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Brief Communication

One-Year Effectiveness and Safety of Dupilumab Treatment for Moderate-to-Severe Atopic Dermatitis in Korean Patients: A Real-World Retrospective Analysis

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ABSTRACT

Dupilumab was the first biological drug to be approved for adult patients with moderate-to-severe atopic dermatitis (AD), and its use is growing exponentially worldwide. Though its therapeutic efficacy and favorable safety profile have been demonstrated, data on real-world long-term experience with the drug are only beginning to accumulate. Herein, we present a retrospective analysis of Korean patients with moderate-to-severe AD who were treated with dupilumab. We observed excellent overall treatment efficacy with the mean Eczema Area and Severity Index (EASI) score decreased from 28.2 to 3.2 at week 52. Notably, the therapeutic effect was maintained despite the considerable number of patients requiring an increase in treatment intervals due to the financial burden in a real clinical setting. In contrast to the previous reports, paradoxical head and neck erythema/dermatitis was rare in our study group, and pre-existing dermatitis in the very region, as well as in the hands, responded well to dupilumab treatment. Additionally, we were able to discontinue dupilumab treatment for two patients who achieved complete clearance of AD symptoms (EASI and Investigator's Global Assessment [IGA] scores of 0) for more than three months. There have been no flare-up events of AD in these patients; with topical corticosteroids alone, one of them has been completely disease-free for 43 weeks and the other has been maintaining an IGA score of 1 for 66 weeks. Furthermore, conjunctivitis was again confirmed to be the most frequent side effect associated with dupilumab, and it generally responded well to conventional conjunctivitis treatment.

Keywords: Atopic dermatitis; dupilumab; biological products; Korea

INTRODUCTION

Dupilumab is a human monoclonal antibody against the interleukin-4 receptor α-subunit (IL-4Rα) that inhibits IL-4 and IL-13 signaling.[1] It was the first biological drug approved for use in the treatment of moderate-to-severe atopic dermatitis (AD) in adult patients, and its

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favorable effects and safety profile have been confirmed by numerous studies.[2,3] However, as the use of dupilumab is growing exponentially worldwide, the importance of reporting/sharing the accumulating experience with dupilumab in clinical practice cannot be stressed enough. Minute differences in terms of nationality, race, or insurance plan can potentially result in meaningful differences in the use of and response to dupilumab. Therefore, we aimed to assess the efficacy and safety of dupilumab in Korean patients with moderate-to-severe AD in real clinical practice.

MATERIALS AND METHODS

A retrospective review of the electronic medical records of patients with moderate-to-severe AD who were administered dupilumab at Seoul National University Hospital or Seoul National University Bundang Hospital during August 2018–October 2019 was performed. The inclusion criteria were as follows: 1) sufficient information regarding the baseline and follow-up disease severities, including Eczema Area and Severity Index (EASI) scores and photographic records and 2) at least two follow-up visits since treatment initiation.[4] Patients who were restarted on dupilumab after being lost to follow-up for more than two weeks were excluded from the study so that the increase in the treatment intervals was not mainly due to the patients being late to the appointment. Among the 61 patients identified, 40 were eligible to be included in the analysis. The clinical data of the eligible patients were evaluated up to March 2021; follow-up loss was defined as missing the appointment and never returning until the end of the observation period. All the patients were administered the standard protocol of 600 mg of dupilumab at week 0 and 300 mg every 2 weeks thereafter. Disease severities were measured using the EASI scores, and the disease severities on the face and hands were also measured using the Investigator's Global Assessment (IGA) score. In addition, any and all adverse events during dupilumab treatment, including conjunctivitis, paradoxical head and neck erythema, and alopecia, were collected from the medical records. Data are expressed as means ± standard deviations for continuous variables and as percentages for categorical variables. This study was reviewed and approved by the Institutional Review Board of Seoul National University Hospital and Seoul National University Bundang Hospital (IRB No. H-2007-119-1142).

RESULTS

General characteristics of the patients

Among the 40 patients identified, most were men (n = 29, 72.5%), and the mean age was 30.9 years. Most had AD since infancy or childhood (n = 35, 87.5%), and concurrent histories of other atopic disorders were common with 18 (45%) patients with allergic rhinitis and 12 (30%) patients with asthma. Regarding previous treatment, cyclosporine was the most frequently used systemic immunosuppressant with 22 (55%) patients. The mean follow-up period in the study population was 74 weeks (**Table 1**).

Compliance with dupilumab treatment and adverse events

Though all patients were initiated on the standard protocol for treatment with dupilumab, due to insufficient coverage by the Korean National Health Insurance, a compulsory Korean social insurance,[5] the change in the treatment intervals due to financial burden was common; dupilumab treatment has been covered in Korea only since 2020 with strict inclusion criteria (patients who failed to achieve EASI50 after more than 3 months of immunosuppressant

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Table 1. General characteristics of the patients (n = 40)

Variables	Values
Age (yr)	30.9 ± 10.0 (15–56)
Sex	
Male	29 (72.5)
Female	11 (27.5)
Disease onset	
Infancy or childhood	35 (87.5)
Adolescence or adulthood	5 (12.5)
Follow-up period (wk)	74 ± 29.9 (4–127)
Allergy history	
Overall allergic comorbidities	22 (55)
Allergic rhinitis	18 (45)
Asthma	12 (30)
Allergic conjunctivitis	2 (5)
Previous use of systemic immunosuppressant	
Cyclosporine	22 (55)
Methotrexate	7 (17.5)
Phototherapy, NB-UVB	19 (47.5)
Adverse events during dupilumab treatment	
Overall	7 (17.5)
Conjunctivitis	6 (15)
Paradoxical head and neck erythema	1 (2.5)
Transient alopecia	1 (2.5)
Transient generalized skin rash	1 (2.5)
Patients receiving dupilumab every 2 weeks	
Week 8 (n = 39)	30 (76.9)
Week 16 (n = 38)	23 (60.5)
Week 24 (n = 35)	15 (42.9)
Week 40 (n = 29)	11 (37.9)
Week 52 (n = 28)	12 (42.9)
Dosing interval at the last follow-up	
Every 2 weeks	23 (57.5)
Every 3 weeks	2 (5)
Every 4 weeks	6 (15)
Every 5 weeks	2 (5)
Every 6 weeks	2 (5)
Every 8 weeks	3 (7.5)
Every 12 weeks	1 (2.5)
Compliance to treatment	
Continuous dupilumab treatment	22 (55)
Discontinuation of dupilumab	18 (45)
Reason for discontinuation (n = 18)	
Cost	5 (27.8)
Complete clearance of atopic dermatitis symptoms > 3 months	2 (11.1)
Follow-up loss	11 (61.1)

Values are expressed as mean ± standard deviation (range) or number (%).
NB-UVB, narrowband ultraviolet B.

treatment [cyclosporine or methotrexate] with the initial EASI score > 23). While 76.9% (30 of 39) of the patients adhered to the standard 2-week interval at week 8, only 42.9% (12 of 28) of the patients followed the standard interval at week 52. One year and four months after the last patient was included in the study, 18 (45%) of the 40 patients no longer received dupilumab. While 11 of these patients were lost to follow-up, 5 (27.8%) decided to stop the treatment course mainly due to financial burden. Adverse events were rare and mostly transient. Seven of the 40 patients (17.5%) reported 9 adverse events in total. Conjunctivitis was the most frequent adverse event (n = 6, 15%) whereas transient cases of paradoxical head and neck erythema (n = 1, 2.5%), alopecia (n = 1, 2.5%), and generalized skin rash (n = 1, 2.5%) were also reported (**Table 1**).

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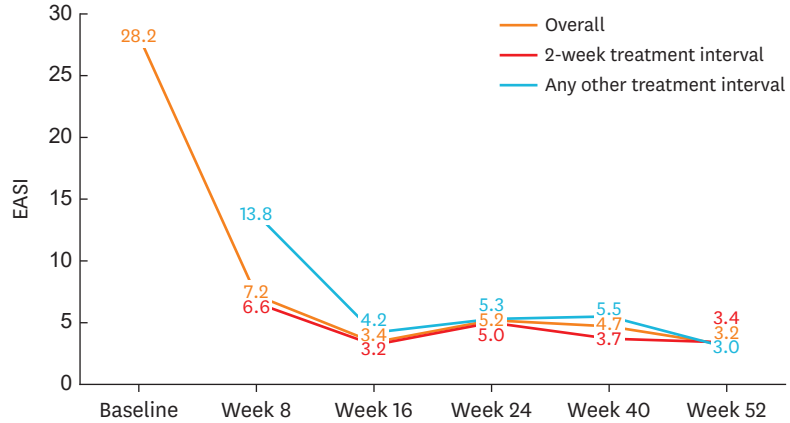
Treatment response

At baseline, the mean EASI score was 28.2; however, by week 8, it dropped to 7.2. The mean EASI scores at weeks 16, 24, 40, and 52 were 3.4, 5.2, 4.7, and 3.2, respectively (**Figure**). At baseline, 64.9% (24 of 37) of the patients had moderate-to-severe facial eczema with IGA scores of 3 or 4, and 28.6% (10 of 35) of the patients had moderate-to-severe hand eczema with IGA scores of 3 or 4. By the last follow-up, 95.8% and 90% of the moderate-to-severe facial and hand lesions, respectively, improved to IGA scores of 0 or 1. Notably, 7 of the 40 patients received combined systemic treatment in the initial phase of dupilumab treatment. A transition to dupilumab treatment alone or in combination with topical corticosteroids/calcineurin inhibitors was achieved in all these patients, with a mean duration of the combined systemic treatment of 11.5 weeks. This is in line with a previous study that suggested discontinuation of the immunosuppressant in good responders after 12 weeks of dupilumab treatment.[6] Among the six patients who developed conjunctivitis during the treatment, four showed complete responses to conventional conjunctivitis treatment with topical antihistamines and/or corticosteroids, whereas the other two reported continuing symptoms at the last follow-up despite treatment. Nevertheless, none of the two patients had to discontinue dupilumab treatment as remaining conjunctivitis symptoms were tolerable with conventional conjunctivitis treatment (**Table 2**).

After discontinuation of dupilumab treatment

Four of the five patients who required discontinuation of dupilumab owing to its financial burden still continued the treatment for atopic dermatitis at our institution. Within the mean average follow-up period of 26.6 weeks, all four were restarted on systemic immunosuppressant treatment owing to flare-up events of AD. Meanwhile, based on the physician's decision, dupilumab treatment was discontinued in two patients who achieved complete clearance of AD symptoms (EASI and IGA scores of 0) for more than three months. Both patients have achieved symptom control with topical corticosteroids alone; one of them has been disease-free with an IGA score of 0 for the last 43 weeks, and the other has been maintaining an IGA score of 1 for 66 weeks.



	Baseline	Week 8	Week 16	Week 24	Week 40	Week 52
Overall (n)	40	26	24	20	15	24
2-week interval (n)		24	19	9	7	15
Other interval (n)		2	5	11	8	9

Figure. Evolution of mean EASI scores from baseline through week 52.
EASI, Eczema Area and Severity Index; n, number of patients with recorded EASI scores.

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Table 2. Clinical response in patients receiving dupilumab (n = 40)

Clinical response	Values
EASI	
Baseline (n = 40)	28.2 ± 12.2 (5.9–57.6)
Week 8 (n = 26)	7.2 ± 7.3 (0.3–34.5)
Week 16 (n = 24)	3.4 ± 3.3 (0–16.0)
Week 24 (n = 20)	5.2 ± 6.2 (0–22.8)
Week 40 (n = 15)	4.7 ± 5.4 (0.6–21.3)
Week 52 (n = 24)	3.2 ± 4.8 (0–24.6)
Facial lesion	
IGA 3 or 4 at baseline (n = 37)	24 (64.9)
Patients with moderate-to-severe baseline facial eczema who reached IGA 0 or 1 at the last follow-up (n = 24)	23 (95.8)
Hand lesion	
IGA 3 or 4 at baseline (n = 35)	10 (28.6)
Patients with moderate to severe baseline hand eczema who reached IGA 0 or 1 at the last follow-up (n = 10)	9 (90)
Conjunctivitis (n = 6)	
Relieved with conventional treatment	4 (66.7)
Patients who received combined systemic treatment during the initial phase of dupilumab treatment	7 (17.5)*
Duration of the combined treatment (wk)	11.5 ± 8.3 (1–24)

Values are expressed as mean ± standard deviation (range) or number (%).
EASI, Eczema Area and Severity Index.
*The patients who received combined systemic treatment included 3 patients who received cyclosporine; 2, oral corticosteroids; and 2, methotrexate.

DISCUSSION

In our retrospective analysis, dupilumab showed excellent therapeutic efficacy with a tolerable safety profile. Notably, in our real-world data, patients who were unable to adhere to the standard 2-week treatment interval of dupilumab were fairly common mainly due to financial burden. However, the increase in the treatment intervals was maintained only when the treatment response was also sustained at an acceptable level with no severe aggravation of AD. Indeed, while only 44.8% (13 of 29) of the patients followed the standard interval at week 52, the mean EASI score at the time was still low (3.2). This indicates that slight flexibility in the treatment schedule may be considered depending on the differences in the medical and insurance systems according to the nation/institution.

Paradoxical facial and neck erythema, which has been reported in the literature,[7] was rare in our Korean study group with its presentation in only one patient. In addition, while persistent facial redness resistant to dupilumab has been previously reported,[8] this case was not found in our study, and 27 of the 28 (96.4%) patients with severe face eczema at baseline reached an IGA score of 0 or 1 at the last follow-up. Notably, most patients with severe hand eczema at baseline also showed excellent responses to dupilumab treatment (9 of the 10 patients, 90%). Conjunctivitis is a well-known side effect associated with dupilumab treatment,[9,10] and our study also confirmed it as the most frequently found adverse side effect with 15% (6 of 40) of the patients developing the symptoms. Two-thirds of these patients showed complete response to the conventional treatment with topical antihistamines and/or corticosteroids, and the remaining symptoms in the other 2 patients were still tolerable, with no patient requiring the discontinuation of dupilumab owing to conjunctivitis. Interestingly, there was a case of transient generalized alopecia that spontaneously resolved without the need to discontinue dupilumab. While anecdotal cases of alopecia associated with dupilumab have been reported in the literature,[11] its exact etiology remains unknown.

Our study had some limitations inherent to a retrospective study setting with a relatively small sample size. Also, there were no definite criteria for determining treatment intervals

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as they were determined and tailored on a patient-by-patient basis considering patients' financial situations, expectations, and treatment responses all together. However, our study confirms the therapeutic efficacy of dupilumab in real clinical practice in a setting where an increase in the treatment interval was frequently required. In addition, our findings showed that new and/or persistent dermatitis in the head and neck region was rare in our Korean study group with pre-existing severe head and neck dermatitis showing excellent response to dupilumab treatment. Also, severe hand eczema responded well to dupilumab, and conjunctivitis mostly responded well to conventional treatment and was at least tolerable for all patients. Future prospective studies are warranted to elucidate the different treatment responses and adverse events in a broader population.

REFERENCES

1. Beck LA, Thaçi D, Hamilton JD, Graham NM, Bieber T, Rocklin R, et al. Dupilumab treatment in adults with moderate-to-severe atopic dermatitis. N Engl J Med 2014;371:130-9.
PUBMED | CROSSREF
2. Deleuran M, Thaçi D, Beck LA, de Bruin-Weller M, Blauvelt A, Forman S, et al. Dupilumab shows long-term safety and efficacy in patients with moderate to severe atopic dermatitis enrolled in a phase 3 open-label extension study. J Am Acad Dermatol 2020;82:377-88.
PUBMED | CROSSREF
3. Ruiz-Villaverde R, Dominguez-Cruz J, Armario-Hita JC, Martinez-Pilar L, Alcantara-Luna S, Pereyra-Rodriguez JJ. Dupilumab: short-term effectiveness and security in real clinical practice - a retrospective multicentric study. J Eur Acad Dermatol Venereol 2019;33:e21-2.
PUBMED | CROSSREF
4. Wang C, Kraus CN, Patel KG, Ganesan AK, Grando SA. Real-world experience of dupilumab treatment for atopic dermatitis in adults: a retrospective analysis of patients' records. Int J Dermatol 2020;59:253-6.
PUBMED | CROSSREF
5. Kim JA, Yoon S, Kim LY, Kim DS. Towards actualizing the value potential of Korea Health Insurance Review and Assessment (HIRA) data as a resource for health research: strengths, limitations, applications, and strategies for optimal use of HIRA data. J Korean Med Sci 2017;32:718-28.
PUBMED | CROSSREF
6. de Wijs LE, Thyssen JP, Vestergaard C, Thio HB, Kunkeler AC, Biedermann T, et al. An approach for the transition from systemic immunosuppressants to dupilumab. J Eur Acad Dermatol Venereol 2021;35:e221-3.
PUBMED | CROSSREF
7. Jo CE, Finstad A, Georgakopoulos JR, Piguet V, Yeung J, Drucker AM. Facial and neck erythema associated with dupilumab treatment: a systematic review. J Am Acad Dermatol 2021;84:1339-47.
PUBMED | CROSSREF
8. Nakanishi M, Tamagawa-Mineoka R, Arakawa Y, Masuda K, Katoh N. Dupilumab-resistant facial erythema - dermoscopic, histological and clinical findings of three patients. Allergol Int 2021;70:156-8.
PUBMED | CROSSREF
9. Katoh N, Kataoka Y, Saeki H, Hide M, Kabashima K, Etoh T, et al. Efficacy and safety of dupilumab in Japanese adults with moderate-to-severe atopic dermatitis: a subanalysis of three clinical trials. Br J Dermatol 2020;183:39-51.
PUBMED | CROSSREF
10. Halling AS, Loft N, Silverberg JI, Guttman-Yassky E, Thyssen JP. Real-world evidence of dupilumab efficacy and risk of adverse events: a systematic review and meta-analysis. J Am Acad Dermatol 2021;84:139-47.
PUBMED | CROSSREF
11. Hendricks AJ, Lio PA, Shi VY. Dupilumab and alopecia: causative or therapeutic? Dermatology 2019;235:306-7.
PUBMED | CROSSREF