

# Suplatast/Tacrolimus Combination Therapy for Refractory Facial Erythema in Adult Patients with Atopic Dermatitis—A Meta-Analysis Study—

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## ABSTRACT

**Background:** Combination of suplatast tosilate with tacrolimus ointment was reported to reduce the dose of tacrolimus ointment with maintained treatment efficacy for refractory facial erythema in atopic dermatitis (AD), however these were only case-controlled studies and the number of cases was not sufficiently large. Thus, the efficacy of a combination therapy of tacrolimus ointment and suplatast tosilate for treating AD including refractory facial erythema was investigated using a method of meta-analysis on the basis of published papers collected by database search.

**Methods:** We searched the literature on the efficacy of a combination of topical tacrolimus and suplatast tosilate for refractory facial erythema in patients with adult atopic dermatitis, and related data were collected for meta-analysis.

**Results:** Our meta-analysis study showed that suplatast/tacrolimus combination therapy revealed better improvement in skin symptom scores and significantly decreased the dose of tacrolimus compared with topical tacrolimus monotherapy. In addition, a significantly greater number of patients could stop using tacrolimus ointment by using the combination with suplatast tosilate than by tacrolimus monotherapy for refractory facial erythema.

**Conclusions:** The combination therapy with suplatast tosilate decreased the effective dosage of tacrolimus ointment supporting use of the combination therapy for refractory facial erythema.

## KEY WORDS

atopic dermatitis, erythema, meta-analysis, suplatast, tacrolimus

## INTRODUCTION

### EFFICACY AND PROBLEMS ASSOCIATED WITH TOPICAL TACROLIMUS FOR REFRACTORY FACIAL ERYTHEMA

Facial erythema in adult AD, which is called refractory facial erythema or an atopic red face, is a heavy psychological burden for a number of patients because it is chronic and resistant to regular treatment. A number of causes, such as involvement of mites, house dusts, and fungi such as *Candida* and *Malassezia*,<sup>1</sup> long-term topical application of steroids,<sup>2</sup>

and concomitant contact dermatitis due to the use of a variety of topical medicines and cosmetics,<sup>3</sup> have been proposed, however, none of these can explain the pathogenesis alone.

Traditionally, AD has been treated by the regular use of topical corticosteroids, which is not a perfect treatment because sufficient results cannot be provided in a number of cases due to adverse events such as steroid-induced skin atrophy. However, since tacrolimus ointment (Protopic®) was launched in 1999, it has brought major changes in the treatment of AD. Tacrolimus ointment exhibits anti-

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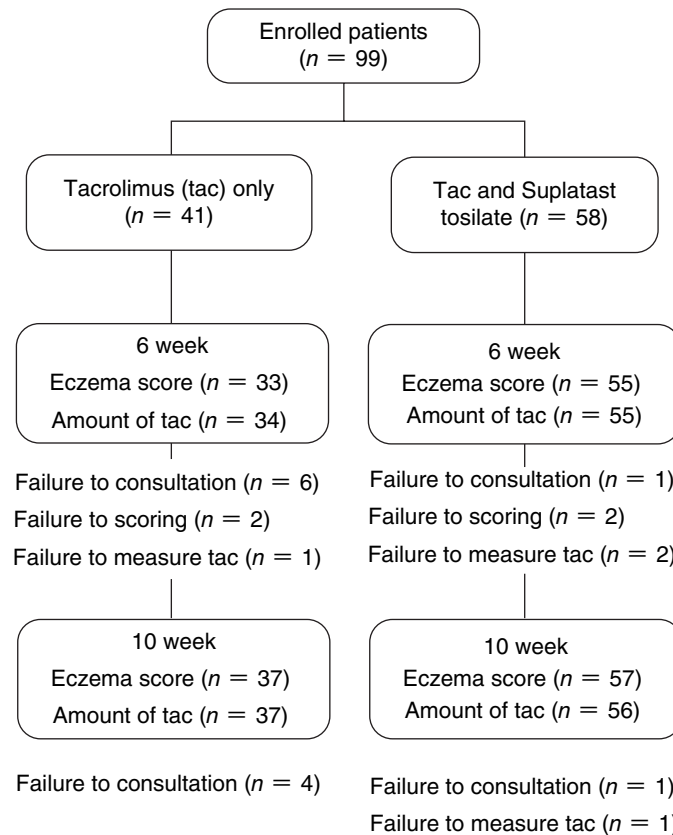


Fig. 1 Study Profile

**Table 1** Patient Background. The results were expressed as means  $\pm$  SD.

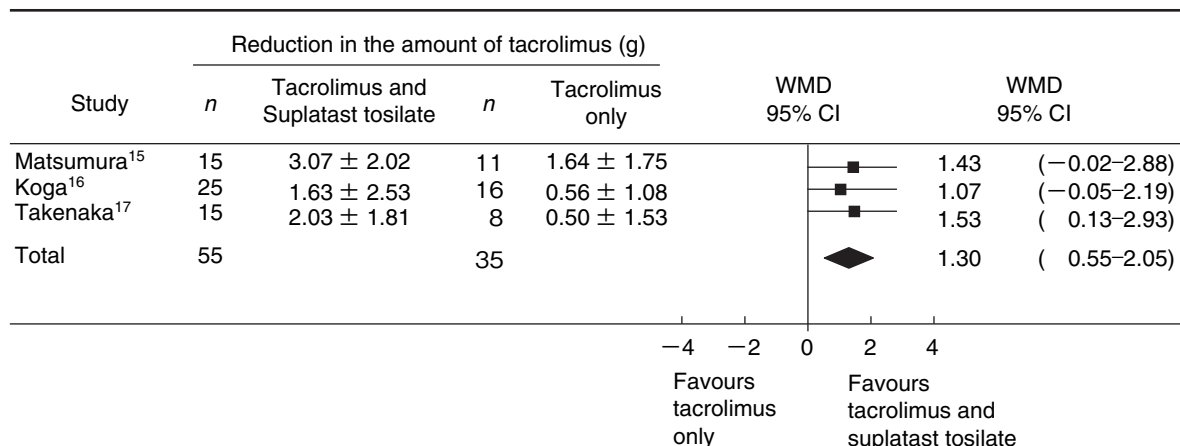
Inventory	Category	Tacrolimus and Suplatast Tosilate Combination	Tacrolimus Alone	Statistics ( <i>p</i> -value)
Number of patients		58	41	
Gender	Male	37	27	0.833 ( $\chi^2$ -test)
	Female	21	14	
Age		27.2 $\pm$ 9.2	27.2 $\pm$ 10.0	0.372 ( <i>t</i> -test)
Eczema scores before treatment	Erythema/edema/acute papule	7.2 $\pm$ 1.7	6.9 $\pm$ 1.8	0.402 ( <i>t</i> -test)
	Chronic papule/nodule/ lichenification	4.7 $\pm$ 2.1	4.0 $\pm$ 2.1	0.097 ( <i>t</i> -test)
	Humectation/erosion/crust	2.1 $\pm$ 2.3	2.3 $\pm$ 1.9	0.677 ( <i>t</i> -test)
	Total	13.9 $\pm$ 3.4	13.1 $\pm$ 2.4	0.196 ( <i>t</i> -test)
Doses of the first tacrolimus ointment	g/week	4.2 $\pm$ 2.8	4.0 $\pm$ 2.5	0.707 ( <i>t</i> -test)

inflammatory properties as effective as strong-class topical corticosteroids, and no local adverse events, such as skin atrophy often observed after the long-term use of corticosteroids, have been reported. Therefore, it has been employed mainly for facial and neck eczema in adult AD patients, and excellent improvements have been reported.<sup>4</sup>

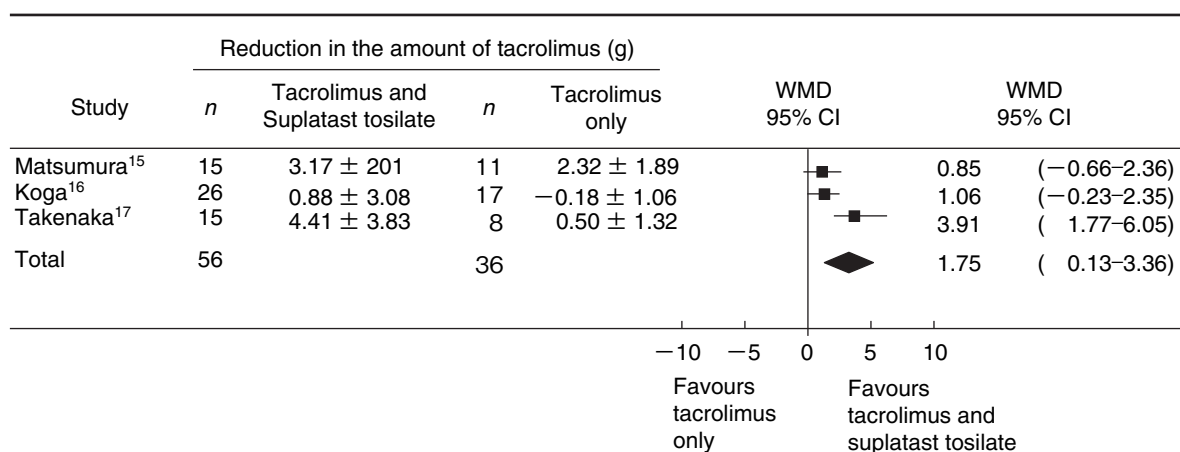
In cases with refractory facial erythema, acute ex-

acerbation associated with edematous erythema is often observed without exudation, papules, or small vesicles. Histologically, accumulation and infiltration of mast cells and eosinophils are often observed in the epidermis. It has been suggested that these symptoms may be caused by eosinophilic inflammation in the dermis due to a late phase allergic reaction.<sup>5</sup> Therefore, the regulation of mast cells, Th2

2–6 week



2–10 week (cases which lack the 10th week values are excepted)

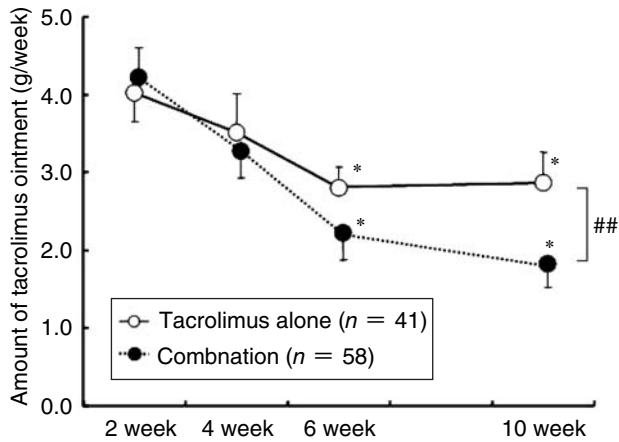


**Fig. 2** Reduction in the Amount of Tacrolimus Ointment by Suplatast Tosilate Combination. Data were pooled according to the random effect model after the test of heterogeneity. Meta-analysis was performed and the results were expressed as means ± SD with the 95% confidence interval and the forest plot was also shown. Differences in the mean value were expressed as weighted mean difference (WMD). Suplatast tosilate was administered 400 mg/day (b.i.d) in the study by Matsumura<sup>15</sup> and Koga,<sup>16</sup> and 300 mg/day (t.i.d) in the study by Takenaka.<sup>17</sup>

type cytokines, and proinflammatory factors from eosinophils that mediate the allergic inflammatory reaction is important. Tacrolimus ointment is often effective for such cases by inhibiting the functions of activated T cell nuclear transcription factors responsible for transcription of a variety of cytokines.<sup>6</sup> On the other hand, tacrolimus ointment causes skin irritation and burning sensation at the beginning of treatment, and infectious skin diseases such as folliculitis, Kaposi's varicelliform eruption, and herpes simplex virus infection have been reported as clinical problems.<sup>7</sup>

#### EFFICACY AND PROBLEMS ASSOCIATED WITH SUPLATAST TOSILATE FOR REFRACTORY FACIAL ERYTHEMA

Suplatast tosilate (IPD<sup>®</sup>) categorized as a Th2 type cytokine inhibitor suppresses the production of IL-4 and IL-5 in Th2 type cells, and preclinical experiments demonstrated inhibition of eosinophil infiltration and release of chemical mediators.<sup>8</sup> In addition, serum IL-5 levels,<sup>9</sup> peripheral eosinophil counts, and eosinophil cationic protein (ECP) were reduced by the administration of suplatast tosilate in clinical studies.<sup>10</sup> Furthermore, a recent prospective study revealed its efficacy for asthma.<sup>11</sup> Before tacrolimus ointment became commercially available, the efficacy of suplatast tosilate for refractory facial erythema was demonstrated, however it takes a relatively long time



**Fig. 3** Day-to-day Changes in the Amount of Tacrolimus Ointment. Data were pooled according to the random effect model after the test of heterogeneity. Differences in the amount of tacrolimus ointment at weeks 6 and 10 were compared between the two groups by Student's *t*-test. \*: significantly different from baseline. ##: significantly different between two groups. The results were expressed as means  $\pm$  SE.

before the emergence of effects and improvement in skin symptoms and is not as remarkable as topical tacrolimus.<sup>12</sup>

## A COMBINATION THERAPY OF TOPICAL TACROLIMUS AND SUPLATAST TOSILATE

It has been reported that a combination with suplatast tosilate after introduction of remission by tacrolimus ointment can reduce the dose of tacrolimus ointment with maintained treatment efficacy for refractory facial erythema in AD. However, the study was non-randomized and non-comparative, and the number of cases was not sufficiently large. Thus, the efficacy of a combination therapy of tacrolimus ointment and suplatast tosilate for treating AD including refractory facial erythema was investigated on the basis of published papers collected by a database search.

## METHODS

### SEARCH STRATEGY

We systematically searched for published works describing a combination of tacrolimus ointment and suplatast tosilate for AD on MEDLINE and Japana Centra Revuo Medicina (Igaku Chuo Zasshi/Japanese Central Medical Journal) databases. Research designs of papers selected for the present study were randomized comparative trials, comparative clinical trials, and comparative trials. "Tacrolimus, Protopic, or FK506", "Suplatast tosilate or IPD", "AD", and "facial erythema" were used as search terms and all published reports were extracted.

## PARAMETERS FOR EVALUATION

Parameters for evaluation were doses of tacrolimus ointment, eczema scores, and adverse events. Amount of tacrolimus ointment used in a week were measured every week. Degree of "erythema · edema · acute papule", "chronic papule · nodule · lichenification", and "humectation · erosion · crust" were graded from 0 to 3, and the total score was evaluated from 0 to 27 as the eczema score.

## DATA ANALYSIS

Background data were summarized as means  $\pm$  SD in each group, and differences between the groups were analyzed by Student's *t*-test and the  $\chi^2$ -test. Average differences in weekly doses of tacrolimus used at week 2 and week 8–10 after the beginning of treatment were calculated in the combination group with suplatast tosilate and the tacrolimus ointment alone group, which were employed as a marker to evaluate the effect. Meta-analysis was performed with the RevMan Analyses (version 1.0.3 for Windows) software in the Review Manager (RevMan) (version 4.2 for Windows, The Nordic Cochrane Centre, Copenhagen, 2003) provided by the Cochrane Collaboration.<sup>13</sup>

Differences in the reduced average dose of tacrolimus ointment and the average improvement in the eczema score were pooled according to the random effect model after the test of heterogeneity.<sup>14</sup> Since the three studies employed the same eczema score, differences in the mean value were expressed as the weighted mean difference (WMD).

The results were expressed as means  $\pm$  SD with the 95% confidence interval and the forest plot was also shown. After all data were collected, differences in the dose of tacrolimus ointment at weeks 6 and 10 were compared between the two groups by Student's *t*-test and presented in a graph. Termination rates of tacrolimus use in trials were compared by Mantel-Haenszel test. Adverse events were analyzed by  $\chi^2$ -test separately in each category. A *p* value less than 0.05 was considered statistically significant.

## RESULTS

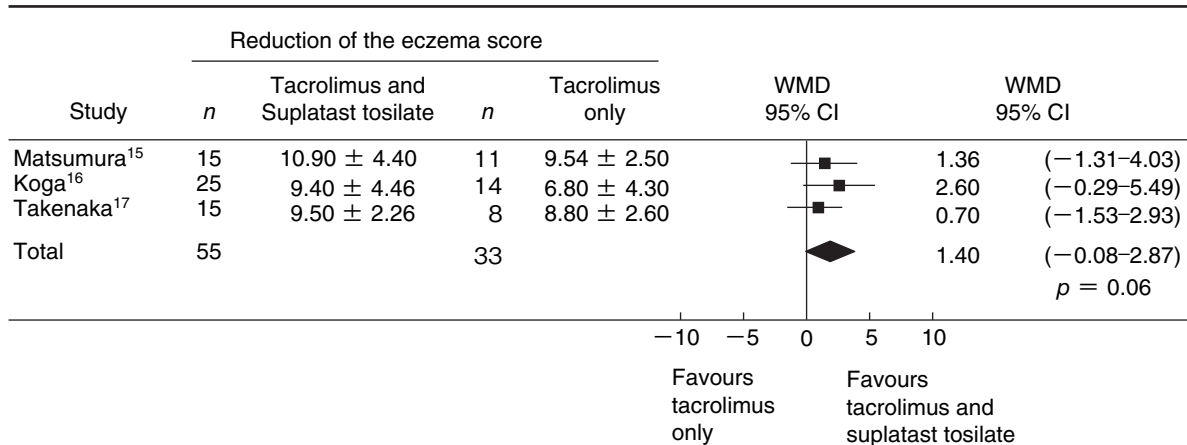
### STUDY SELECTION

Three case-controlled clinical trials published in Japan were verified to be appropriate.<sup>15-17</sup> Data were provided by the researchers that published the trials, which were evaluated as appropriate. Data of individual trials were analyzed and evaluated as follows.

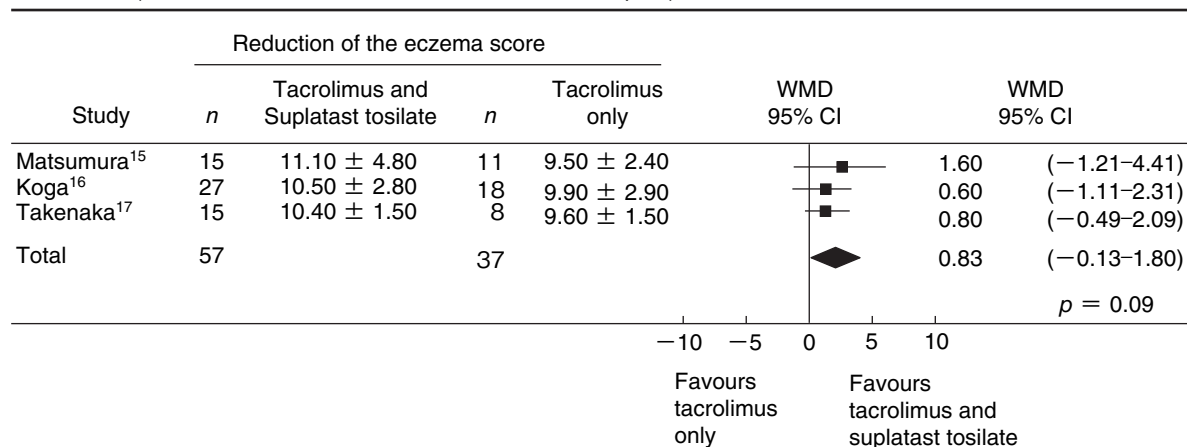
### PATIENT BACKGROUND

The case numbers of the tacrolimus ointment alone group and the suplatast tosilate combination group were 11 and 15 in the first,<sup>15</sup> 20 and 28 in the second,<sup>16</sup> and 10 and 15 in the third study, respectively, and in total these two groups had 41 and 58 registered cases, respectively. Study designs of all studies

0-6 week



0-10 week (cases which lack the 10th week values are excepted)



**Fig. 4** Improvement in the Eczema Score by the Combination of Suplatast Tosilate and Tacrolimus Ointment. Data were pooled according to the random effect model after the test of heterogeneity. Meta-analysis was performed and the results were expressed as means ± SD with the 95% confidence interval and the forest plot was also shown. Differences in the mean value were expressed as weighted mean difference (WMD). Suplatast tosilate was administered 400 mg/day (b.i.d) in the study by Matsumura<sup>15</sup> and Koga,<sup>16</sup> and 300 mg/day (t.i.d) in the study by Takenaka.<sup>17</sup>

are shown in Figure 1. The background in all patients, including gender, age, eczema scores before treatment, and doses of the first tacrolimus ointment were compared between the two groups, but there was no statistically significant bias (Table 1).

## EVALUATION OF EFFICACY

### Reduction in the Dose of Tacrolimus Ointment

In the three studies comparing the dose of tacrolimus ointment in the tacrolimus ointment alone group and the suplatast tosilate combination group between week 2 and 6 and between week 2 and 10, one study showed a significant reduction but two studies revealed no statistical difference. However, when the results of the three studies were meta-analyzed, the doses of tacrolimus ointment were significantly reduced at week 6 and 10 both compared with week 2 (Fig. 2). The suplatast tosilate combination group

showed a significantly reduced amount of tacrolimus ointment used at week 10 compared with the tacrolimus ointment alone group (Fig. 3).

### Improvement in the Eczema Score

In the three studies that compared the tacrolimus ointment alone group and the suplatast tosilate combination group, there was no statistical difference in the eczema score at week 0 and 6, or week 0 and 10. However, when the results of the three studies were meta-analyzed, *p* values for the comparison between week 0 and 6 and between week 0 and 10 were 0.06 and 0.09, respectively, which showed a tendency for improvement (Fig. 4).

Use of tacrolimus ointment was stopped by week 10 in 14 of 58 cases (24.1%) in the suplatast tosilate group and in 3 of 41 cases (7.3%) in the monotherapy group, and the combination with suplatast tosilate

**Table 2** Termination Rates of Tacrolimus Ointment Use.

Group	Combination (n = 58)	Tacrolimus Alone (n = 41)	Statistics (Mantel-Haenszel test)
Number of patients who discontinued the use of tacrolimus	14 (24.1%)	3 (7.3%)	P = 0.0023

**Table 3** Adverse Effects

Inventory	Combination (n = 58)	Tacrolimus Alone (n = 41)	p-value ( $\chi^2$ -test)
Irritation	10	7	0.983
Acne or acne-like eruption	2	3	0.387
Secondary infection	1	0	0.398
Drowsiness	1	0	0.398
Burning sensation	0	1	0.232
Herpes simplex	1	0	0.398

could stop the use of tacrolimus ointment at a significantly higher rate ( $p = 0.002$ ) (Table. 2).

There was no statistical difference in the occurrence of adverse events between the two groups (Table 3).

## DISCUSSION

The underlying mechanisms for the efficacy of topical tacrolimus for facial and neck eczema of adult AD have been reported and include the following: inhibition of (1) cytokine production from Th1 and Th2 cells; (2) antigen presentation by Langerhans cells; (3) histamine release from mast cells and basophils; (4) release of cytotoxic substances from eosinophils; and (5) chemokine production for eosinophils by cytokine-stimulated epidermal cells.<sup>7</sup> Among adult AD cases, the following findings have been made: topical tacrolimus has been used in cases such as eczema on the face and neck that often causes local adverse effects from the long-term use of topical corticosteroids; local adverse effects have already appeared due to topical corticosteroids; and contraindication for corticosteroids. Indeed, a number of cases of excellent improvements have been reported.<sup>4</sup>

On the other hand, approximately 80% of patients who used tacrolimus ointment for neck and facial eczema complained of skin irritation symptoms such as burning sensation, pain, and warmth, and some of them, but not many, were forced to stop the use due to severe irritation. Nakagawa *et al.* reported the results of long-term use of topical tacrolimus, and the occurrence rate of skin infection was 20.8%, which comprised of folliculitis at 12.0%, acne or acne-like eruption at 7.4%, Kaposi's varicelliform eruption at 4.2%, and herpes simplex virus infection at 3.3%. These are clinical problems for the application.<sup>7</sup>

Suplatast tosilate inhibits the production of IL-4 and IL-5 by Th2 type cells and exerts anti-allergic proper-

ties by suppressing not only the release of chemical mediators but also IgE antibody production and infiltration of eosinophils. It has been used to treat AD, bronchial asthma, and allergic rhinitis.

The results of the present study revealed that the combination with suplatast tosilate could reduce the dose or even remove the need for the use of tacrolimus ointment. There was no statistical difference in the improvement of eczema between the suplatast tosilate combination group and the tacrolimus ointment alone group. When the results of the three studies were meta-analyzed, the combination therapy showed a tendency of improvement with  $p$  values of 0.06 and 0.09 between week 0 and 6 and between 0 and 10, respectively, although the lower limits of the confidence interval were below zero and -0.08 and -0.13, respectively. Further accumulation of such cases may eventually indicate a significant improvement by the combination therapy. Because the total number of cases of these studies was small and they were done by case-controlled trials, and there might be a publication bias, analysis further studies are required.

These results suggest that the combination with suplatast tosilate is a useful option for treatment of adult AD. Although the underlying mechanisms that could reduce the amount of tacrolimus ointment remain to be clarified, a combination of steroid inhalation and suplatast tosilate was reported to reduce the amount of inhaled steroids for severe bronchial asthma, similarly to the results in the present study.<sup>10</sup> The similarity implicates the involvement of a certain common mechanism. It is expected that clinical trials with even-higher levels of evidence will verify the results.

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