Effectiveness of tacrolimus ointment on facial lesions refractory to topical corticosteroid in patients with atopic dermatitis receiving dupilumab

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Abstract
Dupilumab demonstrated high efficacy and tolerable safety profiles in moderate-to-severe atopic dermatitis (AD) patients in clinical trials; however, certain patients suffer from facial redness, while obtaining good responses on the trunk and limbs to dupilumab in the real-world setting. In our study, we investigated the effectiveness of tacrolimus ointment on facial lesions refractory to topical corticosteroid in patients with AD receiving dupilumab. This study included Japanese adult patients with moderate-to-severe AD who developed facial lesions during dupilumab treatment and whose facial lesions became refractory to topical corticosteroid treatment. Nine patients (one female, eight males) were included in this study. One patient newly developed facial erythema after initiating dupilumab. Facial lesions were refractory to dupilumab treatment in the other patients. Five of the nine patients showed improvement in EASI scores of head and neck by switching the facial treatment from topical corticosteroid to tacrolimus ointment. The patient who developed newly facial erythema showed improvement after applying tacrolimus ointment. Although we explored the predictors of effectiveness of tacrolimus ointment in patients with facial lesions during dupilumab treatment, no significant differences were observed in age, duration of dupilumab prior treatment, or prior head and neck EASI between patients who showed improvement after changing to tacrolimus and those who did not. Tacrolimus ointment is worth trying if facial lesions are refractory to topical corticosteroid.

KEYWORDS
atopic dermatitis, calcineurin, dupilumab, interleukin-4 receptor, tacrolimus
1 | INTRODUCTION

Atopic dermatitis (AD) is a chronic inflammatory skin disease with pruritus, characterized by recurrent eczema with exacerbations and remissions, and impairs patients’ quality of life. Dupilumab, an anti-interleukin (IL)-4 receptor α antibody, demonstrated high efficacy and tolerable safety profiles in patients with moderate-to-severe AD in clinical trials.\(^1\)\(^2\) In the real-world setting, dupilumab also showed high effectiveness;\(^3\)\(^-\)\(^5\) however, certain patients showed poor improvement on the head and neck while obtaining good responses on the trunk and limbs to dupilumab.\(^3\)

Zhu et al.\(^6\) reported that among 73 patients with a median duration of dupilumab therapy of 181 days, 14 patients (19.2%) developed new regional dermatoses of the face. These facial lesions that develop during dupilumab treatment are often refractory to topical corticosteroid, and bother patients. We experienced nine adult patients with facial lesions that were refractory to topical corticosteroid during dupilumab treatment who changed their facial treatment from topical corticosteroid to tacrolimus ointment and herein discuss the effectiveness of tacrolimus for these facial lesions.

2 | METHODS

This study included Japanese adult patients with moderate-to-severe AD who developed facial lesions during dupilumab treatment and whose facial lesions became refractory to topical corticosteroid treatment. Under the insurance system in Japan, dupilumab is indicated only for AD patients over 15 years old with a total eczema area and severity index (EASI) score of greater than 16 or a head and neck EASI score of greater than 2.4, an investigator’s global assessment score of >3, and affected body surface area of greater than 10%, who have been refractory to topical corticosteroid and/or tacrolimus for more than six months or cannot use them due to adverse effects. All patients received a 600 mg loading dose of dupilumab once; then, starting two weeks later, 300 mg of dupilumab was administered subcutaneously every two weeks, in addition to treatment with topical corticosteroid and/or tacrolimus for lesions other than lesions on the face. Facial lesions were initially treated with topical corticosteroid. If improvement in the facial lesions was not observed under the treatment of topical corticosteroid at more than two consecutive visits, the patients changed the facial treatment from topical corticosteroid to tacrolimus ointment. The severity of AD was evaluated by dermatologists using EASI. All data were collected retrospectively from their charts. Statistical differences in demographic and clinical backgrounds between patients who showed improvement after changing to tacrolimus and those who did not (data are not shown).

3 | RESULTS

Patients’ demographics, clinical characteristics, and change in EASI scores of the head and neck over time are shown in Table 1. Two representative cases are described below. Among the nine patients who met the study criteria, eight were male and one was female. The mean age of the nine patients was 45.7 (range, 33–59) years. They applied hydrocortisone butyrate, betamethasone valerate, dexamethasone propionate, or prednisolone valerate acetate ointment on their face for the facial lesions. One patient newly developed facial erythema after initiating dupilumab (Case 2). Facial lesions were refractory to dupilumab treatment in the other patients. After the topical corticosteroid treatment became ineffective, the medication was switched to tacrolimus ointment. Five (55.6%) of the nine patients showed improvement in EASI score of the head and neck by switching the facial treatment from topical corticosteroid to tacrolimus ointment. The patient who developed newly facial erythema showed improvement after applying tacrolimus ointment. Although we explored the predictors of effectiveness of tacrolimus ointment in patients with facial lesions during dupilumab treatment, no significant differences were observed in age, duration of dupilumab prior treatment, or prior head and neck EASI between patients who showed improvement after changing to tacrolimus and those who did not (data are not shown).

3.1 | Case 1

A 49-year-old man with AD since childhood had been treated with clobetasol propionate ointment and diflorasone diacetate ointment for lesions on his trunk and extremities, and with betamethasone valerate ointment for lesions on his face until initiating dupilumab. At the time of beginning dupilumab treatment, his total EASI score was 39.1, and EASI score of the head and neck was 5.4. One month later, his total EASI score and EASI score of the head and neck decreased to 27.45 and 4, respectively. On four months after initiation of dupilumab, erythema and papules were still persistent on his face despite treatment with topical corticosteroid, with a head and neck EASI score of 2.2. For his refractory residual facial lesions, the topical corticosteroid was switched to tacrolimus ointment. After eight months, his erythematous facial lesions ameliorated, with a head and neck EASI score of 1.6 (Figure 1A).

3.2 | Case 2

A 59-year-old man had suffered from AD and bronchial asthma since he was three years old. He has applied betamethasone butyrate propionate ointment on his trunk and extremities, and hydrocortisone butyrate ointment on his face for the treatment of AD. His total EASI score was 26.9 and the EASI score of the head and neck was 3 at the time of beginning dupilumab. Six-month treatment with dupilumab in addition to corticosteroid ointment
decreased his total EASI score to 21.8, whereas it did not bring any improvement in his facial lesions. Rather, new erythematous lesions developed on his face, with a head and neck EASI score of 5. Since hydrocortisone butyrate ointment did not bring any improvement in his facial lesions under the treatment of dupilumab, he started to apply tacrolimus ointment instead. Application of tacrolimus ointment on his face for 8 months resulted in certain improvement of facial lesions, with a head and neck EASI score of 1.5 (Figure 1B).

### TABLE 1
Demographics and clinical characteristics of patients who applied tacrolimus ointment for the treatment of facial lesions that had been refractory to topical corticosteroid during dupilumab therapy

| Case | Age (year) | Sex | Duration of dupilumab therapy before initiating application of tacrolimus ointment (months) | Treatment prior to applying tacrolimus ointment | Type of facial redness | EASI (H&N) before applying tacrolimus ointment | Duration of applying tacrolimus ointment (months) | EASI (H&N) after application of tacrolimus | Outcome: Change in EASI (H&N) |
|------|------------|-----|--------------------------------------------------------------------------------------------|---------------------------------------------|------------------------|---------------------------------------------|---------------------------------------------|---------------------------------------------|----------------------------------------|
| 1    | 49         | M   | 4                                                                                          | Betamethasone valerate                      | Refractory             | 2.2                                         | 8                                           | 1.6                                         | -0.6                                   |
| 2    | 59         | M   | 4                                                                                          | Hydrocortisone butyrate                     | Newly developed        | 5                                           | 8                                           | 1.5                                         | -3.5                                   |
| 3    | 33         | M   | 6                                                                                          | Dexamethasone propionate hydrocortisone butyrate | Refractory             | 0.3                                         | 6                                           | 0.1                                         | -0.2                                   |
| 4    | 56         | M   | 7                                                                                          | Hydrocortisone butyrate                     | Refractory             | 1.5                                         | 6                                           | 3.5                                         | +2                                    |
| 5    | 49         | M   | 7                                                                                          | Hydrocortisone butyrate                     | Refractory             | 0.2                                         | 5                                           | 0                                           | -0.2                                   |
| 6    | 40         | M   | 5                                                                                          | Hydrocortisone butyrate                     | Refractory             | 1.2                                         | 6                                           | 1.6                                         | +0.4                                   |
| 7    | 35         | M   | 3                                                                                          | Betamethasone valerate                      | Refractory             | 0.2                                         | 9                                           | 0.9                                         | +0.7                                   |
| 8    | 35         | M   | 3                                                                                          | Prednisolone valerate acetate               | Refractory             | 2.4                                         | 3                                           | 0.4                                         | -2                                    |
| 9    | 55         | F   | 2                                                                                          | Hydrocortisone butyrate                     | Refractory             | 0.8                                         | 10                                          | 1.2                                         | +0.4                                   |

Abbreviations: EASI, eczema area and severity index; H&N, head and neck.
The pathogenesis of facial redness that develops after some AD patients initiate dupilumab treatment remains to be elucidated. Waldman et al. reported that prevailing theories for the pathogenesis of dupilumab facial redness were hypersensitivity reaction, site-specific failure, seborrheic dermatitis, and allergic contact dermatitis. There is some evidence supporting each theory, while there is other refuting evidence. Heibel et al. reported a case with rosacea associated with dupilumab therapy. De Wijis et al. reported heterogeneous clinical and histopathological characteristics of paradoxical head and neck erythema in atopic dermatitis patients treated with dupilumab and advocated the possibility of a drug-induced skin reaction. These previous literatures indicate that facial redness after dupilumab treatment is heterogeneous, and that further accumulation of cases is needed to elucidate its pathogenesis.

Our study showed that in five of nine patients, tacrolimus ointment was effective for facial lesions that had been refractory to topical corticosteroid during dupilumab treatment. Previous literatures revealed differences in the mechanism of the effectiveness of corticosteroid and tacrolimus for AD, although there are certain common mechanisms of action between them. Noguchi et al. developed NC/Nga mice with AD-like dermatitis by repeated topical application of Dermatophagoides farinae body ointment and reported that transepidermal water loss was significantly lower in tacrolimus-treated AD mice, but not in clobetasol propionate-treated AD mice. In in vitro studies, Kato et al. stimulated human peripheral blood-derived mast cells with anti-IgE antibody in the presence of dexamethasone or tacrolimus. Induction of CCL2, CCL7, CXCL3, and CXCL8 by anti-IgE was significantly inhibited by dexamethasone but was enhanced by tacrolimus. In contrast, induction of CCL1, CCL3, CCL4, and CCL18 was significantly inhibited by tacrolimus but, with the exception of CCL1, was enhanced by dexamethasone, indicating that the corticosteroid and tacrolimus inhibited the expression of distinct subsets of chemokines in mast cells. Inagaki et al. reported that in a mouse allergic dermatitis model involving frequent scratching behavior by repeated painting with 2,4-dinitrofluorobenzene acetone solution onto the mouse skin, tacrolimus significantly inhibited scratching behavior that was associated with the inhibition of nerve fiber extension into the epidermis, whereas dexamethasone failed to have any effect.

These previous literatures demonstrated the difference in the mechanism of action between corticosteroid and tacrolimus. In AD, heterogeneity is identified by the race, the biomarkers, and severity of itch and skin lesions. This concept of heterogeneity in the pathogenesis of AD is also supported by the fact that there are still a certain number of patients with significant failure even in any systemic therapies. Considering this heterogeneity and the different mechanisms of actions between corticosteroid and tacrolimus, it is reasonable that there are some patients with facial lesions during dupilumab treatment, which are refractory to topical corticosteroid but responsive to topical tacrolimus.

Regarding the four cases without improvement after switching to tacrolimus ointment, topical corticosteroid might have been more effective than tacrolimus ointment due to their different mechanism of action; however, tacrolimus ointment is recommended in terms of adverse effects of long-term use of topical corticosteroids such as telangiectasia and thinning of the skin. As another possibility, AD is a chronic inflammatory disease with flares and remissions, which may affect the results. In addition, adherence is another problem considering topical treatment. Generally, as treatment become longer, the adherence of topical treatment decreases. In our study, we did not investigate the adherence, which is one of the limitations. Further investigation is needed to elucidate the reason of the four cases without improvement after switching to tacrolimus ointment.

We could not find any statistical differences in demographic and clinical backgrounds between patients who showed improvement after changing to tacrolimus and those who did not. This may be due to the small sample of our study, which is one of limitations. Further accumulation of cases is needed to clarify this issue.

In conclusion, we experienced patients with facial lesions that were refractory to topical corticosteroid during dupilumab treatment who were successfully treated with tacrolimus ointment. Our study suggests that tacrolimus may be one of the good treatment options for patients who develop refractory facial lesions while receiving dupilumab. Tacrolimus ointment is worth trying even if the facial lesions had been refractory to topical corticosteroid.

DECLARATION SECTION

Approval of the research protocol: This study was approved by the ethics committee of Teikyo University and was carried out under the principles of the Declaration of Helsinki.

Informed Consent: Informed consent was obtained in the form of opt-out on the website.

Registry and the Registration No. of the study/trial: N/A.

Animal Studies: N/A.

CONFLICT OF INTEREST

M.K. received lecture fees from Sanofi and Maruho Co., Ltd. Y.T. received research grants, which are not related to this work from Sanofi and Maruho Co., Ltd.

H.U. and M.K. designed the study and wrote the manuscript. All authors contributed to data collection. H.U. performed the statistical analysis and interpretation of the results. All authors read and approved the final manuscript.

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How to cite this article: Uchida H, Kamata M, Egawa S, Nagata M, Fukaya S, Hayashi K, et al. Effectiveness of tacrolimus ointment on facial lesions refractory to topical corticosteroid in patients with atopic dermatitis receiving dupilumab. J Cutan Immunol Allergy. 2022;5:17–21. [https://doi.org/10.1002/cia2.12201]