Consensus Guidelines for the Treatment of Atopic Dermatitis in Korea (Part II): Systemic Treatment

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Background: Since the treatment guidelines for atopic dermatitis (AD) were issued by the Korean Atopic Dermatitis Association (KADA) work group in 2006, there have been further advances in the systemic treatment of AD. Objective: We aimed to establish updated evidence- and experience-based systemic treatment guidelines for Korean AD. Methods: We compiled a database of references from relevant systematic reviews and guidelines regarding the systemic management of AD, including antihistamines, antimicrobials, systemic immunomodulators, allergen-specific immunotherapy, phototherapy, adjunctive treatment, and complementary and alternative medicines. Evidence for each statement was graded and classified based on the strength of the recommendation. Thirty-nine council members of KADA participated in the three rounds of votes and expert consensus recommendations were established. Results: The use of antihistamines is recommended to relieve pruritus and to prevent exacerbation due to scratching in AD patients. Infection should be controlled as needed and long-term medication should be avoided. For moderate to severe AD patients, concomitant active treatments with systemic immunomodulators are indicated. Cyclosporine is the first choice among systemic immunomodulators and others should be considered as second-line alternatives. Allergen-specific immunotherapy could be effective in AD patients with Aeroallergen hypersensitivity. Phototherapy can be useful for moderate to severe AD patients and narrowband ultraviolet B is the most effective option. Complementary and alternative medicines cannot be recommended for treating AD. Conclusion: We expect these recommendations to be a reference guide for physicians and AD patients in choosing the appropriate treatment to improve quality of life and decrease unnecessary social medical costs. (-Keywords- Administration, oral, Dermatitis, Guideline, Korea, Therapeutics
**INTRODUCTION**

Since the publication of the previous Korean guidelines for atopic dermatitis (AD) in 2006, there has been a growing need for an update based on new clinical evidence. The current consensus guidelines presented here have been developed to incorporate up-to-date evidence- and experience-based recommendations for both physicians-including dermatologists, pediatricians, general practitioners, and allergists caring for patients with AD-and patients.

The Korean Atopic Dermatitis Association (KADA) was aimed to develop updated guidelines for AD treatment based on the Korean health care system and patient adherence. These revised treatment guidelines suggest up-to-date, evidence-based consensus recommendations and a systematic combined treatment algorithm for basic, active, proactive, and adjunctive AD treatment. In addition, the average level of agreement scores by KADA expert panel members are provided for each key statement.

Recommendations for AD treatment are divided into two sections: general management and topical treatment of AD, and systemic treatment of AD. This document is the second part of a two-publication series of guidelines. It discusses the systemic management of AD using antihistamines, antimicrobials, systemic immunomodulators, allergen-specific immunotherapy (ASIT), phototherapy, adjunctive treatment, and complementary and alternative medicines. The clinical questions focus on the therapeutic effect, detailed action plans, side effects, cost-effectiveness, and measures to enhance patient compliance with each treatment.

**MATERIALS AND METHODS**

In developing the Korean guidelines for AD management, the KADA convened a work group of 12 dermatologists representing AD experts nationwide. The panel followed the methodology for developing guidelines detailed in the 2011 guide for the development of clinical practice guidelines from the National Evidence-based Healthcare Collaborating Agency.

**Database and literature research**

A comprehensive database search was performed individually by the members of the working group. They performed computerized database searches of Medline (accessed by PubMed) and Embase for articles published between January 1, 2005, and December 31, 2014, using combinations of “atopic eczema”, “atopic dermatitis”, “antihistamine”, “antimicrobial”, “antifungal”, “antiviral”, “corticosteroids”, “cyclosporine”, “azathioprine”, “methotrexate”, “mycophenolate mofetil”, “biologics”, “interferon-γ”, “altretinoin”, “immunoglobulin”, “thymopentin”, “allergen-specific immunotherapy”, “phototherapy”, “complementary and alternative medicines”, “probiotics”, “prebiotics”, “vitamin D”, “essential fatty acid”, “herb medicine”, and “acupuncture”. The searches were supplemented by manual searches of references from relevant systematic reviews and guidelines of other groups. The members collected all relevant statements relating to AD management.

**Evaluation of the literature**

The members of the working group graded the evidence and then classified the strength of recommendation for each statement. The evidence for each statement was graded as follows: level 1, systematic review of randomized controlled trials (RCTs) or individual RCT; level 2, systematic review of cohort studies and individual cohort study (including low-quality RCT); level 3, systematic review of case-control studies and individual case-control study; level 4, case series (and poor-quality cohort and case-control studies); and level 5, expert opinion. The strength of recommendation was classified as A (level 1), B (level 2 and 3), C (level 4), or D (level 5) (Table 1).

**Consensus process**

Fifty-four council members of the KADA were asked to provide their level of agreement with each draft statement, using a voting scale of 1–9 (where 1 denotes strong disagreement and 9 denotes strong agreement). Thirty-nine Korean experts participated in the vote. Each voting score was allocated to one of three groups: 1–3 (disagreement), 4–6 (neutrality), and 7–9 (agreement). Consensus was defined as ≥75% of participants providing a score within the 7–9 range (agreement). Consensus recommendations were derived after three rounds of voting.

| Strength of recommendation | Level of evidence                  |
|---------------------------|-----------------------------------|
| A                         | 1a Systematic review of RCT       |
|                           | 1b Individual RCTs                |
| B                         | 2a Systematic review of cohort studies |
|                           | 2b Individual cohort study (including low quality RCT) |
| C                         | 4 Case series (and poor-quality cohort and case-control studies) |
| D                         | 5 Expert opinion                  |

RCT: randomized controlled trial.
RESULTS

Antihistamines

AD is characterized by itching as a subjective symptom. Sedating and non-sedating antihistamines have been used for decades to treat AD. There is insufficient evidence to recommend the general use of either type of antihistamine in AD treatment, as other pruritogenic substances and histamines contribute to pruritus-related AD³. However, Korean experts recommend the use of antihistamines in attempts to relieve pruritus and prevent exacerbation due to scratching in patients with mild to severe AD (Table 2)⁴⁻⁹. Short-term, intermittent use of sedating antihistamines, such as hydroxyzine and chlorpheniramine, may be beneficial when there is sleep loss due to itching⁹.

An RCT confirmed that the addition of fexofenadine to a topical corticosteroid (TCS) reduces pruritus associated with AD⁴. The long-term use of cetirizine in infants with severe AD had TCS-sparing effects, which were used as an indirect measure of the efficacy of cetirizine in treating pruritus⁵. Non-sedating antihistamines may be helpful, particularly when the patient has comorbidities such as bronchial asthma, rhinoconjunctivitis, or urticaria³⁻⁶.

General recommendations for antihistamine selection and dosing regimens (dosage, and continuous vs. intermittent administration) have not been established and treatment should consider individual factors.

Common side effects of antihistamines include undesired sedation, even with non-sedating formulations, and anticholinergic symptoms, such as dry mouth, blurred vision, and tachycardia³. In general, the long-term use of antihistamines is safe. No laboratory monitoring is required. If cardiac toxicity is suspected, an electrocardiogram should be obtained to assess dysrhythmia³.

Antimicrobials

Having an impaired skin barrier, patients with AD are likely to develop various secondary infections, including *Staphylococcus*, herpes simplex, molluscum contagiosum, and *Malassezia furfur* fungal infection. Although *S. aureus* can be cultured from the skin of an estimated 5% of the population without AD, this microbe has been isolated from more than 90% of adult AD patients¹⁰. The clinical relevance of bacterial overgrowth is patient-dependent, so the use of systemic or topical antibiotics to treat non-infected AD is not recommended. Short-term treatment with topical or systemic antibiotics may be beneficial in addition to standard, appropriate treatment if the skin is obviously superinfected with bacteria (1a, A)³⁻¹¹. In particular, the continuous use of antibiotics, regardless of whether they are topical or systemic, should be avoided to reduce the risk of bacterial resistance (Table 3)³⁻¹¹. Bacterial culture with antibiotic susceptibility profiling may be appropriate for recurrent or non-re-

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Table 2. Expert consensus recommendations for antihistamines

| Recommendation                                      | Level of evidence | Strength of recommendation | Mean agreement score (range) | % of respondents (agreement score ≥ 7) (n=39) | References |
|-----------------------------------------------------|-------------------|-----------------------------|-----------------------------|-----------------------------------------------|------------|
| The use of antihistamines is recommended to control pruritus in AD, although their role is limited. | 4                 | C                           | 7.8 (3⁻⁹)                   | 87.9%                                         | 5⁻⁹       |
| The addition of antihistamines to topical corticosteroids reduces pruritus associated with AD. | 1b                | A                           | 7.7 (3⁻⁹)                   | 94.9%                                         | 4         |

AD: atopic dermatitis.

Table 3. Expert consensus recommendations for antimicrobial drugs

| Recommendation                                      | Level of evidence | Strength of recommendation | Mean agreement score (range) | % of respondents (agreement score ≥ 7) (n=39) | References |
|-----------------------------------------------------|-------------------|-----------------------------|-----------------------------|-----------------------------------------------|------------|
| An antymycotic therapy against Malassezia infection may be effective in AD patients suffering from "head and neck" dermatitis. | 2b                | B                           | 7.2 (2⁻⁹)                   | 79.5%                                         | 15, 16     |
| Long-term use of systemic and topical antibiotic therapy should be avoided to reduce the risk of bacterial resistance and sensitization. | 2b                | B                           | 7.2 (2⁻⁹)                   | 79.5%                                         | 11         |

AD: atopic dermatitis.
Table 4. Expert consensus recommendations for systemic immunomodulators

| Recommendation                                      | Level of evidence | Strength of recommendation | Mean agreement score (range) | % of respondents (agreement score ≥ 7) (n=39) | References |
|-----------------------------------------------------|-------------------|-----------------------------|-----------------------------|-----------------------------------------------|------------|
| **Systemic corticosteroids**                        |                   |                             |                             |                                               |            |
| Systemic corticosteroids have a largely unfavorable risk/benefit ratio in AD treatment, but may be an option in acute flare treatment. | 5                 | D                           | 8.3 (5-9)                       | 100%                                                | 3, 5       |
| **Cyclosporine**                                    |                   |                             |                             |                                               |            |
| Cyclosporine is the first choice among systemic immunomodulators in moderate to severe AD patients who are unresponsive to conventional treatment methods. | 1a                | A                           | 7.8 (3-9)                       | 87.2%                                                | 3, 19      |
| **Azathioprine**                                    |                   |                             |                             |                                               |            |
| Azathioprine may cause more severe side effects than cyclosporine and is not as effective. It should be considered as a second-line choice among systemic immunomodulators in adult patients unresponsive to or experiencing side effects with cyclosporine. | 1a                | A                           | 7.3 (3-9)                       | 84.6%                                                | 5, 20      |
| **Methotrexate**                                    |                   |                             |                             |                                               |            |
| Methotrexate is considered as a second-line choice among systemic immunomodulators after cyclosporine. | 5                 | D                           | 7.2 (2-9)                       | 87.2%                                                | 3, 5       |
| **Mycophenolate moftel**                            |                   |                             |                             |                                               |            |
| When administered at 1.5 g/day or less, long-term use of mycophenolate moftel can be safe. | 1b                | A                           | 7.3 (3-9)                       | 85.0%                                                | 18         |

AD: atopic dermatitis.
verse effects and the rebound phenomenon. Rebound flare is frequently observed after the abrupt cessation of systemic corticosteroids. Increased production of IgE by B cells in AD patients has been reported after treatment with oral prednisolone\textsuperscript{21,22}. Once clinical improvement has been achieved, it is very important to taper the dosage gradually over time to minimize the likelihood of a rebound effect.

Clinical trials have shown that corticosteroid concentrations in the skin following the administration of a potent TCS (clobetasol propionate 0.05%, hydrocortisone 2.3%, or triamcinolone 0.1%) are similar to those achieved with medium doses of oral prednisone\textsuperscript{23}. If the skin is severely damaged, however, the distribution of topical treatments is extremely irregular and oral administration is safer and more controllable. In all other situations, TCSs are the preferred option.

Continuous or chronic intermittent use of systemic corticosteroids in AD is discouraged. However, acute usage may be considered as a transitional therapy in severe, rapidly progressive, or debilitating cases during the initiation of treatment with nonsteroidal systemic immunomodulatory agents that have more favorable side-effect profiles, or phototherapy\textsuperscript{3}. Some clinicians argue that systemic corticosteroids can be used safely for up to six weeks in combination with TCSs or topical calcineurin inhibitors\textsuperscript{23}.

Dosage is based on body weight, ranging from 0.5 to 1.0 mg/kg per day during acute flares\textsuperscript{24}. Significant adverse effects of the chronic use of systemic corticosteroids include hypertension, diabetes, glucose intolerance, gastritis, weight gain, osteoporosis, skin atrophy, glaucoma, Cushing’s syndrome, and emotional lability\textsuperscript{3}. Children and adolescents receiving systemic steroids continuously may exhibit decreased linear growth while taking the medication\textsuperscript{25}.

**Cyclosporine**

Cyclosporine is the primary choice for systemic immunomodulators in moderate to severe AD patients who are unresponsive to topical therapy and oral antihistamines. The effects of treatment appear two weeks after initiation, with 50%–60% improvement expected in 6–8 weeks\textsuperscript{26,27}. However, symptoms may manifest themselves again within 8–12 weeks of termination of medication\textsuperscript{27,28}.

Cyclosporine can be used in children older than two years of age. Long-term safety in children has not yet been established and caution should be exercised, though many studies have shown that it can be relatively safe in young children\textsuperscript{27,29}.

The dosage is commonly started with 2.5 mg/kg/day and increased by 0.5–1.0 mg/kg/day at 2- to 4-week intervals, up to 5 mg/kg/day. Compared to this low dose, faster induction can be achieved by starting treatment with a high dose relative to body weight (5 mg/kg/day) and reducing the dose by 0.5–1.0 mg/kg/day every two weeks based on the clinical response\textsuperscript{18}. There is a report that microemulsion formulations have faster effects than usual formulations\textsuperscript{30}. The effects of treatment appear two weeks after initiation, a relatively fast induction rate compared to other systemic immunomodulators.

The maximum duration for medication has not yet been established, but cyclosporine can be used safely for about 1–2 years\textsuperscript{31}. Common and important side effects include nephrotoxicity, hypertension, tremors, headaches, paresthesia, hypertrichosis, gingival hyperplasia, gastrointestinal (GI) symptoms (nausea, vomiting, diarrhea), flu-like symptoms (myalgia, fatigue), hypertriglyceridemia, electrolyte imbalance (hypomagnesemia, hyperkalemia), jaundice, and susceptibility to infection\textsuperscript{32}. Routine follow-up examinations are required before and after administration. Blood pressure should be measured at every visit. Laboratory testing should be performed upon initiation of medication and every 2–4 weeks for several months as the drug dosage is being increased. During the long-term maintenance period, laboratory testing should be performed at least once every three months (Table 5)\textsuperscript{3}. The drug dosage should be lowered when blood creatinine rises by more

### Table 5. Dosing regimen and monitoring guidelines for cyclosporine use

| Dosing regimen | Baseline monitoring | Follow-up monitoring |
|----------------|---------------------|---------------------|
| Initially 5 mg/kg/day and dose reduction by 0.5–1.0 mg/kg/day every 2 weeks based on clinical response or Initially 2.5 mg/kg/day and dose increase by 0.5–1.0 mg/kg/day every 2 weeks based on clinical response* | Blood pressure CBC, fasting lipid profile, renal and liver function, magnesium, potassium, uric acid Urinalysis with microscopic analysis Tuberculosis testing HIV (if indicated) Pregnancy (if indicated) | Blood pressure (every visit) CBC, fasting lipid profile, renal and liver function, magnesium, potassium, uric acid (every 2 weeks for 2 months, then every 2–3 months) Tuberculosis testing (annual) HIV (if indicated) Pregnancy (if indicated) |

CBC: complete blood count (differential/platelets), HIV: human immunodeficiency virus. Modified from Sidbury et al. (J Am Acad Dermatol 2014;71:327-349)\textsuperscript{3}. *If the dose is increased, laboratory results should be checked after 2–4 weeks.
than 25% and the patient should be closely monitored to decide whether to stop or continue the medication. Long-term use of cyclosporine raises the possibility of skin cancer and lymphoma.

**Azathioprine**

Considering the risk and benefits of AZP, it can be used in patients with moderate to severe AD who do not respond to primary treatment modalities. However, as AZP may cause more severe side effects than cyclosporine and is not as effective, it should be considered as a secondary choice for systemic immunomodulator therapy in adult patients who are unresponsive to or experience side effects with cyclosporine.

The dosage range of AZP is 1.5 to 3 mg/kg/day, usually starting with 1.5 mg/kg/day and increasing by 0.5 mg/kg/day at every visit if the disease does not improve by 25%, up to 2.5 mg/kg/day (Table 6).

Myelosuppression is the common and important side effect. Recently, side effects such as skin cancer, T-cell lymphoma of the liver and spleen, and progressive multifocal leukoencephalopathy have raised issues regarding AZP use. Caution should be exercised in long-term use.

Because of hematological side effects, the dosage should be established after determining the level of thiopurine methyltransferase (TPMT) in the blood. However, since the test is only available in a few facilities in Korea and is relatively expensive, it is difficult to apply this test to all patients. To reduce the risk of myelosuppression, the drug dosage should be increased when TPMT levels are high and reduced when TPMT levels are low.

One study reported the use of AZP in children aged two years and older, but the results of one study are not sufficient to recommend AZP use in children.

**Methotrexate**

MTX is considered as a second-line systemic immunomodulator therapy in adult patients who are unresponsive to or experiencing side effects with cyclosporine. MTX has a favorable risk-benefit ratio, considering the clinical experience in psoriasis patients, and could be used in the long-term maintenance treatment of AD. Patient compliance is relatively satisfactory, thanks to the once-weekly administration regimen. However, further investigations are needed to determine the dose and effects of MTX.

Dosage usually does not depend on body weight. MTX is usually administered in a dosage of 7.5 to 25 mg per week, starting with 10 mg per week via oral administration and increasing by 2.5 to 5 mg after every visit, if improvement is less than 25%, up to 25 mg/week (Table 7).

### Table 6. Dosing regimen and monitoring guidelines for azathioprine use

| Dosing regimen | Baseline monitoring | Follow-up monitoring |
|----------------|---------------------|---------------------|
| Initially 1.5 mg/kg/day and increasing by 0.5 mg/kg/day at every visit if the disease does not improve by 25%, up to 2.5 mg/kg/day* | CBC, liver function, and renal function | CBC, liver function, and renal function |
| | Hepatitis B and C | every 2 weeks for 2 months, then every 2~3 months, tuberculosis testing (annual) |
| | Thiopurine methyltransferase | | |
| | Tuberculosis testing | | |
| | HIV (if indicated) | | |
| | Pregnancy (if indicated) | | |

CBC: complete blood count (differential/platelets), HIV: human immunodeficiency virus. Modified from Sidbury et al. (J Am Acad Dermatol 2014;71:327-349). *If the dose is increased, laboratory results should be checked.

### Table 7. Dosing regimen and monitoring guidelines for methotrexate use

| Dosing regimen | Baseline monitoring | Follow-up monitoring |
|----------------|---------------------|---------------------|
| Initial dose: 10 mg/week via oral administration | CBC | CBC, liver function (every 2 weeks for 2 months, then every 2~3 months) |
| Increasing by 2.5~5 mg after every visit, if improvement is less than 25%, up to 25 mg/week* | Liver function | Renal function (every 6~12 month) |
| | Renal function | Tuberculosis testing (annual) |
| | Hepatitis B and C | Pregnancy (if indicated) Liver biopsy (considering: if cumulative dose ≥3.5 g in adults, not for children) |
| | Tuberculosis testing | |
| | HIV (if indicated) | Pulmonary function tests (if indicated) |
| | Pregnancy (if indicated) | Chest X-ray (if respiratory symptoms arise) |

CBC: complete blood count (differential/platelets), HIV: human immunodeficiency virus. Modified from Sidbury et al. (J Am Acad Dermatol 2014;71:327-349). *If the dose is increased, laboratory results should be checked 1 week after each major dose increase.
same amount can be divided into three doses at 12-hour intervals. In addition to oral administration, MTX can also be given by intramuscular or subcutaneous injection. Injection can lead to high bioavailability, but compliance is low due to the invasiveness of the technique.

Patients can expect a 40% – 50% improvement after 12 weeks of MTX use, with one report showing an effect similar to AZP and cyclosporine24,32. The maximum effect is usually achieved after about 10 weeks.

Common side effects of MTX include GI symptoms, which can be reduced by switching from oral medication to injection19. The most significant side effects include liver cirrhosis (liver toxicity), myelosuppression, and pulmonary fibrosis. The need for routine liver biopsies is controversial, as the incidence of liver cirrhosis is very low and it is not easy to perform liver biopsies for the cumulative doses of MTX used in the treatment of dermatologic disorders. A test for procollagen type III amino-terminal peptide can be used as a substitute for liver biopsy, but is not applied in Korea. Myelosuppression is reversible once drug administration has been stopped or reduced. Studies have reported pulmonary fibrosis in patients on low-dose regimens and MTX is not recommended in patients with asthma or chronic coughing. Folic acid (1 mg daily) can be added to reduce the incidence of myelosuppression and GI symptoms.

Guidelines for use in children with AD have not yet been established, because of the lack of studies. However, studies and clinical experience in children with psoriasis suggest that MTX can also be expected to be safe for use in children with AD17.

**Mycophenolate mofetil**

MMF can be used as a second-line systemic immunomodulator therapy in adult patients with severe AD who are unresponsive to or experiencing side effects with cyclosporine, especially in long-term maintenance therapy18. Clinical improvement using MMF begins after 4 – 8 weeks, which is slower than cyclosporine, and some patients may experience symptom aggravation in the early phases of treatment20. MMF is known to have a therapeutic effect similar to cyclosporine. However, the effects of MMF are more durable than those of cyclosporine and one study showed effective maintenance four months after discontinuation of the drug36.

MMF therapy can be started at 0.5 g/day and increased up to 3 g/day, depending on the clinical response. The recommended dosage is 1 – 2 g/day (Table 8)3,36. MMF is generally tolerated, although common side effects include GI symptoms, headache, flu-like symptoms, and fatigue. Serious side effects, such as leukocytopenia, anemia, thrombocytopenia, or alteration of liver function, are rare compared with other immunomodulators. When administered in doses of 1.5 g/day or less, MMF can be used safely for a long period18. It is known to be relatively safe in children17.

**Allergen-specific immunotherapy**

Candidates for ASIT are AD patients whose symptoms are not manageable with proper medication and avoidance measures, those experiencing unacceptable side effects with medication, or those wishing to avoid long-term medication use. A recent meta-analysis provides a moderate level of evidence for the efficacy of ASIT in AD management, although these results are based on a small number of RCTs38. ASIT can be recommended for AD patients with hypersensitivity to house dust mites, pollen, animal allergens, mold or fungi, and hymenoptera39. Appropriate examination of medical history, immediate hypersensitivity skin tests, or tests for serum-specific IgE should be performed before applying ASIT. Currently, house dust mite allergen shows the best therapeutic response to AD treatment using ASIT5. ASIT can be administered by subcutaneous injections (subcutaneous immunotherapy, SCIT) or sublingual drops or tablets (sublingual immunotherapy, SLIT)40. SCIT is effective in the treatment of AD with aeroallergen sensitivity41-43. Recently, Novak et al.44 reported the efficacy and safety of SCIT using depigmented poly-
merized mite extract. In their study, SCIT significantly reduced the total SCORAD in a subgroup of patients with severe AD. One limitation of SCIT is the risk of potential side effects, which include systemic allergic reactions, occasional anaphylaxis, and even fatalities. As serious side effects of SCIT typically occur within 30 minutes of subcutaneous injection, it is necessary to closely monitor the patient for 30 minutes after injection. In one RCT, SLIT with a standardized mite extract was shown to be effective in treating children with mild-to-moderate AD. However, the benefit was inconsistent in the severe form of AD. There have been no well-organized comparison studies comparing SLIT and SCIT. SLIT is self-administered by patients or their caregivers at home, although the initial dose is usually given under medical supervision. The main advantages of SLIT over SCIT are safety and the convenience of self-administration. Recommendations for ASIT are summarized in Table 9.

### Phototherapy

Phototherapy is a common treatment modality in AD patients. Various types of photo (chemo) therapy, light sources, and laser devices can be applied in AD treatment. These include narrowband ultraviolet B (NB-UVB), ultraviolet A1 (UVA1), and light-emitting diodes. Phototherapy with medium-dose UVA1 can be used to control acute flares of AD. NB-UVB can be applied to manage the chronic stage of AD. A recent study indicated the beneficial effect of NB-UVB on immune and barrier abnormalities in AD patients. Twelve patients with moderate-to-severe chronic AD received NB-UVB phototherapy three times weekly for up to 12 weeks. All patients achieved a reduction of at least 50% in SCORAD index scores with NB-UVB phototherapy. Moreover, the Th2 and Th1 immune pathways were suppressed and measures of epidermal hyperplasia and differentiation normalized. There is still no standard protocol for the optimal dose, duration, and frequency of NB-UVB treatment. The optimal treatment dose of UVA1 has also not yet been determined. Several studies reported that high and medium doses of UVA1 were superior to a low-dose regimen. Tzaneva et al. also reported that medium-dose UVA1 was as effective as high-dose treatment. The comparative efficacy of the two UV treatments was studied in 28 AD patients who received a six-week course of medium-dose UVA1 or NB-UVB. In addition, the efficacy and tolerability of both modalities may be considered similarly favorable. When the side effects of NB-UVB and UVA1 are compared, the total amount of irradiation necessary for effective phototherapy is lower for NB-UVB than for medium-dose UVA1. The exposure time is therefore shorter and less heat is produced during NB-UVB treatment compared with medium-dose UVA1. NB-UVB therapy is more comfortable, particularly for AD patients, in which heat can be a trigger for itchiness. As the long-term effects of phototherapy have not been described, treatment should be reserved for adults and children older than 12 years of age with severe, recalcitrant AD. Considering the low accessibility of UVA1 devices compared to other modalities of phototherapy, NB-UVB offer the most efficacious and cost-effective evidence-based treatment for patients with chronic AD. Recommendations for phototherapy are summarized in Table 10.

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**Table 9. Expert consensus recommendations for ASIT**

| Recommendation                                                                 | Level of evidence | Strength of recommendation | Mean agreement score (range) | % of respondents (agreement score ≥ 7) (n = 39) | References |
|--------------------------------------------------------------------------------|-------------------|-----------------------------|-----------------------------|-------------------------------------------------|------------|
| AD patients with aeroallergen sensitivity might benefit from ASIT.              | 1a                | A                           | 7 (1 ∼ 9)                   | 78.1%                                           | 38, 39     |
| Proper examination of medical history, skin tests, and serum IgE tests are needed before ASIT. | 2a                | B                           | 7.7 (1 ∼ 9)                 | 89.7%                                           | 39         |
| If indicated, ASIT can be used in patients 5 years of age or older.          | 2a                | B                           | 7.4 (2 ∼ 9)                 | 81.6%                                           | 39         |
| SCIT is more effective than SLIT in AD patients with aeroallergen hypersensitivity. | 1a                | A                           | 7.1 (2 ∼ 9)                 | 76.0%                                           | 38         |
| House dust mite aeroallergen responds best to ASIT.                          | 2a                | B                           | 7.5 (5 ∼ 9)                 | 88.0%                                           | 5, 39      |
| SCIT is generally a safe treatment option for AD patients, but patients receiving SCIT should be monitored at a physician’s office for 30 minutes because of the possibility of anaphylaxis. | 5                 | D                           | 7.6 (5 ∼ 9)                 | 88.0%                                           | 5, 39      |

ASIT: allergen-specific immunotherapy, AD: atopic dermatitis, SCIT: subcutaneous immunotherapy, SLIT: sublingual immunotherapy.
Interferon-γ

IFN-γ can be used in patients with severe AD as a second-line systemic immunomodulator treatment after cyclosporine. However, it is not commonly used in Korea, since the therapeutic effects of IFN-γ in AD patients have not yet been elucidated and some reports showed only a moderate therapeutic effect. There is no consensus regarding the dosage or administration method. Some reports used a dosage of 50 μg/m² body surface area via subcutaneous injection, either daily or three times a week, depending on the side effects (Table 11). In terms of side effects, 30% ~ 60% of patients experience intermittent headaches, myalgia, and chills, but these can be controlled with acetaminophen and are relatively safe. The use of IFN-γ in children is not recommended because of the lack of clinical data.

Alitretinoin

Alitretinoin, also known as 9-cis-retinoic acid, is a recently developed retinoid derivative. It can be administered orally in patients with severe AD-related chronic hand eczema (1a, A). It is not recommended as a routine treatment because of the lack of evidence from treating areas other than the hands of AD patients.

### Table 10. Expert consensus recommendations for phototherapy

| Recommendation                                                                 | Level of evidence | Strength of recommendation | Mean agreement score (range) | % of respondents (agreement score ≥ 7) (N = 39) | References |
|--------------------------------------------------------------------------------|-------------------|-----------------------------|-------------------------------|-------------------------------------------------|------------|
| UV therapy can be one of useful treatment modalities for moderate to severe AD. | 2a                | B                           | 7.2 (4 ~ 9)                   | 87.2%                                            | 46, 47     |
| UVA1 (acute phase) and NB-UVB (chronic phase) are the most suitable phototherapy modalities for AD treatment. | 2a                | B                           | 7.3 (5 ~ 9)                   | 89.5%                                            | 46, 47     |
| NB-UVB is the most effective phototherapy option available.                     | 2a                | B                           | 7.7 (5 ~ 9)                   | 94.9%                                            | 46, 47     |
| NB-UVB is more comfortable in particular for patients with AD, where heat can be an itch trigger. | 1b                | A                           | 7.2 (3 ~ 8)                   | 83.8%                                            | 53         |

AD: atopic dermatitis, UVA: ultraviolet A, NB-UVB: narrowband ultraviolet B.

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### Table 11. Dosing regimen and monitoring guidelines for interferon-gamma use

| Dosing regimen                                                                 | Baseline monitoring       | Follow-up monitoring                        |
|--------------------------------------------------------------------------------|----------------------------|---------------------------------------------|
| 50 μg/m² body surface area via subcutaneous injection, either daily or three times a week | CBC, Liver function, Renal function, Urinalysis | CBC, liver function, renal function, urinalysis (every 3 month) |
|                                                                                | Renal function             | Pregnancy (if indicated)                    |
|                                                                                | Urinalysis                 |                                             |
|                                                                                | Pregnancy (if indicated)   |                                             |

CBC: complete blood count (differential/platelets). Modified from Sidbury et al. (J Am Acad Dermatol 2014;71:327-349).
logics, including omalizumab, rituximab, alefacept, and mepolizumab, in AD were intriguing. However, it is clearly premature to recommend off-label use of these biologics for recalcitrant AD, unless other therapies have failed or are contraindicated (Table 12). Ongoing studies aim to identify appropriate therapeutic targets.

**Adjunctive treatment**

1) Probiotics/prebiotics

In a meta-analysis of the current literature in relation to the effects of probiotics for AD treatment, Kim et al. reviewed and analyzed 25 RCTs. The overall results of the meta-analysis suggested that probiotics could be applied in AD treatment, especially for moderate to severe AD in children and adults (1a, A). The effect of symbiotic use was not significantly different from that of probiotic use. Treatment with a mixture of different bacterial species or Lactobacillus species was more beneficial than treatment with *Bifidobacterium* species alone. However, there is no evidence to support the benefit of probiotics in infants. In another meta-analysis of 16 RCTs that focused on the primary preventative effects of probiotics in AD, Panduru et al. found that probiotics (Lactobacillus alone or Lactobacillus with *Bifidobacterium*) appeared to play a protective role in AD prevention upon administration in the pre- and postnatal periods, in both the general population and those at risk for allergies. Probiotics/prebiotics could be an option for adjuvant therapy of AD; however, most of the Korean experts in this study adopted a neutral position regarding the use of probiotics/prebiotics for either AD prevention or treatment.

2) Essential fatty acids

Diet supplementation with evening primrose oil or an omega-3 fatty acid (docosahexaenoic acid) is very safe and rarely has side effects in AD patients. This may be helpful in improving dryness and pruritus in certain AD patients. However, there is still insufficient RCT data assessing clinical efficacy for this method to be recommended. Close observation of future RCT results may be needed. Consistently, our Korean experts did not recommend essential fatty acids for AD treatment.

3) Vitamin D

Vitamin D intake is a low-risk adjunctive therapy for AD patients. Several RCTs have reported contradictory results for the therapeutic efficacy of vitamin D in AD. Korean experts remained neutral regarding the recommendation of vitamin D for AD treatment.

**Complementary and alternative therapy**

The use of complementary and alternative therapy in AD is common in Korea. There are insufficient RCT data concerning complementary and alternative therapies, such as traditional Korean medicine and acupuncture. The results

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### Table 12. Expert consensus recommendations for biologics

| Recommendation | Level of evidence | Strength of recommendation | Mean agreement score (range) | % of respondents (agreement score ≥ 7) (n=39) | References |
|----------------|-------------------|-----------------------------|------------------------------|---------------------------------------------|------------|
| In patients with recalcitrant atopic dermatitis, biologics can be used in off-label therapy. However, the cost-effectiveness should be seriously considered. | 5 | D | 7.5 (0–9) | 79.5% | 5, 58 |

### Table 13. Expert consensus recommendations for complementary and alternative medicines

| Recommendation | Level of evidence | Strength of recommendation | Mean agreement score (range) | % of respondents (agreement score ≥ 7) (n=39) | References |
|----------------|-------------------|-----------------------------|------------------------------|---------------------------------------------|------------|
| Patients should be warned of possible contamination of traditional Korean herbal medicine with steroid medication. | 4 | C | 7.1 (1–8) | 79.5% | 72 |
| Patients should be advised that complementary therapies have various possible complications, in particular liver toxicity. | 4 | C | 7.9 (1–9) | 94.9% | 73 |
| Acupuncture cannot be recommended for treating atopic dermatitis. | 5 | D | 7.8 (1–9) | 87.2% | 71 |
generally suggest a limited role and a potential for serious side effects, such as liver toxicity, for complementary therapy in AD treatment. The consensus recommendations of experts also showed the same results (Table 13)\textsuperscript{71-73}.

**DISCUSSION**

This report presents a systematic review of AD management and provides the level of evidence, strength of recommendation, and average agreement scores of the AD
These guidelines will be a reference guide for physicians and AD patients in choosing the appropriate treatment to improve quality of life and decrease unnecessary social medical costs.

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