Ann Dermatol Vol. 27, No. 5, 2015 http://dx.doi.org/10.5021/ad.2015.27.5.578

CONSENSUS GUIDELINE

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

Jung Eun Kim, Hyun Jeong Kim[1], Bark-Lynn Lew[2], Kyung Ho Lee, Seung Phil Hong[3], Yong Hyun Jang[4], Kui Young Park[5], Seong Jun Seo[5], Jung Min Bae, Eung Ho Choi[6], Ki Beom Suhr[7], Seung Chul Lee[8], Hyun Chang Ko[9], Young Lip Park[10], Sang Wook Son[11], Young Jun Seo[12], Yang Won Lee[13], Sang Hyun Cho, Chun Wook Park[14], Joo Young Roh[15]

Department of Dermatology, College of Medicine, The Catholic University of Korea, [1]Department of Dermatology, Seoul Medical Center, [2]Department of Dermatology, Kyung Hee University College of Medicine, Seoul, [3]Department of Dermatology, Dankook University Medical College, Cheonan, [4]Department of Dermatology, Kyungpook National University School of Medicine, Daegu, [5]Department of Dermatology, Chung-Ang University College of Medicine, Seoul, [6]Department of Dermatology, Yonsei University Wonju College of Medicine, Wonju, [7]Department of Dermatology, SA Dermatology Clinic, Daejeon, [8]Department of Dermatology, Chonnam National University Medical School, Gwangju, [9]Department of Dermatology, Pusan National University School of Medicine, Busan, [10]Department of Dermatology, Soonchunhyang University Bucheon Hospital, Bucheon, [11]Department of Dermatology, Korea University College of Medicine, Seoul, [12]Department of Dermatology, Chungnam National University College of Medicine, Daejeon, [13]Department of Dermatology, Konkuk University School of Medicine, [14]Department of Dermatology, Kangnam Sacred Heart Hospital, Hallym University College of Medicine, Seoul, [15]Department of Dermatology, Gachon University Gil Medical Center, Incheon, Korea

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. **(Ann Dermatol 27(5) 578～592, 2015)**

-Keywords-
Administration, oral, Dermatitis, Guideline, Korea, Therapeutics

Received May 27, 2015, Revised August 12, 2015, Accepted for publication August 16, 2015

Corresponding author: Joo Young Roh, Department of Dermatology, Gachon University Gil Medical Center, 21 Namdong-daero 774beon-gil, Namdong-gu, Incheon 21565, Korea. Tel: 82-32-460-2763, Fax: 82-32-460-2374, E-mail: jyroh1@gilhospital.com

Conflict of interest: Joo Young Roh is an investigator in the clinical trials of Astellas and Novartis. Hyun Chang Ko is an investigator in the clinical trials of Astellas.

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[1].

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", "alitretinoin", "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)[2].

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.

Table 1. Level of evidence and strength of recommendation[2]

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)
	3a	Systematic review of case-control studies
	3b	Individual case-control study
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 AD[3]. 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 itching[3].
An RCT confirmed that the addition of fexofenadine to a topical corticosteroid (TCS) reduces pruritus associated with AD[4]. 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 pruritus[5]. Non-sedating antihistamines may be helpful, particularly when the patient has comorbidities such as bronchial asthma, rhinoconjunctivitis, or urticaria[5,6].
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 tachycardia[3]. 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 dysrhythmia[3].

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 patients[3,10]. 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)[3,10,11]. 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-

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 antimycotic 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 riskof bacterial resistance and sensitization.	2b	B	7.2 (2~9)	79.5%	11

AD: atopic dermatitis.

sponsive skin infections[3].

In patients with moderate to severe AD and clinical signs of secondary bacterial infection, bleach baths and intranasal mupirocin may be recommended to reduce disease severity[12].

Eczema herpeticum occurs more frequently in AD patients than in normal individuals and has a tendency to disseminate. Patients with severe AD, untreated skin lesions, early disease onset, and high total serum immunoglobulin E (IgE) levels are at high risk of developing eczema herpeticum. Pretreatment with TCSs does not imply higher risk[13]. Eczema herpeticum should be treated without delay using systemic antiviral therapy.

Secondary infections with yeasts have also been implicated as trigger factors in AD[14].

Therefore, systemic and topical antifungal agents have been proposed for treatment of "head and neck" dermatitis in AD (Table 3)[15,16].

Systemic immunomodulators

Systemic immunomodulators can be used in AD patients who show an inadequate response to conventional topical agents or phototherapy—which may have a negative impact on sleep, emotional stress, or social activities—or in patients with a SCORing AD (SCORAD) index of 40 or more[17]. Systemic immunomodulators, such as corticosteroids, cyclosporine, methotrexate (MTX), mycophenolate mofetil (MMF), and azathioprine (AZP), are used in clinical settings. In contrast, there are only limited reports on leukotriene inhibitors, oral calcineurin inhibitors, and interferon γ (IFN-γ). Further investigations are necessary before these options can be used in routine treatment. Aside from corticosteroids, all systemic immunomodulators may increase the risk of photocarcinogenesis when used together with phototherapy; this combination is therefore not recommended. Live attenuated vaccination is usually contraindicated when systemic immunomodulators are used. The dosage and material in the vaccine should be carefully examined when vaccine use is considered. Recommendations for systemic immunomodulators are summarized in Table 4[3,5,18-20].

Systemic corticosteroids

Corticosteroids are natural products of the adrenal gland that are used to regulate the immune system and stress response in humans. Although systemic corticosteroids dramatically improve the clinical symptoms of AD, their administration should generally be avoided because of ad-

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 mofetil					
When administered at 1.5 g/day or less, long-term use of mycophenolate mofetil 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[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[21]. 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[3]. Some clinicians argue that systemic corticosteroids can be used safely for up to six weeks in combination with TCSs or topical calcineurin inhibitors[23].

Dosage is based on body weight, ranging from 0.5 to 1.0 mg/kg per day during acute flares[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[3]. Children and adolescents receiving systemic steroids continuously may exhibit decreased linear growth while taking the medication[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[26]. However, symptoms may manifest themselves again within 8～12 weeks of termination of medication[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[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[18]. There is a report that microemulsion formulations have faster effects than usual formulations[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[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[19]. 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)[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)[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[3]. Long-term use of cyclosporine raises the possibility of skin cancer and lymphoma[19].

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[5,20].

The dosage range of AZP is 1～3 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)[3,32].

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[19,33].

Because of hematological side effects, the dosage should be established after determining the level of thiopurine methyltransferase (TPMT) in the blood[34]. 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[35].

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 7.5～25 mg per week, starting with 10 mg per week via oral administration and increasing by 2.5～5 mg after every visit, if improvement is less than 25%, up to 25 mg/week (Table 7)[3,32]. The

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 Hepatitis B and C Thiopurine methyltransferase Tuberculosis testing HIV (if indicated) Pregnancy (if indicated)	CBC, liver function, and renal function (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)[3]. *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 Increasing by 2.5～5 mg after every visit, if improvement is less than 25%, up to 25 mg/week*	CBC Liver function Renal function Hepatitis B and C Tuberculosis testing HIV (if indicated) Pregnancy (if indicated) Pulmonary function tests (if indicated)	CBC, liver function (every 2 weeks for 2 months, then every 2～3 month) Renal function (every 6～12 month) Tuberculosis testing (annual) Pregnancy (if indicated) Liver biopsy (considering: if cumulative dose ≥3.5 g in adults, not for children) Pulmonary function tests (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)[3]. *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 cyclosporine[24,32]. 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 injection[19]. 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 AD[17].

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 therapy[18].

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 treatment[20]. 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 drug[36].

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 period[18]. It is known to be relatively safe in children[37].

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 RCTs[38]. ASIT can be recommended for AD patients with hypersensitivity to house dust mites, pollen, animal allergens, mold or fungi, and hymenoptera[39]. 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 ASIT[5]. 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 sensitivity[41-43]. Recently, Novak et al.[44] reported the efficacy and safety of SCIT using depigmented poly-

Table 8. Dosing regimen and monitoring guidelines for mycophenolate mofetil use

Dosing regimen	Baseline monitoring	Follow-up monitoring
Initial dose: 0.5 g/day Increasing by 1～2 g/day, depending on the clinical response up to 3 g/day	CBC Liver function Renal function Tuberculosis testing HIV (if indicated) Pregnancy (if indicated)	CBC, liver function (every 2 weeks for 2 months, then every 2～3 months) Tuberculosis testing (annual) 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)[3].

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[45]. 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[5,38,39].

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[46]. 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[47]. A recent study indicated a 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[48]. There is still no standard protocol for the optimal dose, duration, and frequency of NB-UVB treatment[49]. 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[50]. Tzaneva et al.[51] 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[52]. 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[53]. 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[23]. 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[46,47,53].

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[54]. 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/m^2 body surface area via subcutaneous injection, either daily or three times a week, depending on the side effects (Table 11)[3,54,55]. 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)[56]. It is not recommended as a routine treatment because of the lack of evidence from treating areas other than the hands of AD patients.

Thymopentin and intravenous immunoglobulin

Thymopentin (Timunox; Janssen, DE) is a synthetic peptide of amino acids 32～36 (Arg-Lys-Asp-Val-Tyr) of the 52-amino acid thymic hormone thymopoietin. Because of the immunoregulatory effects of thymopentin, subcutaneous thymopentin has been tried in patients with AD[57]. A randomized sampling study of 39 patients, including children and adults with moderate AD, reported that the group treated with thymopentin for 12 weeks showed better average improvement than the placebo group, without specific adverse events[57]. However, thymopentin is not yet recommended for treating severe AD because of the lack of evidence and follow-up studies[19]. Some reports have shown intravenous immunoglobulin to be effective in patients with severe AD. Nevertheless, these therapies are not currently recommended for AD treatment, as no significant effects have been demonstrated in an RCT comparing them with cyclosporine and placebo.

Biologics

Compared to psoriasis, AD appears to be an orphan disease in the development of targeted therapies and biologics. In AD, there are too many potential targets for directed therapeutic attack, impeding the development of novel biologics[58]. The results of several small trials of bio-

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.

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

Dosing regimen	Baseline monitoring	Follow-up monitoring
50 μg/m^2 body surface area via subcutaneous injection, either daily or three times a week	CBC Liver function Renal function Urinalysis Pregnancy (if indicated)	CBC, liver function, renal function, urinalysis (every 3 month) Pregnancy (if indicated)

CBC: complete blood count (differential/platelets). Modified from Sidbury et al. (J Am Acad Dermatol 2014;71:327-349)[3].

logics, including omalizumab, rituximab, alefacept, and mepolizumab, in AD were intriguing[59-62]. 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)[5,58]. 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.[63] 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[63]. In another meta-analysis of 16 RCTs that focused on the primary preventative effects of probiotics in AD, Panduru et al.[64] 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[65,66]. However, there is still insufficient RCT data assessing clinical efficacy for this method to be recommended[67]. 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[68-70]. 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

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 fortreating 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)[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

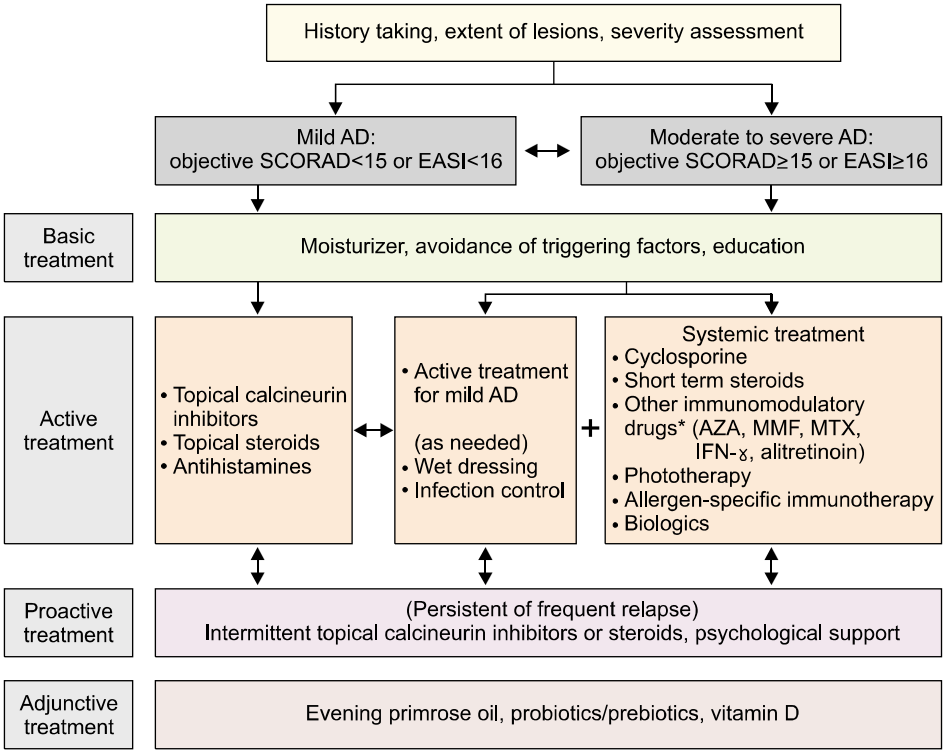

Fig. 1. Treatment algorithm for atopic dermatitis (AD). SCORAD: SCORing atopic dermatitis, EASI: eczema area and severity index, AZA: azathioprine, MMF: mycophenolate mofetil, MTX: methotrexate, IFN-γ: interferon-γ.

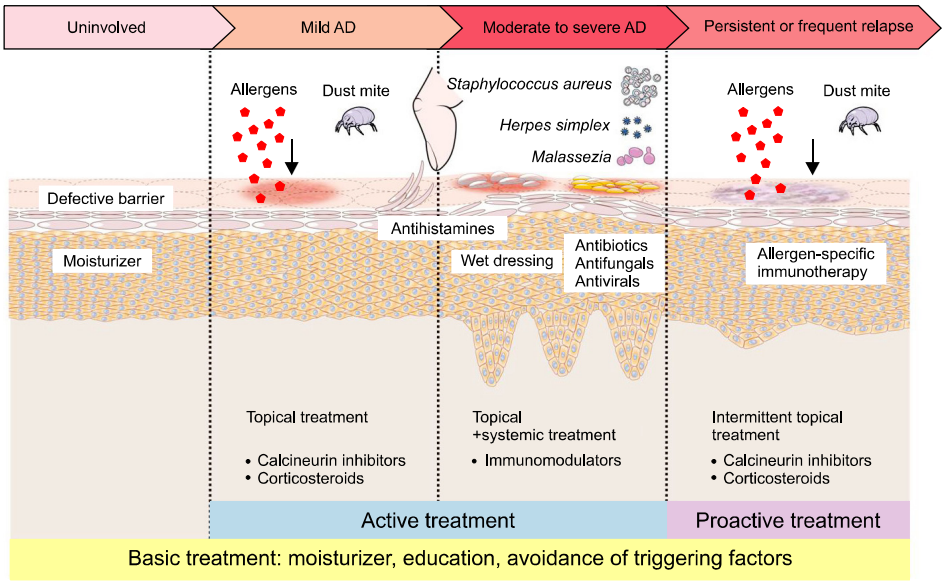

Fig. 2. Strategy for tailored treatment of atopic dermatitis (AD).

expert panel.

To achieve high treatment efficacy and patient satisfaction, treatment decisions should be made jointly by the physician and patient. They should consider the disease severity, socioeconomic factors, psychological status, and the patient's desire for treatment.

The new concepts of the AD management guidelines include basic treatment, active treatment, and proactive treatment, according to the severity and the current status of the lesions. The objective SCORAD index is commonly used for describing AD severity, as follows: mild AD, SCORAD $<$ 15; moderate AD, 15 $\leq$ SCORAD $<$ 40; and severe AD, SCORAD $\geq$ 40[74]. The eczema area and severity index (EASI) score is a relatively simple assessment tool for assessing AD severity, and is graded as follows: mild, EASI score $<$ 16; moderate, EASI score $\geq$ 16; and severe, EASI score $>$ 27[75,76]. Current AD management guidelines suggest a treatment algorithm for mild AD versus moderate to severe AD (Fig. 1, 2).

All AD patients require basic treatment, including moisturizer use, avoidance of triggering factors, and education about the prevention of frequent flares due to the chronic and recurrent disease course[76,77]. During flare-ups, active topical anti-inflammatory treatment should be applied primarily. For moderate to severe AD patients, concomitant active treatments with topical and systemic anti-inflammatory modalities are indicated, but this can also be the treatment for patients who suffer psychosocial stress, regardless of their AD severity. Even after the AD lesions disappear, patients with frequently relapsing disease courses require proactive treatment with topical anti-inflammatory treatment and psychosocial support. Antimicrobial therapy may be needed to control infection. Wet dressings can facilitate a faster recovery of AD lesions in the absence of infection. ASIT may be helpful in selected cases. Adjunctive treatment can be used at any stage of the disease course, because it is very safe and rarely has side effects; however, its therapeutic efficacy is not sufficiently high for it to be recommended (Fig. 1, 2).

Because of their cultural background, many Koreans rely on traditional Korean herbal medicines and home remedies, which amount to more than 100 million dollars of the direct and indirect medical costs of AD in Korea[78,79]. However, there are insufficient data to support the efficacy of traditional Korean herbal medicines and home remedies in the treatment of AD, while there is a risk of side effects, even serious ones such as liver toxicity. The report may require supplementary statements or a revision of recommendations based on upcoming publications and results of the many ongoing clinical studies.

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.

ACKNOWLEDGMENT

This work was supported by the Korean Atopic Dermatitis Association. We appreciate the active participation and advice of 54 council members of the Korean Atopic Dermatitis Association in developing this expert opinion consensus.

REFERENCES

1. Kim SY, Jee SM, Lee SJ, Lee YJ, Park JE, Nam MH, et al. Guidance for development of clinical practice guidelines. 1st ed. Seoul: National Evidence-Based Healthcare Collaborating Agency, 2011:607-608.
2. Phillips B, Ball C, Sackett D, Badenoch D, Straus S, Haynes B, et al. Oxford Centre for Evidence-based Medicine-Levels of evidence [Internet]. Oxford: Centre for Evidence Based Medicine; 2001 May [updated 2009 March; cited 2014 March 4]. Available froom: http://www.cebm.net/oxford-centre-evidence-based-medicine-levels-evidence-march-2009/.
3. Sidbury R, Davis DM, Cohen DE, Cordoro KM, Berger TG, Bergman JN, et al; American Academy of Dermatology. Guidelines of care for the management of atopic dermatitis: section 3. Management and treatment with phototherapy and systemic agents. J Am Acad Dermatol 2014;71:327-349.
4. Kawashima M, Tango T, Noguchi T, Inagi M, Nakagawa H, Harada S. Addition of fexofenadine to a topical corticosteroid reduces the pruritus associated with atopic dermatitis in a 1-week randomized, multicentre, double-blind, placebo-controlled, parallel-group study. Br J Dermatol 2003;148:1212-1221.
5. Ring J, Alomar A, Bieber T, Deleuran M, Fink-Wagner A, Gelmetti C, et al. Guidelines for treatment of atopic eczema (atopic dermatitis) part I. J Eur Acad Dermatol Venereol 2012;26:1045-1060.
6. Diepgen TL; Early Treatment of the Atopic Child Study Group. Long-term treatment with cetirizine of infants with atopic dermatitis: a multi-country, double-blind, randomized, placebo-controlled trial (the ETAC trial) over 18 months. Pediatr Allergy Immunol 2002;13:278-286.
7. Langeland T, Fagertun HE, Larsen S. Therapeutic effect of loratadine on pruritus in patients with atopic dermatitis. A multi-crossover-designed study. Allergy 1994;49:22-26.
8. La Rosa M, Ranno C, Musarra I, Guglielmo F, Corrias A, Bellanti JA. Double-blind study of cetirizine in atopic eczema in children. Ann Allergy 1994;73:117-122.
9. Wahlgren CF, Hägermark O, Bergström R. The antipruritic effect of a sedative and a non-sedative antihistamine in atopic dermatitis. Br J Dermatol 1990;122:545-551.
10. Boguniewicz M, Sampson H, Leung SB, Harbeck R, Leung DY. Effects of cefuroxime axetil on Staphylococcus aureus

colonization and superantigen production in atopic dermatitis. J Allergy Clin Immunol 2001;108:651-652.
11. Bath-Hextall FJ, Birnie AJ, Ravenscroft JC, Williams HC. Interventions to reduce Staphylococcus aureus in the management of atopic eczema: an updated Cochrane review. Br J Dermatol 2010;163:12-26.
12. Eichenfield LF, Tom WL, Berger TG, Krol A, Paller AS, Schwarzenberger K, et al. Guidelines of care for the management of atopic dermatitis: section 2. Management and treatment of atopic dermatitis with topical therapies. J Am Acad Dermatol 2014;71:116-132.
13. Wollenberg A, Zoch C, Wetzel S, Plewig G, Przybilla B. Predisposing factors and clinical features of eczema herpeticum: a retrospective analysis of 100 cases. J Am Acad Dermatol 2003;49:198-205.
14. Lübbe J. Secondary infections in patients with atopic dermatitis. Am J Clin Dermatol 2003;4:641-654.
15. Lintu P, Savolainen J, Kortekangas-Savolainen O, Kalimo K. Systemic ketoconazole is an effective treatment of atopic dermatitis with IgE-mediated hypersensitivity to yeasts. Allergy 2001;56:512-517.
16. Mayser P, Kupfer J, Nemetz D, Schäfer U, Nilles M, Hort W, et al. Treatment of head and neck dermatitis with ciclopiroxolamine cream--results of a double-blind, placebo-controlled study. Skin Pharmacol Physiol 2006;19:153-158.
17. Flohr C, Irvine AD. Systemic therapies for severe atopic dermatitis in children and adults. J Allergy Clin Immunol 2013;132:774-774.e6.
18. Haeck IM, Knol MJ, Ten Berge O, van Velsen SG, de Bruin-Weller MS, Bruijnzeel-Koomen CA. Enteric-coated mycophenolate sodium versus cyclosporin A as long-term treatment in adult patients with severe atopic dermatitis: a randomized controlled trial. J Am Acad Dermatol 2011; 64:1074-1084.
19. Roekevisch E, Spuls PI, Kuester D, Limpens J, Schmitt J. Efficacy and safety of systemic treatments for moderate-to-severe atopic dermatitis: a systematic review. J Allergy Clin Immunol 2014;133:429-438.
20. Berth-Jones J, Graham-Brown RA, Marks R, Camp RD, English JS, Freeman K, et al. Long-term efficacy and safety of cyclosporin in severe adult atopic dermatitis. Br J Dermatol 1997;136:76-81.
21. Forte WC, Sumita JM, Rodrigues AG, Liuson D, Tanaka E. Rebound phenomenon to systemic corticosteroid in atopic dermatitis. Allergol Immunopathol (Madr) 2005;33:307-311.
22. Garnacho-Saucedo G, Salido-Vallejo R, Moreno-Giménez JC. Atopic dermatitis: update and proposed management algorithm. Actas Dermosifiliogr 2013;104:4-16.
23. Rubel D, Thirumoorthy T, Soebaryo RW, Weng SC, Gabriel TM, Villafuerte LL, et al; Asia-Pacific Consensus Group for Atopic Dermatitis. Consensus guidelines for the management of atopic dermatitis: an Asia-Pacific perspective. J Dermatol 2013;40:160-171.
24. Schmitt J, Schäkel K, Fölster-Holst R, Bauer A, Oertel R, Augustin M, et al. Prednisolone vs. ciclosporin for severe adult eczema. An investigator-initiated double-blind placebo-controlled multicentre trial. Br J Dermatol 2010;162: 661-668.
25. Daley-Yates PT, Richards DH. Relationship between systemic corticosteroid exposure and growth velocity: development and validation of a pharmacokinetic/pharmacodynamic model. Clin Ther 2004;26:1905-1919.
26. Czech W, Bräutigam M, Weidinger G, Schöpf E. A body-weight-independent dosing regimen of cyclosporine microemulsion is effective in severe atopic dermatitis and improves the quality of life. J Am Acad Dermatol 2000; 42:653-659.
27. El-Khalawany MA, Hassan H, Shaaban D, Ghonaim N, Eassa B. Methotrexate versus cyclosporine in the treatment of severe atopic dermatitis in children: a multicenter experience from Egypt. Eur J Pediatr 2013;172:351-356.
28. Hoare C, Li Wan Po A, Williams H. Systematic review of treatments for atopic eczema. Health Technol Assess 2000;4:1-191.
29. Berth-Jones J, Finlay AY, Zaki I, Tan B, Goodyear H, Lewis-Jones S, et al. Cyclosporine in severe childhood atopic dermatitis: a multicenter study. J Am Acad Dermatol 1996;34:1016-1021.
30. Zurbriggen B, Wüthrich B, Cachelin AB, Wili PB, Kägi MK. Comparison of two formulations of cyclosporin A in the treatment of severe atopic dermatitis. Aa double-blind, single-centre, cross-over pilot study. Dermatology 1999; 198:56-60.
31. Berth-Jones J, Takwale A, Tan E, Barclay G, Agarwal S, Ahmed I, et al. Azathioprine in severe adult atopic dermatitis: a double-blind, placebo-controlled, crossover trial. Br J Dermatol 2002;147:324-330.
32. Schram ME, Roekevisch E, Leeflang MM, Bos JD, Schmitt J, Spuls PI. A randomized trial of methotrexate versus azathioprine for severe atopic eczema. J Allergy Clin Immunol 2011;128:353-359.
33. Schmedt N, Andersohn F, Garbe E. Signals of progressive multifocal leukoencephalopathy for immunosuppressants: a disproportionality analysis of spontaneous reports within the US Adverse Event Reporting System (AERS). Pharmacoepidemiol Drug Saf 2012;21:1216-1220.
34. Meggitt SJ, Gray JC, Reynolds NJ. Azathioprine dosed by thiopurine methyltransferase activity for moderate-to-severe atopic eczema: a double-blind, randomised controlled trial. Lancet 2006;367:839-846.
35. Caufield M, Tom WL. Oral azathioprine for recalcitrant pediatric atopic dermatitis: clinical response and thiopurine monitoring. J Am Acad Dermatol 2013;68:29-35.
36. Ballester I, Silvestre JF, Pérez-Crespo M, Lucas A. Severe adult atopic dermatitis: treatment with mycophenolate mofetil in 8 patients. Actas Dermosifiliogr 2009;100:883-887.
37. Heller M, Shin HT, Orlow SJ, Schaffer JV. Mycophenolate mofetil for severe childhood atopic dermatitis: experience in 14 patients. Br J Dermatol 2007;157:127-132.
38. Bae JM, Choi YY, Park CO, Chung KY, Lee KH. Efficacy of allergen-specific immunotherapy for atopic dermatitis: a systematic review and meta-analysis of randomized controlled trials. J Allergy Clin Immunol 2013;132:110-117.

39. Cox L, Nelson H, Lockey R, Calabria C, Chacko T, Finegold I, et al. Allergen immunotherapy: a practice parameter third update. J Allergy Clin Immunol 2011;127(1 Suppl):S1-S55.
40. Burks AW, Calderon MA, Casale T, Cox L, Demoly P, Jutel M, et al. Update on allergy immunotherapy: American Academy of Allergy, Asthma & Immunology/European Academy of Allergy and Clinical Immunology/PRACTALL consensus report. J Allergy Clin Immunol 2013;131:1288-1296.e3.
41. Bussmann C, Böckenhoff A, Henke H, Werfel T, Novak N. Does allergen-specific immunotherapy represent a therapeutic option for patients with atopic dermatitis? J Allergy Clin Immunol 2006;118:1292-1298.
42. Bussmann C, Maintz L, Hart J, Allam JP, Vrtala S, Chen KW, et al. Clinical improvement and immunological changes in atopic dermatitis patients undergoing subcutaneous immunotherapy with a house dust mite allergoid: a pilot study. Clin Exp Allergy 2007;37:1277-1285.
43. Werfel T, Breuer K, Ruéff F, Przybilla B, Worm M, Grewe M, et al. Usefulness of specific immunotherapy in patients with atopic dermatitis and allergic sensitization to house dust mites: a multi-centre, randomized, dose-response study. Allergy 2006;61:202-205.
44. Novak N, Bieber T, Hoffmann M, Fölster-Holst R, Homey B, Werfel T, et al. Efficacy and safety of subcutaneous allergen-specific immunotherapy with depigmented polymerized mite extract in atopic dermatitis. J Allergy Clin Immunol 2012;130:925-931.e4.
45. Pajno GB, Caminiti L, Vita D, Barberio G, Salzano G, Lombardo F, et al. Sublingual immunotherapy in mite-sensitized children with atopic dermatitis: a randomized, double-blind, placebo-controlled study. J Allergy Clin Immunol 2007;120:164-170.
46. Garritsen FM, Brouwer MW, Limpens J, Spuls PI. Photo(chemo)therapy in the management of atopic dermatitis: an updated systematic review with implications for practice and research. Br J Dermatol 2014;170:501-513.
47. Meduri NB, Vandergriff T, Rasmussen H, Jacobe H. Phototherapy in the management of atopic dermatitis: a systematic review. Photodermatol Photoimmunol Photomed 2007;23:106-112.
48. Tintle S, Shemer A, Suárez-Fariñas M, Fujita H, Gilleaudeau P, Sullivan-Whalen M, et al. Reversal of atopic dermatitis with narrow-band UVB phototherapy and biomarkers for therapeutic response. J Allergy Clin Immunol 2011;128:583-593.e1-4.
49. Grundmann SA, Beissert S. Modern aspects of phototherapy for atopic dermatitis. J Allergy (Cairo) 2012;2012:121797.
50. Suh KS, Kang JS, Baek JW, Kim TK, Lee JW, Jeon YS, et al. Efficacy of ultraviolet A1 phototherapy in recalcitrant skin diseases. Ann Dermatol 2010;22:1-8.
51. Tzaneva S, Seeber A, Schwaiger M, Hönigsmann H, Tanew A. High-dose versus medium-dose UVA1 phototherapy for patients with severe generalized atopic dermatitis. J Am Acad Dermatol 2001;45:503-507.
52. Gambichler T, Othlinghaus N, Tomi NS, Holland-Letz T, Boms S, Skrygan M, et al. Medium-dose ultraviolet (UV) A1 vs. narrowband UVB phototherapy in atopic eczema: a randomized crossover study. Br J Dermatol 2009;160:652-658.
53. Majoie IM, Oldhoff JM, van Weelden H, Laaper-Ertmann M, Bousema MT, Sigurdsson V, et al. Narrowband ultraviolet B and medium-dose ultraviolet A1 are equally effective in the treatment of moderate to severe atopic dermatitis. J Am Acad Dermatol 2009;60:77-84.
54. Panahi Y, Davoudi SM, Madanchi N, Abolhasani E. Recombinant human interferon gamma (Gamma Immunex) in treatment of atopic dermatitis. Clin Exp Med 2012;12:241-245.
55. Hanifin JM, Schneider LC, Leung DY, Ellis CN, Jaffe HS, Izu AE, et al. Recombinant interferon gamma therapy for atopic dermatitis. J Am Acad Dermatol 1993;28:189-197.
56. D'Erme AM, Milanesi N, Agnoletti AF, Maio V, Massi D, Gola M. Efficacy of treatment with oral alitretinoin in patient suffering from lichen simplex chronicus and severe atopic dermatitis of hands. Dermatol Ther 2014;27:21-23.
57. Stiller MJ, Shupack JL, Kenny C, Jondreau L, Cohen DE, Soter NA. A double-blind, placebo-controlled clinical trial to evaluate the safety and efficacy of thymopentin as an adjunctive treatment in atopic dermatitis. J Am Acad Dermatol 1994;30:597-602.
58. Taïeb A, Seneschal J, Mossalayi MD. Biologics in atopic dermatitis. J Dtsch Dermatol Ges 2012;10:174-178.
59. Kim DH, Park KY, Kim BJ, Kim MN, Mun SK. Anti-immunoglobulin E in the treatment of refractory atopic dermatitis. Clin Exp Dermatol 2013;38:496-500.
60. Simon D, Hösli S, Kostylina G, Yawalkar N, Simon HU. Anti-CD20 (rituximab) treatment improves atopic eczema. J Allergy Clin Immunol 2008;121:122-128.
61. Moul DK, Routhouska SB, Robinson MR, Korman NJ. Alefacept for moderate to severe atopic dermatitis: a pilot study in adults. J Am Acad Dermatol 2008;58:984-989.
62. Oldhoff JM, Darsow U, Werfel T, Katzer K, Wulf A, Laifaoui J, et al. Anti-IL-5 recombinant humanized monoclonal antibody (mepolizumab) for the treatment of atopic dermatitis. Allergy 2005;60:693-696.
63. Kim SO, Ah YM, Yu YM, Choi KH, Shin WG, Lee JY. Effects of probiotics for the treatment of atopic dermatitis: a meta-analysis of randomized controlled trials. Ann Allergy Asthma Immunol 2014;113:217-226.
64. Panduru M, Panduru NM, Sălăvăstru CM, Tiplica GS. Probiotics and primary prevention of atopic dermatitis: a meta-analysis of randomized controlled studies. J Eur Acad Dermatol Venereol 2015;29:232-242.
65. Mohajeri S, Newman SA. Review of evidence for dietary influences on atopic dermatitis. Skin Therapy Lett 2014;19:5-7.
66. Bamford JT, Ray S, Musekiwa A, van Gool C, Humphreys R, Ernst E. Oral evening primrose oil and borage oil for eczema. Cochrane Database Syst Rev 2013;4:CD004416.
67. Morse NL, Clough PM. A meta-analysis of randomized, placebo-controlled clinical trials of Efamol evening primrose oil in atopic eczema. Where do we go from here in light of more recent discoveries? Curr Pharm Biotechnol

2006;7:503-524.
68. Camargo CA Jr, Ganmaa D, Sidbury R, Erdenedelger Kh, Radnaakhand N, Khandsuren B. Randomized trial of vitamin D supplementation for winter-related atopic dermatitis in children. J Allergy Clin Immunol 2014;134:831-835.e1.
69. Hata TR, Audish D, Kotol P, Coda A, Kabigting F, Miller J, et al. A randomized controlled double-blind investigation of the effects of vitamin D dietary supplementation in subjects with atopic dermatitis. J Eur Acad Dermatol Venereol 2014; 28:781-789.
70. Bath-Hextall FJ, Jenkinson C, Humphreys R, Williams HC. Dietary supplements for established atopic eczema. Cochrane Database Syst Rev 2012;2:CD005205.
71. Higgins E, Bennett M, Murphy A, Markham T. Disseminated parapox (orf) in a 13-year-old boy with atopic dermatitis following acupuncture. Clin Exp Dermatol 2011;36:809-811.
72. Tan HY, Zhang AL, Chen D, Xue CC, Lenon GB. Chinese herbal medicine for atopic dermatitis: a systematic review. J Am Acad Dermatol 2013;69:295-304.
73. Perharic L, Shaw D, Leon C, De Smet PA, Murray VS. Possible association of liver damage with the use of Chinese herbal medicine for skin disease. Vet Hum Toxicol 1995; 37:562-566.
74. Oranje AP, Glazenburg EJ, Wolkerstorfer A, de Waard-van der Spek FB. Practical issues on interpretation of scoring atopic dermatitis: the SCORAD index, objective SCORAD and the three-item severity score. Br J Dermatol 2007; 157:645-648.
75. Hanifin JM, Thurston M, Omoto M, Cherill R, Tofte SJ, Graeber M. The eczema area and severity index (EASI): assessment of reliability in atopic dermatitis. EASI Evaluator Group. Exp Dermatol 2001;10:11-18.
76. Choi WJ, Ko JY, Kim JW, Lee KH, Park CW, Kim KH, et al. Prevalence and risk factors for atopic dermatitis: a cross-sectional study of 6,453 Korean preschool children. Acta Derm Venereol 2012;92:467-471.
77. Shin JY, Kim DW, Park CW, Seo SJ, Park YL, Lee JR, et al. An educational program that contributes to improved patient and parental understanding of atopic dermatitis. Ann Dermatol 2014;26:66-72.
78. Seo SJ. Research of understanding and social loss of atopic dermatitis in Korea. Seoul: Korean Center for Disease Control and Prevention (Korea); 2011 Feb. Report No.: 2010 E 3302600.
79. Kim JE, Lee YB, Lee JH, Kim HS, Lee KH, Park YM, et al. Disease awareness and management behavior of patients with atopic dermatitis: a questionnaire survey of 313 patients. Ann Dermatol 2015;27:40-47.