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ORIGINAL ARTICLE

Therapeutic Efficacy and Safety of Methotrexate in Moderate-to-Severe Atopic Dermatitis: A Retrospective Study of Korean Patients at Tertiary Referral Hospital

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Background: Methotrexate (MTX) has been prescribed to suppress atopic dermatitis (AD) symptoms and flares in moderate-to-severe cases. **Objective:** The purpose of this study was to evaluate the therapeutic efficacy and safety of MTX as well as the suppressive activity of MTX to reduce flares in moderate-to-severe AD patients. **Methods:** Patients with moderate-to-severe AD who were treated with MTX at the Chonnam National University Hospital were retrospectively studied. **Results:** Total 102 patients (79 males, 23 females) with a median age of 22.0±10.3 years were studied. The median initial dose of MTX was 10.3±2.6 mg/week, and the MTX-weekly dose was increased by 2.5 to 5 mg at an interval of 2 to 4 weeks to a maximum dose of 17.5±2.7 mg/week. The median maintenance dose was 11.7±2.1 mg/week; the median duration of treatment with MTX was 34.0±38.8 weeks. The initial response was noted after 5.8±3.7 weeks. Of the 102 patients, 60.8% (62/102) showed successful treatment response and 39.2% (40/102) showed mild or no improvement. MTX therapy effectively suppressed the frequency of AD flares by more than 50% in 71.1% (32/45) of the patients who responded among the MTX responders group. The most common adverse events were transient liver abnormality (5.9%, 6/102) and gastrointestinal discomfort (3.9%, 4/102), but no serious adverse events occurred. **Conclusion:** Our results reveal that MTX is a relatively safe drug to control moderate-to-severe AD with satisfactory therapeutic efficacy and inhibitory activity against AD flares. **(Ann Dermatol 32(5) 402～408, 2020)**

-Keywords-
Atopic dermatitis, Flare, Methotrexate, Therapeutic efficacy

INTRODUCTION

Atopic dermatitis (AD) is a common inflammatory skin disease associated with significant physical, psychological and social morbidity. Patients with moderate-to-severe disease that is refractory to treatment with topical corticosteroids or calcineurin inhibitors may require second-line treatments such as phototherapy or systemic immunosuppressants. Considering the chronic, relapsing nature of AD as well as different individual prognosis, the long-term use of systemic immunomodulatory drugs is a challenge for dermatologists managing moderate-to-severe AD. Ideally, the therapeutic goal in moderate-to-severe AD should involve satisfactory therapeutic efficacy, stabilization of AD flares, and no serious adverse events (SAEs) due to therapeutic drugs.

A set of systemic immunomodulatory drugs including corticosteroids (CS), cyclosporine A (CsA), methotrexate (MTX), azathioprine, mycophenolate mofetil (MMF), and others have been used to control moderate-to-severe AD. Systemic CS are fast-acting and highly efficient drugs used to control severe inflammatory conditions of AD. However,

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long-term administration of systemic CS for moderate-to-severe AD is associated with complications of serious internal diseases and rebound phenomenon, leading to the relapse or aggravation of eczema symptoms. So, CS should be reserved for acute, severe exacerbation as a short-term bridge therapy with other systemic non-steroidal drugs. As a steroid-sparing drug, CsA is recommended as a first-line treatment for short-term management of moderate-to-severe AD cases that cannot be controlled by optimized topical regimens and phototherapy[1]. Treatment with CsA was successful in approximately 80% of patients with severe or refractory AD[2,3]. Unfortunately, the efficacy of CsA is not long-lasting, and the rapid relapse of AD symptoms is annoying for CsA-treated AD patients following drug withdrawal[2-4]. Relapse after discontinuation of CsA was generally observed, with a reported relapse rate of 23.5%～54.8%[2-4] and CsA-related rebound phenomena such as systemic CS was detected in 8% of CsA-treated AD patients[2]. Furthermore, long-term use of CsA medication is not recommended due to renal toxicity as well as high drug cost.

Originally, MTX was developed as a chemotherapeutic drug against myeloproliferative neoplasms such as acute leukemia and lymphoma. Low doses of MTX at a level of 1/100th dose used in chemotherapy have been used to treat a variety of inflammatory and immune-related diseases. MTX can be prescribed as an off-label drug to control eczema symptoms in AD. Studies demonstrate that MTX is a good candidate drug in controlling moderate-to-severe AD in both children and adults[5-9]. The purpose of this study was to investigate retrospectively the long-term efficacy and safety of MTX as well as the suppressive activity of MTX to reduce flares in moderate-to-severe AD patients.

MATERIALS AND METHODS

Study design and participants

A retrospective study was undertaken based on the review of medical records, photographs and telephone calls of patients with moderate-to-severe AD who were treated with MTX between January 2014 and December 2018 at the Chonnam National University Hospital. All patients were diagnosed with AD based on Hanifin and Rajka's diagnostic criteria and were refractory to long-term therapy with oral antihistamines and local treatment with topical emollients, CS and calcineurin inhibitors. The disease severity was measured before MTX treatment using Eczema Area and Severity Index (EASI) score, and patients with EASI score less than 16 were regarded as mild cases and excluded from the study. It was our policy not to administer MTX to patients with pregnancy, hepatic, renal or hematological disease, abnormal liver or renal function test. For this, laboratory tests including serologic tests for hepatitis B and C were performed before the treatment, followed by periodic monitoring routinely. If abnormal blood tests were repeated and persistent, the dosage of MTX was either reduced or stopped.

The initial dose of MTX was 5 to 15 mg per week given orally (the starting dose of MTX used in young children was 5 mg per week for patients aged 0～5 years, 7.5～10 mg for patients aged 6～10 years), and if the patient did not respond, MTX dose was increased by 2.5 to 5 mg at an interval of 2 to 4 weeks up to the maximum dose of 22.5 mg. And if a patient clearly shows treatment response to a given MTX dose to show improvement of Investigator Global Assessment (IGA) score, no further increases of MTX was tried, thereby minimizing the likelihood of adverse events (AEs). When treatment response was achieved, the weekly dose of MTX was decreased by 2.5 to 5 mg at an interval of 2 to 4 weeks, and then the MTX-dose with therapeutic efficacy was maintained. This study was approved by the hospital Institutional Review Boards of Chonnam National University Hospital (IRB no. CNUH-2019-344) and informed consents of AD patients were obtained for this study.

Validation of therapeutic efficacy of methotrexate

Efficacy of MTX was assessed only in patients who had completed more than four weeks of treatment. Patients who refused to maintain MTX medication due to personal reasons (for example, lack of efficacy in relation with slow onset of MTX action) or complained MTX-related AEs during the early stage of treatment were excluded in this study. Treatment efficacy of patients at each visit was recorded using an IGA tool by the treating dermatologist (0＝clear, 1＝almost clear, 2＝mild, 3＝moderate, 4＝severe, 5＝very severe) and successful treatment response was defined as an IGA score of 0 to 2. Overall efficacy of MTX was assessed based on the latest IGA score, considering the quality and extent of lesions relative to baseline assessment. Also, we evaluated the safety and treatment-related AEs of MTX.

Validation of suppressive activity of methotrexate against AD flares

We defined AD flares as an aggravation of disease severity resulting in escalation of treatment or further medical recommendations. To analyze the suppressive activity of MTX against AD flares, we evaluated patients who showed successful treatment response with MTX. We inquired about the frequency of flares during the three months of MTX treatment and compared the frequency before and

after taking MTX. When the frequency of flare decreased by more than 50% after taking MTX, we concluded that the drug was effective in controlling AD flares.

Statistical analysis

For statistical analysis, data were evaluated using the statistical package IBM SPSS ver. 25.0 (IBM Corp., Armonk, NY, USA) and expressed as means with standard deviations or as medians with ranges.

RESULTS

Patient characteristics

Of the 102 patients, 77.5% (n=79) were male and 22.5% (n=23) were female. The patients' mean age was 22.0±10.3 (range, 2~60) years, and about half of the patients were over 20 years old. All patients had previous topical treatment and 99 patients (97.1%) were treated with systemic CsA. Systemic CS was administered previously to 43 patients (42.2%). One patient (1.0%) had a previous trial of azathioprine. These patients were eligible for other systemic immunosuppressants because most of them showed low response to previous treatment (59.8%, 61/102) or showed poor compliance (24.5%, 25/102), AEs (15.7%, 16/102). When moderate-to-severe AD patients were divided according to EASI score 26, severe patients constituted 74.5% (76/102) in our study (Table 1).

Table 1. Patient demographics and baseline characteristics

Characteristic	Value
Sex	
Male	79 (77.5)
Female	23 (22.5)
Age (yr)	
Mean age	22.0±10.3
1~9	6 (5.9)
10~19	45 (44.1)
20~29	34 (33.3)
30~39	10 (9.8)
≥40	7 (6.9)
EASI score	
16~26	26 (25.5)
≥26	76 (74.5)
Previous treatment	
Topical treatment	102 (100)
Oral CS	43 (42.2)
Oral CsA	99 (97.1)
Other systemic treatment	1 (1.0)
Reason for other systemic immunosuppressants	
Low response	61 (59.8)
Poor compliance*	25 (24.5)
Showing adverse events	16 (15.7)

Values are presented as number (%) or mean±standard deviation. Percentages have been rounded and may not total 100. EASI: Eczema Area and Severity Index, CS: corticosteroid, CsA: cyclosporine. *Patients showed poor compliance with previous treatment because of high drug cost, discomfort associated with daily treatment, and other factors.

Therapeutic efficacy of methotrexate in moderate-to-severe AD

All patients received MTX orally or via intramuscular injection for the treatment of moderate-to severe AD and folic acid supplements were administered in a weekly dose of 5 to 6 mg the day after the last dose of MTX. The median initial dose of MTX was 10.3±2.6 mg/week, and the timing for showing initial response to MTX was between 2 and 18 weeks (median 5.8±3.7 weeks). The median maintenance dose was 11.7±2.1 mg/week, the median maximum dose was 17.5±2.7 mg/week, and the median duration of treatment with MTX was 34.0±38.8 weeks, the cumulative dose was 414.4±379.7 mg (Table 2). Our study included young children from 1 to 9 years of age and their median initial dose of MTX was 7.9±2.5 mg/week, the median maintenance dose was 8.8±3.4 mg/week, and the median maximum dose was the same. Their median duration of treatment with MTX was 28±33.9 weeks, the cumulative dose was 294.6±379.5 mg. Of the 102 patients, 60.8% (62/102) showed successful treatment response (IGA score 0~2) and 39.2% (40/102) showed mild or no improvement (IGA score 3~5). In the unresponsive group (n=40), 87.5% (35/40) stopped MTX medication except 5 patients (12.5%) who still continued with MTX medication (Table 3).

Methotrexate as a candidate drug for suppressing AD flares during long-term management of moderate-to-severe AD

Some of patients manifested acute flares while taking MTX, which could/could not be controlled by intermittent short-term treatment with systemic CS or CsA. In the successful response group (n=62), 45 patients responded to

Table 2. Methotrexate treatment parameters

Parameter	Value
Median starting dose (mg/wk)	10.3±2.6
Maintenance dose (mg/wk)	11.7±2.1
Maximum dose (mg/wk)	17.5±2.7
Cumulative dose (mg)	414.4±379.7
Initial response (wk)	5.8±3.7
Duration of treatment (wk)	34.0±38.8

Values are presented as mean±standard deviation.

our questionnaire regarding their AD flares during the three months of treatment when followed up via telephone. When patients were asked to compare the frequency of their AD flare before and after taking MTX, 71.1% of respondents (32/45) answered that MTX was effective in suppressing the frequency of AD flares by more than 50%. However, 28.9% (13/45) responded that there was no difference in the frequency of AD flares following MTX treatment (Fig. 1).

Table 3. Clinical effect of treatment in 102 atopic dermatitis patients with MTX

Clinical effect of MTX	Number (%)
Overall response to MTX (latest evaluation)	
IGA score 0	3 (2.9)
IGA score 1	32 (31.4)
IGA score 2	27 (26.5)
IGA score 3	25 (24.5)
IGA score 4	12 (11.8)
IGA score 5	3 (2.9)
Successful response group	62 (60.8)
MTX only	13 (21.0)
MTX+other immunosuppresants*	49 (79.0)
MTX+CsA	43 (87.8)
MTX+CS	6 (12.2)
Stable without taking MTX†	16 (25.8)
Being followed-up	9 (56.2)
Follow-up loss	7 (43.8)
No-response group	40 (39.2)
MTX hold	35 (87.5)
MTX maintenance	5 (12.5)
Adverse event group	16 (15.7)
MTX hold	6 (37.5)
MTX maintenance	10 (62.5)

Percentages have been rounded and may not total 100. MTX: methotrexate, IGA: Investigator Global Assessment, CsA: cyclosporine, CS: corticosteroid. *MTX+other immunosuppressants: patients treated with MTX mainly but intermittently with other immunosuppressants during flare-up. †Patients who remain stable during at least three months with an IGA score of 0~2 in the absence of MTX treatment.

In the successful response group (n=62), 21.0% (13/62) used only MTX, 79.0% (49/62) were stable under MTX treatment in conjunction with intermittent CS or CsA. Among the 49 patients controlled by the combination therapy, 87.8% (43/62) were prescribed MTX+CsA, and 12.2% (6/62) were treated with MTX+CS. They did not continuously take CsA or CS when taking MTX, but they took intermittently only when their acute flares were not suppressed with MTX alone and eczema symptoms became severe. Their median duration of combined therapy with MTX and CsA was 7.0±3.2 weeks and their median dose was 100 mg/day.

Patients who remained stable during at least three months with an IGA score of 0 to 2 without taking MTX accounted for 25.8% (16/62) and nine patients were followed-up in our hospital. Their mean period of stability (IGA 0~2) without MTX medication was 20.0±10.4 months. Among nine patients, two showed recurrence after 19 and 24 months, respectively, and restarted MTX but the remaining seven patients still remained stable without MTX treatment and were controlled with first-line therapy such as topical CS or calcineurin inhibitors (Table 3).

Methotrexate as a relatively safe drug for long-term management of moderate-to-severe AD

Among 16 patients (15.7%) who experienced AEs during MTX treatment, 37.5% (6/16) stopped MTX medication and 62.5% (10/16) still used MTX by adjusting doses or briefly stopping MTX medication (Table 3). The mean duration of MTX treatment until AEs appeared was 7.3±7.0 months (range, 1~24 months). The most common AEs were elevation of liver enzymes (5.9%, 6/102), followed by nausea/vomiting (3.9%, 4/102). The most common concern about MTX-induced liver dysfunction was clinically

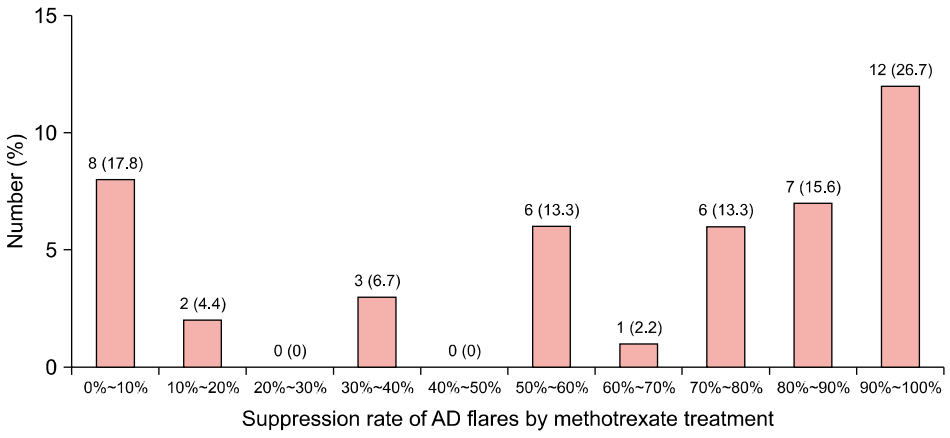

Fig. 1. Suppression of atopic dermatitis (AD) flares by methotrexate in moderate-to-severe atopic dermatitis patients. The horizontal axis shows the extent to which AD flares have been reduced during three months of treatment and the vertical axis shows the number of people.

Table 4. Treatment-induced adverse events

Adverse event	Number (%)
Major adverse events	
Hepatotoxicity	0 (0)
Myelosuppression	0 (0)
Pulmonary fibrosis	0 (0)
TB reactivation	0 (0)
Lymphoma	0 (0)
Teratogenecity	0 (0)
Minor adverse events	
Liver enzyme elevation	6 (5.9)
Nausea/vomiting	4 (3.9)
Headache	2 (2.0)
Hair loss	2 (2.0)
Fatigue/malaise	1 (1.0)
Visual disturbance	1 (1.0)
Verruca development	1 (1.0)
Palpitation, chest pain	0 (0)
Stomatitis	0 (0)

Sixteen patients (15.7%) experienced adverse events during MTX treatment. Total number of adverse event was greater than 16 because one patient complained of headache and nausea at the same time.

transient, reversible liver abnormality. The elevated liver enzymes were normalized after adjusting the doses or briefly stopping MTX medication. Gastrointestinal abnormalities such as nausea and vomiting were partly controlled by antacids. However, no SAEs were noted (Table 4).

DISCUSSION

Low-dose MTX has been widely used to treat inflammatory and immune-mediated diseases including rheumatoid arthritis and psoriasis. Folate supplements are required to alleviate AEs of MTX by bypassing the biochemical requirement for dihydrofolate reductase. The anti-inflammatory mechanism of MTX is mediated via adenosine pathways as well as suppression of T cell activation via inhibition of DNA and RNA synthesis[10]. The suppression of the JAK/STAT pathway is another mechanism underlying the anti-inflammatory and immunomodulatory activities of MTX[11]. In dermatology, MTX has been used to treat psoriasis, AD, lymphoproliferative disorders (mycosis fungoides, lymphomatoid papulosis, and pityriasis lichenoides), connective tissue diseases (lupus erythematosus, dermatomyositis, and systemic sclerosis), autoimmune bullous diseases (pemphigus, bullous pemphigoid, and Hailey-Hailey disease) and others[7]. Interestingly, the abundance of evidence supporting the therapeutic efficacy of MTX suggests that MTX is a promising drug for the control of AD in children and adults[12-14]. However, MTX has not been routinely prescribed by clinicians due to poor experience with the drug as well as the relatively higher possibility of adverse reactions. Based on our study, the expected therapeutic response to IGA 0～2 by MTX treatment was achieved in 60.8% (62/102 MTX-treated patients), in which 2.9% (3/102) was recorded as clear (IGA 0), 31.4% (32/102) was recorded as almost clear (IGA 1) and 26.5% (27/102) was recorded as moderately improved (IGA 3) (Table 3). In previous reports related to the efficacy of MTX in children with severe AD, the mean IGA improved from 4.3 to 2.8 at 3 to 5 months after MTX treatment, and further improved to IGA score of 1.9 at 10 months after continuing MTX treatment. At the same time, the Children's Dermatology Life Quality Index (CDLQI) improved from 14.4 at the start of the treatment to 7.5 after 3 to 5 months of treatment, and then declined to 6.6 after 10 months of treatment[8]. Recently, 83% of severe AD patients showed improved response following MTX treatment with a median duration of 17 months. Furthermore, after discontinuation of MTX for approximately two years, one-third of AD patients were clear and one-third had mild-to-moderate AD, suggesting that MTX has a long-term effect in childhood AD[13]. Knöpfel et al.[15] reported their experience with severe nummular eczema in children in that 96.4% of patients among 28 MTX-treated patients improved with MTX treatment: 35.7% (10/28 patients) exhibited complete or almost complete clearance of eczema (＞90% improvement); 46.4% (13/28 patients) showed marked improvement (50%～89% improvement); and 14.3% (4/28 patients) had mild improvement (＜50% improvement). No SAEs were recorded except for gastrointestinal intolerance (21.4%) and no significant increase in liver enzymes (17.9%) was detected.

One of the important therapeutic goals to treat AD patients is to maintain stable eczema without flares. Until now, there is no consensus on the definition of AD flare. Langan et al.[16] first proposed the provisional definition of AD flare as an episode requiring escalation of treatment via additional medical advice in response to worsening of disease. There was good agreement between the definition of AD flares and changes in global status[17].

Despite the limited number of studies, MTX represents an acceptable candidate drug for long-term management of moderate-to-severe AD. Previously, global response rated as 'marked improvement' was obtained by MTX at a weekly dose of 15 mg in 5 to 6 out of 12 cases with moderated-to-severe AD (41.7%～50.0% success rate), as it improved disease activity by 52% from baseline[12]. Importantly, almost all the MTX-response group (eight of nine patients) showed persistent improvement 12 weeks after discontinuation of MTX, suggesting that the disease activ-

ity remained 34% below baseline[12]. Consistently, our study demonstrated that MTX administration at relatively low doses induced a stable status of AD after discontinuation of MTX. Sixteen patients (25.8%, 16/62) remained stable during at least three months with an IGA score of 0～2 without taking MTX. Their mean period of stability (IGA 0～2) without MTX medication was 20.0±10.4 months. A few patients in the MTX-response group, with uncontrolled AD flares might be attributed to changes in environmental or aggravating factors or poor host emotional or physical conditions. Such patients could be controlled by short-term treatment of CsA or CS combined with MTX therapy. Most of the AD patients showed symptom aggravation or AD flares when the drugs were discontinued or reduced in dosage (rebound phenomenon). Long-term management of moderate-to-severe AD with MTX and azathioprine suppressed the flare-up of AD symptoms. MTX, an antifolate metabolite drug, blocks the synthesis of DNA, RNA, and purines and acts as a negative regulator of T-cell function. Also MTX was reported to exhibit anti-inflammatory activity by decreasing leukotriene B4 (LTB4) and 5-lipoxygenase (5-LO) levels in neutrophils and other blood cells, especially in rheumatoid polyarthritis[18]. In this study, we also focused on the suppressive activity of MTX to prevent AD flares during treatment. Among 62 patients showing a successful MTX treatment response, 45 responded to our questionnaire: 71.1% of MTX-treated patients (32/45) reported a decrease in flare-up frequency more than 50% during three months of treatment, while 28.9% (13/45) reported no difference in symptoms after MTX therapy (Fig. 1). Our results suggest that treatment with low-dose MTX has an anti-inflammatory effect in AD patients, which decreased the frequency of AD flares during or after treatment of MTX.

The first head-to-head study on the efficacy and safety of MTX and CsA in adults with moderate-to-severe AD showed that CsA (2.5 mg/kg/day) was more effective than MTX (15 mg/week) based on the primary end points at week 8 after treatment, indicating that CsA was more effective than MTX during the early stages of treatment. However, all the therapeutic indices of Scoring Atopic Dermatitis Index (SCORAD) 50, EASI 50 and Dermatology Life Quality Index (DLQI)＜5 improved dramatically after 12 weeks of MTX treatment (25 mg/week), showing similar therapeutic results in the MTX-treated (92% to achieve EASI 50) and CsA-treated (87% to achieve EASI 50) groups at week 20 post-treatment. Taken together, the therapeutic efficacy of MTX is almost similar to that of CsA following long-term treatment of moderate-to-severe AD, and resulted in a dose-dependent therapeutic response. The dose-dependent therapeutic response of MTX was also observed in psoriasis[19]. In our study, patients responded to MTX with a median initial response period of 5.8±3.7 weeks, and the minimum and maximum period taken to initial treatment response to MTX was 2 and 18 weeks, respectively. Personal and environmental factors are one of the causes for such big difference in the period of response to MTX. Because each individual has a different immunological background, the timing of showing treatment response to MTX should be different among patients. Therefore, the dose range and the duration of treatment should be adjusted while observing the treatment response of patients taking MTX.

Surprisingly, MTX was reported to be as safe as CsA due to the lower incidence of treatment-related AEs[20]. Also in this study, except for the transient elevation of liver enzymes (5.9%, 6/102) and gastrointestinal discomfort (3.9%, 4/102), our patients did not experience any SAEs in relation to MTX administration. Given that the therapeutic efficacy of MTX is dependent on MTX dosage, our experience with AD patients suggests that the therapeutic efficacy of MTX can be improved by increasing the weekly dose of MTX by 25 mg.

This study had several limitations. First, in the successful response group, most patients (79.0%, 49/62) had combined therapy with MTX and other systemic immunosuppressants such as CsA or CS. However, because patients took CsA or CS only intermittently when their symptoms become severe, drug dosage and the frequency of drug use vary from patient to patient. In addition, although they were taken intermittently and the period was relatively short, there is a limitation that the therapeutic efficacy of CsA or CS cannot be excluded in evaluating the treatment response of MTX. Second, this is a retrospective study, having no control group. Third, patients have very different treatment periods and the same end-point has not been established to evaluate treatment response among patients. In addition, it was difficult to measure the EASI score at each visit, so there was a limitation in that EASI 50 or 75 was not evaluated in all patients, and treatment evaluation means other than the IGA score were not assessed in evaluating the treatment response of patients. Therefore, prospective studies on the use of MTX in patients with AD will be needed to show the efficacy and safety of MTX.

This is the first paper to analyze the therapeutic efficacy and AEs of MTX to treat moderate-to-severe AD for Koreans. In summary, based on its satisfactory therapeutic efficacy, MTX was found to be an effective drug to control eczema symptoms of AD patients and to suppress the frequency of AD flares. Also it was found to be relatively safe drug to maintain long-term management of moderate-to-severe AD

patients.

CONFLICTS OF INTEREST

The authors have nothing to disclose.

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DATA SHARING STATEMENT

The data that support the findings of this study are available from the corresponding author upon reasonable request.

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