous treatments, and characteristics of dupilumab treatment and treatment responses with disease severity scores [eczema area and severity index (EASI)] before and after dupilumab treatment[8]. Dupilumab was used in line with the legislation of the Ministry of Health and is administered subcutaneously every other week at a dose of 300 mg after the initial dose of 600 mg that is divided into two separate 300 mg doses and given on the same day in two sites. Follow-up visits after initiating the treatment were scheduled between 4 and 8 weeks, with subsequent visits to monitor the progress approximately every 12 weeks. No other specific laboratory monitoring was performed.

Statistical Analysis

Data were analyzed using the SPSS software 23. P-values of 0.05 were set as a cutoff for statistical significance. Descriptive analyses were used to characterize demographic and clinical factors, continuous variables were expressed as mean ± standard deviation, and categorical variables as the number and percentage to define the sample. Continuous variables were compared using the Mann-Whitney U test and the Kruskal-Wallis test as adequate. The differences between pre- and post-treatment values were examined for statistical significance using Wilcoxon's signed-rank test.

Results

A total of 21 patients (13 males and 8 females) between June 2019 and March 2021 were detected. The mean age of patients was 40.62±15.13 years, and the mean age of onset of the complaints was 21.29±16.92 years. The demographic characteristics of patients are summarized in Table 1. All patients had a history of topical moisturizer, topical CS, systemic antihistamines, systemic CS, and CsA use, and 81% used topical calcineurin inhibitor, 38.1% had MTX, 33.3% had

Table 1. The sociodemographic and clinical characteristics of patients with AD treated with dupilumab

Sex	Male: 13 (61.9%)
	Female: 8 (38.1%)
Age	Mean age: 40.62±15.13 years (minimum: 18; maximum: 70)
Age at the initiation of AD	Mean age: 21.29±16.92 years (minimum: 1, maximum: 55)
Duration of symptoms	Mean: 218.80±197.51 months (minimum: 23, maximum: 720)
Eosinophilia	Positive: 14 (66.7%)
	Negative: 5 (23.8%)
High levels of IgE	Positive:11 (52.4%)
	Negative: 7 (33.3%)
EASI	
Before treatment of dupilumab	15.35±8.03
After treatment of dupilumab	4.6±2.9

AD: Atopic dermatitis, EASI: Eczema area and severity index, IgE: Immunoglobulin E

omalizumab, 19% had phototherapy, and 4.8% had AZA. The mean EASI score was 15.35±8.03 at the beginning of the dupilumab therapy, whereas 4.6±2.9 after treatment (after a mean: 6.59±5.88 months of duration of dupilumab treatment) (Table 1). Regular usage of dupilumab was significantly higher in females than males ($p<0.05$) but without significant difference between genders in other aspects. An improvement in the range of 70-100% was detected in approximately 75% of patients (Figure 1, 2), and dupilumab was discontinued in four patients (19%), due to inadequate treatment response in one patient and unresponsiveness in the remaining three patients.

Discussion

With the highest number of patients reported in our country so far, our study has shown that dupilumab is a highly effective and safe option in patients with conventional treatment-resistant AD. The improvement of ≥70% that we achieved in three-quarters of our patients is consistent with previous dupilumab studies.

Dupilumab is the first and only FDA-approved biological agent in AD treatment. Its effectiveness was mainly shown by three randomized, double-blind, placebo-controlled phase III clinical trials that assess the safety and efficacy of dupilumab, SOLO1, SOLO2, and CHRONOS[7,9]. They demonstrated that dupilumab achieved 75% improvement in AD lesion severity index in half of the patients (50% and 48%, respectively) in SOLO1 and 2-phase-3 studies. Furthermore, a significant improvement was observed in the dermatology quality of life (QoL) index and itching scores in the dupilumab group compared to placebo[7]. Additionally, in the phase-3 study-CRONO, dupilumab and topical CS combination therapy was compared to the control group who received placebo and topical CS, whereas the SOLO studies evaluated the efficacy of dupilumab therapy alone, and revealed that 75% more patients achieve greater remission in the dupilumab + topical CS therapy group. With the continuation of topical CS and dupilumab treatment, remission continued in 61% of the patients during the 1-year follow-up. Additionally, the need for topical CS was less in the group that received dupilumab[9].

In the last 2 years, many single or multicenter retrospective studies have been published to determine the real-life data of dupilumab therapy[10-13]. A small retrospective study with 14 patients with AD that are treated with dupilumab was also recently published in İstanbul, Turkey[10]. The SCORing Atopic Dermatitis (SCORAD) scores, the serum total immunoglobulin E (IgE) levels, and the visual analog scale (VAS)-itch scores of the patients who received dupilumab therapy were investigated by Askin et al.[10], wherein all scores demonstrated a significant decrease before and after 3-months of dupilumab treatment. However, no significant correlation was found between the initial SCORAD scores and the serum total IgE values.

Ferrucci et al.[11] showed that ~70% of their patients achieved EASI75 accompanied by significant reductions in dermatology life quality index, patient-oriented eczema measure (POEM), Hospital Anxiety and Depression Scale, Peak Pruritus Numerical Rating Scale, and VAS-sleep scores at week 16 after starting dupilumab. In a multivariate analysis, AD onset before 18 years [odds ratio (OR): 2.9; 95% confidence interval (CI): 1.2-7.2; p=0.0207] and absence of hypereosinophilia (OR: 2.24; 95% CI: 1.03-4.86; p=0.0412) were determined as significant predictive parameters for response to dupilumab in terms of EASI75

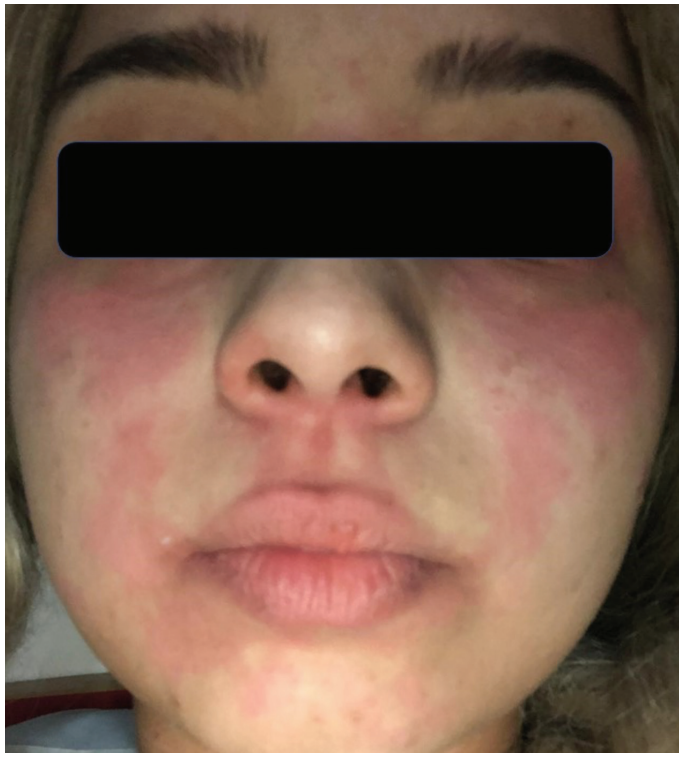

Figure 1. A female patient with generalized eczematous eruption both on the face and body, covering >60% of her body surface area before dupilumab treatment

Figure 2. Same female patient after 6 months of treatment with a drastic dupilumab response

at week 4 but not at week 16, suggesting the possible use as an early response marker. They suggested a possible relationship with eosinophils and inhibition of group 2 innate lymphoid cells in response to dupilumab[11]. Their study also showed similar effectiveness of dupilumab in patients who experienced ineffective previous course of CsA and patients without a history of CsA ineffective usage.

Jang et al.[12] revealed similar efficacy of dupilumab in real-life to that of the existing clinical trials. Elevated lactate dehydrogenase levels at 16 weeks were associated with poor treatment response, whereas the female gender was associated with good treatment response (OR: 5.4, p=0.04). The same study related the high eosinophil count to the lower change in EASI and POEM scores[12].

Nettis et al.[13] conducted the broadest real-life study that included the retrospective analysis of 543 patients and revealed that AD lesions, as measured by the EASI score, had significantly improved after 16 weeks of dupilumab treatment. During treatment, 12.2% of the patients developed conjunctivitis, and the risk of developing dupilumab-related conjunctivitis was associated with early onset of AD (OR: 2.25; 95% CI: 1.07-4.70; p=0.03) and presence of eosinophilia (OR: 1.91; 95% CI: 1.05-3.39; p=0.03) in the multivariate logistic regression model[13].

With the successful treatment of adult patients with AD, dupilumab has been also evaluated in other age groups[14,15]. Napolitano et al.[14] performed a retrospective observational study on elderly (≥65 years) patients who are treated with dupilumab and observed optimal efficacy and a favorable safety profile in this vulnerable and challenging age group. Similarly, a multicenter retrospective, observational, real-life study by Patruno et al.[15] examined 276 patients with 11.37% of all patients being elderly with severe AD, and efficacy and safety of dupilumab were established, which is specifically important since elderly patients often have multiple comorbidities and associated polypharmacy. Common therapeutic options in moderate-to-severe AD, such as systemic CS and CsA, are often contraindicated and/or inappropriate for long-term use in this age group. Therefore, new therapeutic options, like dupilumab, might represent better therapeutic choice or, sometimes, even the only possible drug for elderly patients[14].

Moreover, one of the latest research, Paller et al.[16] evaluated the efficacy and safety of dupilumab + topical CS in children aged 6-11 years with severe AD who are inadequately controlled with topical therapies. In their double-blind, 16-week, phase 3 trial (NCT03345914), patients (n=367) were randomized 1:1:1 to 300 mg dupilumab every 4 weeks (300 mg-q4w), a weight-based regimen of dupilumab every 2 weeks (100 mg-q2w, baseline weight of <30 kg; 200 mg-q2w, ≥30 kg), or placebo, with concomitant medium potency topical CS. Both the q4w and q2w dupilumab + topical CS regimens resulted in clinically meaningful and statistically significant improvement in signs, symptoms, and QoL versus placebo + topical CS, concluding the effectiveness and tolerability of dupilumab in children with severe AD. However, they suggested weight-dependent dosing (300 mg-q4w in children weighing <30 kg and 200 mg-q2w in children weighing ≥30 kg) schedule would be necessary for this age group for optimal results regarding efficacy and safety[16].

The evaluation of the characteristics of dupilumab therapy revealed high dupilumab therapy persistence, and more than three-quarters of patients needed reinitiating of dupilumab within 4 months with its discontinuation[1]. Silverberg et al.[1] also compared 12-month persistence with biologics used for psoriasis and the persistence with dupilumab and revealed that the high level of persistence with dupilumab at 12 months in their study, suggesting that dupilumab is well-tolerated and patients are satisfied with its administration effectiveness and frequency for AD management.

Conjunctivitis (n=2) and injection-site reactions (n=8) were the most commonly observed side effects in our study group. No systemic side effect was reported during the study period. The underlying mechanism of blepharoconjunctivitis in patients with AD remains controversial; however, some authors have suggested that the blockade of IL-4 and IL-13 may increase the activity of specific ligands, such as OX40 ligand that are involved in atopic keratoconjunctivitis[11,17]. Other commonly reported side effects are self-limiting conjunctivitis, blepharoconjunctivitis, cicatricial ectropion, follicular conjunctivitis, keratitis, eye pruritus, and dry eye, all of which was classified as a dupilumab-induced ocular surface disease (DIOSD)[18,19].

AD by itself is a risk factor for conjunctivitis development in patients. A meta-analysis of randomized controlled trials reported several risk factors for DIOSD including increased AD severity, self-reported previous conjunctivitis, and higher blood levels of IgE and eosinophils[20]. Liberman et al. [21] suggested that patients with severe AD or a history of conjunctivitis should be evaluated by an ophthalmologist using a slit lamp before treatment initiation. If ocular symptoms occurred, prompt action for eye specialist referral is necessary. However, local treatment with artificial tears, CS drops, antihistamines, or mast cell stabilizers, and topical tacrolimus are efficient enough to continue with dupilumab therapy in most cases with ocular side effects[21,22].

Study Limitations

Limitations of our study include its retrospective nature and small sample size.

Conclusion

Dupilumab therapy is promising in terms of its success rate and the innovation it brings to the long-awaited AD treatment. Furthermore, like biological agents in the treatment of other inflammatory skin diseases, especially psoriasis, dupilumab has opened a new way of treatment to both patients with AD and physicians dealing with this disease. Our study, which reflects real-life data, albeit in a limited number of patients, revealed that dupilumab treatment was effective and safe in most patients with AD who were resistant to many conventional treatments. A better understanding of the disease pathogenesis will pave the way for the development of new effective treatment agents with higher safety and efficacy profiles regarding conventional AD treatments.

Ethics

Ethics Committee Approval: This study was approved by the Akdeniz University Faculty of Medicine Clinical Research Ethics Committee, with permission from the Ministry of Health (approval number: 660, date: 26.08.2020).

Informed Consent: It was obtained.

Peer-review: Externally and internally peer-reviewed.

Authorship Contributions

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Interpretation: A.B., Literature Search: G.Y., A.B., Writing: G.Y., A.B., E.Y.

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