therapy plus olopatadine than in the group treated with topical therapy alone. Kojima *et al.* reported that the oral administration of olopatadine significantly reduced the skin concentration of SP as well as eruption scores in the murine contact hypersensitivity model induced by hapten painting.[26] Izu and Tokura examined the effects of antihistamines on the serum SP levels of patients with AD, concluding that only olopatadine, but not cetirizine, fexofenadine or epinastine, was capable of reducing the serum SP levels.[17] They also found that there was not a significant reduction of SP levels in the group treated with topical therapy alone.[17]

The present study demonstrated the efficacy of standard therapy in the treatment of AD, although the number of AD cases examined in the study was relatively small. The 4-week topical therapy with oral olopatadine was feasible to efficiently control the severe AD patients with high SCORAD scores. Amounts of topical steroids used by Japanese AD patients were small,[27,28] which may be in part attributable to the widespread fear of steroids or steroid phobia.[29] However, the fact that addition of oral olopatadine to the standard topical therapy efficiently decreased the plasma SP levels may be favorable evidence for the patients with such steroid phobia because decreased SP would slow down itch–scratch and stress–scratch cycles that precipitate the formation and aggravation of clinical symptoms in most patients with AD.[10,30]

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Report

Severity of disease, rather than xerosis, correlates with pruritus in patients with atopic dermatitis

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Abstract

Background Atopic dermatitis (AD) is a chronic, relapsing skin disease characterized by xerosis and pruritus. As pruritus is an unpleasant sensation and the associated scratching aggravates the skin eruption considerably, it is important to control this symptom when treating AD. Dry skin is generally considered to be a potential cause of pruritus in xerotic skin diseases, but a clear correlation between pruritus and atopic xerosis has not been demonstrated.
Aim To examine the contribution of atopic xerosis to the development of pruritus in AD.
Methods Twenty-two patients with AD (12 males and 10 females; mean age, 27.5 years) were examined. Xerosis and the severity of disease were evaluated using the Objective Severity Assessment of Atopic Dermatitis (OSAAD) and the SCORing Atopic Dermatitis (SCORAD) index, respectively. A modified SCORAD index was calculated by removing the symptoms potentially associated with pruritus (intensity of itching and insomnia) from the standard SCORAD index. Pruritus was evaluated using both a visual analog scale and the Verbal Itch Score.
Results The severity of AD (modified SCORAD index) correlated better than atopic xerosis (OSAAD score) with both pruritus scores, possibly indicating that the use of appropriate anti-inflammatory agents may be helpful in controlling pruritus as well as skin eruption in AD.
Conclusion Our data suggest that the severity of disease (or skin inflammation) provides a greater contribution than xerosis to the development of pruritus in AD.

Introduction

Atopic dermatitis (AD) is a chronic, relapsing skin disease characterized by xerosis (dry skin) and pruritus (itching), and affecting at least 7–10% of children[1,2] and 3–7% of adults[3,4] in the Japanese population. In patients with AD with severe pruritus, intensive scratching often causes skin erosion, exudates, and even minor bleeding, which can aggravate the skin eruption considerably. In addition, pruritus is an unpleasant sensation, and involuntary nocturnal scratching frequently causes insufficient sleep in patients with AD; both of these factors can have a detrimental effect on a patient's quality of life.

The mechanism behind the highly problematic pruritus in AD is not fully understood. Xerosis has been considered to be a potential cause of pruritus in AD, as itching is a common symptom in dry skin diseases, such as xerosis in the elderly.[5,6] Various factors contribute to the development of xerosis, including impaired stratum corneum hydration, epidermal hyperproliferation, inadequate lipid synthesis, and barrier damage.[7] Barrier function has been shown to be defective in both lesional and nonlesional skin in patients with AD.[8,9]

The Objective Severity Assessment of Atopic Dermatitis (OSAAD) score[10] is a new measure for the objective evaluation of atopic xerosis using parameters of cutaneous moisture permeability and stratum corneum hydration on representative areas of lesional and nonlesional skin. In this study, the OSAAD score and other measures of AD and pruritus were used to evaluate the correlation between xerosis, disease severity, and the intensity of pruritus in AD.

Materials and Methods

Patients

Twenty-two patients with AD (12 males and 10 females; age range, 9–57 years; mean age, 27.5 years), who met the AD criteria of Hanifin and Rajka,[11] were recruited at the Department of Dermatology, Kyushu University Hospital, Fukuoka, Japan. These patients were acclimatized to room temperature for at least 15 min before examination.

Assessment of atopic xerosis

Atopic xerosis was assessed using OSAAD, with all scoring performed by a single investigator in order to prevent interobserver variability. Transepidermal water loss (TEWL; which reflects the permeability barrier) and corneometry (CM; which reflects skin hydration) were assessed using a Tewameter® TM 210 and

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Corneometer® CM 825, respectively (Courage and Khazaka Electronic, Cologne, Germany). In each subject, three representative skin areas with varying degrees of disease severity (severely affected, mildly affected, and unaffected) were assessed, as the anatomical sites used for OSAAD assessment can vary depending on the patient's disease distribution and severity. The body surface area (BSA) of total affected skin was estimated using a computer-assisted method based on OSAAD software (Courage and Khazaka Electronic). The OSAAD score was then calculated automatically according to the formula, OSAAD score = $A + B + C + D + E + F$, where:

$A = \Delta TEWL_{uninvolved} \times \%BSA_{uninvolved}$

$B = \Delta TEWL_{mild} \times \%BSA_{mild}$

$C = \Delta TEWL_{severe} \times \%BSA_{severe}$

$D = \Delta CM_{uninvolved} \times \%BSA_{uninvolved}$

$E = \Delta CM_{mild} \times \%BSA_{mild}$

$F = \Delta CM_{severe} \times \%BSA_{severe}$

Assessment of severity of AD

The severity of disease was evaluated using the widely accepted SCORing Atopic Dermatitis (SCORAD) index,[12] with all the scoring performed by a single investigator. Symptoms potentially associated with pruritus [i.e. the intensity of itching and insomnia, both based on a visual analog scale (VAS)] were removed from the standard SCORAD index, and the modified SCORAD index was used for subsequent analysis of correlation with pruritus scores. The BSA value used for SCORAD index calculation was the same as that used for OSAAD score calculation.

Assessment of pruritus

Pruritus was evaluated using two independent scales measuring the intensity of itching. In the first evaluation, the patients themselves indicated a point on a 10-cm VAS according to the intensity of itching during the examination (VAS-assessed pruritus), with possible scores ranging from zero (no pruritus) to 10 (maximum pruritus) points. Secondly, employing the Verbal Itch Score introduced by Kawashima *et al.*,[13] the intensity of pruritus was determined using a five-point scale (0, none; 4, very severe), measuring the levels of itching-related behavior during the day and night, with the final score being the total of the diurnal and nocturnal pruritus scores (range, 0–8 points).

Statistical analysis

Excel 2002 (Microsoft Inc., Tokyo, Japan) was used for statistical analysis. Spearman rank correlation was used to explore the correlation between xerosis (OSAAD score), the severity of disease (modified SCORAD index), and both pruritus scores. A P value of less than 0.05 was considered to indicate statistical significance.

Results

Atopic xerosis correlated with VAS-assessed pruritus, but not with Verbal Itch Score

Atopic xerosis, as measured by the OSAAD score, correlated moderately with the VAS-assessed pruritus score ($P = 0.009$, $r = 0.541$; Fig. 1a), but not with the Verbal Itch Score ($P = 0.257$, $r = 0.252$; Fig. 1b).

Positive correlation between disease severity and both pruritus scores

Disease severity, as measured by the modified SCORAD index, correlated significantly with both the VAS-assessed pruritus score ($P < 0.001$, $r = 0.692$; Fig. 2a) and the Verbal Itch Score ($P = 0.006$, $r = 0.570$; Fig. 2b). Both the pruritus scores correlated better with the modified SCORAD index than with the OSAAD score (Fig. 1a,b), as evidenced by the higher correlation coefficients (r values) associated with the modified SCORAD index (Fig. 2a,b). The standard SCORAD index also correlated significantly with both the VAS-assessed pruritus score ($P < 0.001$, $r = 0.753$; Fig. 2c) and Verbal Itch Score ($P = 0.002$, $r = 0.617$; Fig. 2d).

Positive correlation between VAS-assessed pruritus and Verbal Itch Score

There was a significant positive correlation between the VAS-assessed pruritus score and the Verbal Itch Score ($P < 0.001$, $r = 0.759$; Fig. 3). The mean intensity of itching (± standard deviation) was 4.2 ± 2.1 for the VAS-assessed pruritus score and 3.5 for the Verbal Itch Score in the study patients with AD.

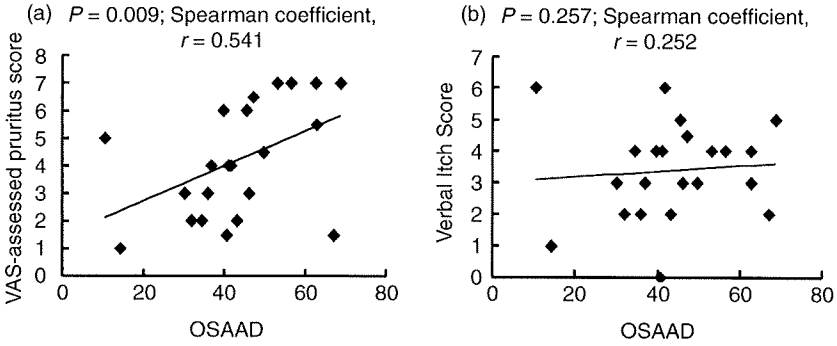

Figure 1 Moderate to no positive correlation between atopic xerosis and pruritus scores. The Objective Severity Assessment of Atopic Dermatitis (OSAAD) score correlated moderately with visual analog scale (VAS)-assessed pruritus (a) ($P = 0.009$, $r = 0.541$), but not with the Verbal Itch Score (b) ($P = 0.257$, $r = 0.252$)

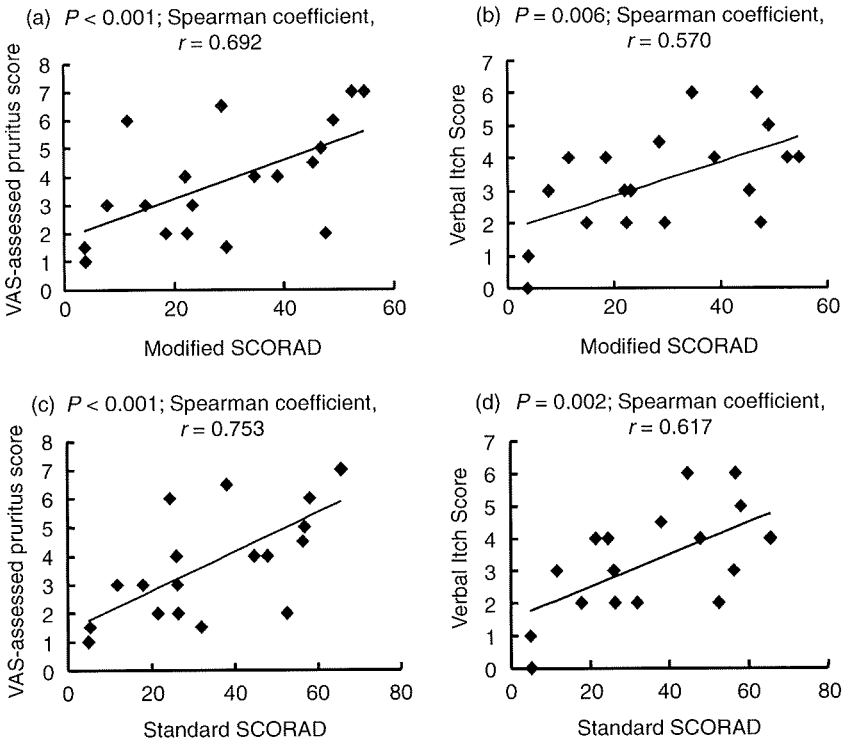

Figure 2 Positive correlation between the severity of atopic dermatitis and pruritus scores. The modified SCORing Atopic Dermatitis (SCORAD) index correlated significantly with both visual analog scale (VAS)-assessed pruritus (a) ($P < 0.001$, $r = 0.692$) and the Verbal Itch Score (b) ($P = 0.006$, $r = 0.570$). The standard SCORAD index also correlated significantly with both VAS-assessed pruritus (c) ($P < 0.001$, $r = 0.753$) and the Verbal Itch Score (d) ($P = 0.002$, $r = 0.617$)

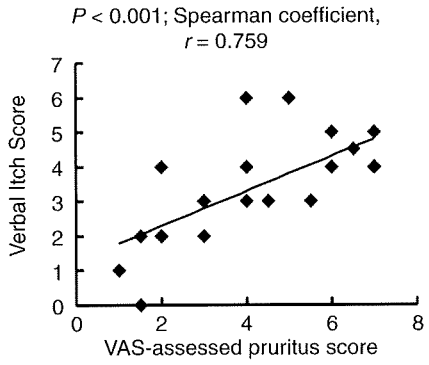

Figure 3 Positive correlation between the two pruritus scores. Visual analog scale (VAS)-assessed pruritus correlated with the Verbal Itch Score ($P < 0.001$, $r = 0.759$)

Positive correlation between disease severity and atopic xerosis

The modified SCORAD index correlated significantly with the OSAAD score ($P = 0.002$, $r = 0.619$; Fig. 4a), as did the standard SCORAD index ($P = 0.002$, $r = 0.619$; Fig. 4b). The OSAAD score ranged from 10.6 to 70.0 (mean OSAAD score, 44.3) in the patients with AD. The data on TEWL and cutaneous capacitance in severely affected, mildly affected, and unaffected areas of skin were compared for the validation of the study's OSAAD results. Lesions that were more severely affected tended to have higher local TEWL and lower cutaneous capacitance than did unaffected areas, in agreement with the results presented in the original report on the OSAAD score (data not shown).[10] In the current study, the standard SCORAD index ranged from 4.8 to 64.7 (mean score, 38.7), suggesting that the majority of study patients suffered from moderate to severe AD. There were no gender differences in the OSAAD, SCORAD, and pruritus scores, and only the OSAAD score (but not the SCORAD index or the intensity of pruritus) correlated significantly with age ($P = 0.003$, $r = 0.601$).

Discussion

The control of pruritus is important in the treatment of AD, because itching is an unpleasant sensation and the associated scratching behavior aggravates the skin eruption. The current study examined the contribution of atopic xerosis to the development of pruritus in patients with AD whose symptoms were primarily moderate to severe. The intensity of itching was measured using VAS-assessed pruritus and the Verbal Itch Score. Although these pruritus scores were determined in totally different ways, they nevertheless showed a significant positive correlation with each other (Fig. 3), indicating an overall similarity between these methods of assessment of pruritus in practice.

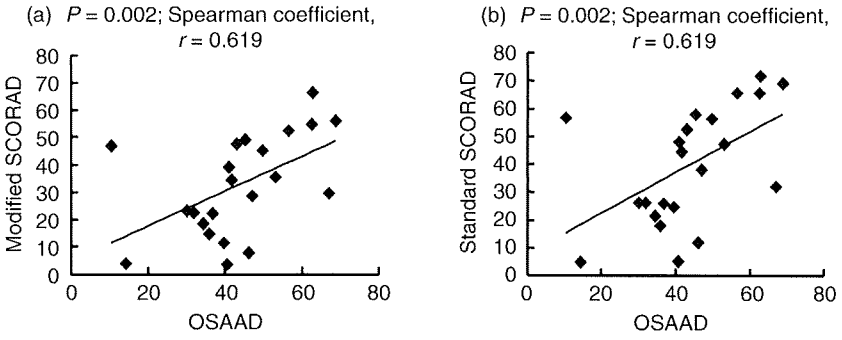

Figure 4 Positive correlation between severity of atopic dermatitis and atopic xerosis. The Objective Severity Assessment of Atopic Dermatitis (OSAAD) score correlated with both the modified SCORing Atopic Dermatitis (SCORAD) index (a) (P = 0.002, r = 0.619) and the standard SCORAD index (b) (P = 0.002, r = 0.619)

Xerosis is considered to be a potential cause of pruritus in xerotic skin diseases, including AD,[9] but the precise mechanism remains unclear. In AD, xerosis-induced pruritus may be caused by the relatively easy entry of irritants and/or antigens via the impaired epidermal barrier,[14] or by increased dermal mast cell numbers and histamine content resulting from conditions of low humidity (as observed in a murine study).[15] On the basis of these hypotheses and findings, it may be speculated that pruritus is caused by skin inflammation, probably through the activation of mast cells; however, it has been reported that the experimental induction of xerosis, using water and an acetone–ether mixture, does not affect mast cell numbers or degranulation in mice, and that scratching behavior is similar between mast cell-deficient mice and controls.[16] These findings suggest the possible existence of a non-mast cell-mediated mechanism in xerosis-induced pruritus/scratching. Indeed, the use of emollients, which are unlikely to modulate directly mast cell activation, can be effective in soothing pruritus in AD. Furthermore, the use of strong anti-inflammatory agents, such as topical steroids, the first-line treatment for AD, can reduce the pruritus of skin.[17,18] Ultraviolet phototherapy, another anti-inflammatory treatment for AD, is also effective in the control of pruritus in AD.[19] The mechanism of this type of phototherapy, however, may be through a reduction in epidermal nerve elongation,[20] a recently reported pruritus-associated factor,[21,22] as well as the induction of apoptosis/inactivation of various inflammatory cells.[23] These findings imply that skin inflammation may contribute substantially to the elicitation and/or exaggeration of pruritus in AD.

This study has demonstrated that the severity of AD (modified SCORAD index) correlates well with both pruritus scores (Fig. 2a,b), whereas atopic xerosis (OSAAD score) correlates only with VAS-assessed pruritus and with a lower correlation coefficient (Fig. 1a,b). This finding may indicate that skin inflammation provides a greater contribution than dry skin to the development of pruritus in AD, because our modified SCORAD index reflects various inflammatory items (e.g. erythema, papulae, edema, exudates, and lichenification), in addition to xerosis, whereas the OSAAD score merely reflects xerosis-related factors (TEWL and cutaneous capacitance).[10] This finding may also suggest that the reversal of xerosis alone may not be effective in the full control of pruritus, and that a combination of emollients with appropriate anti-inflammatory agents, such as steroid or tacrolimus, may be more helpful in controlling pruritus and skin eruption in AD. Nevertheless, the contribution of xerosis to pruritus in AD cannot be denied. It should also be mentioned that the OSAAD score correlated positively with the standard (and modified) SCORAD index in the present study, in agreement with the original OSAAD report,[10] thereby validating the data obtained using both OSAAD and SCORAD.

In conclusion, disease severity (or skin inflammation), rather than xerosis, correlates with pruritus in patients with AD, particularly in those suffering from moderate to severe AD.

Acknowledgements

This work was supported by the research grant from The Ministry of Health, Labour and Welfare of Japan.

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JAPANESE DERMATOLOGICAL ASSOCIATION
THE JOURNAL OF DERMATOLOGY
doi: 10.1111/j.1346-8138.2009.00706.x
Journal of Dermatology 2009; **36**: 563–577

GUIDELINE

Guidelines for management of atopic dermatitis

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ABSTRACT

Atopic dermatitis (AD) is a chronic relapsing eczematous skin disease characterized by pruritus and inflammation and accompanied by cutaneous physiological dysfunction (dry and barrier-disrupted skin). Most of the patients have atopic diathesis. A standard guideline for the management (diagnosis, severity classification and therapy) of AD has been established. In our guideline, the necessity of dermatological training is emphasized in order to assure diagnostic skill and to enable evaluation of the severity of AD. The definitive diagnosis of AD requires the presence of all three features: (i) pruritus; (ii) typical morphology and distribution; and (iii) chronic and chronically relapsing course. For the severity classification of AD, three elements of eruption (erythema/acute papules, exudation/crusts and chronic papules/nodules/lichenification) are evaluated in the most severely affected part of each of the five body regions (head/neck, anterior trunk, posterior trunk, upper limbs and lower limbs). The areas of eruption on the five body regions are also evaluated, and both scores are totaled (maximum 60 points). The present standard therapies for AD consist of the use of topical corticosteroids and tacrolimus ointment as the main treatment for the inflammation, topical application of emollients to treat the cutaneous physiological dysfunction, systemic antihistamines and anti-allergic drugs as adjunctive treatments for pruritus, avoidance of apparent exacerbating factors, psychological counseling and advice about daily life. Tacrolimus ointment (0.1%) and its low-density ointment (0.03%) are available for adult patients and 2–15-year-old patients, respectively. The importance of the correct selection of topical corticosteroids according to the severity of the eruption is also emphasized. Furthermore, deliberate use of oral cyclosporine for severe recalcitrant adult AD is referred.

Key words: atopic dermatitis, cyclosporine, guidelines, systemic antihistamines, tacrolimus ointment, topical corticosteroids.

INTRODUCTION

Atopic dermatitis (AD) is a disease that occurs frequently in daily medical management. It requires sufficient explanation to patients to achieve compliance/adherence for medical treatments. Treatment guidelines for AD have been published in various countries in the world recently. All these treatment guidelines are based on similar disease definitions and treatment systems. AD is a chronic

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Received 23 July 2009; accepted 31 July 2009.

relapsing inflammatory skin disease caused by the intervention of plural unspecific stimulation or specific allergens accompanied with cutaneous physiological dysfunction. The standard therapies for AD consist of topical corticosteroids and tacrolimus ointment as the main treatment for the inflammation, topical application of emollients to treat the physiological dysfunction, systemic antihistamines and anti-allergic drugs as adjunctive treatments for pruritus, and the avoidance of apparent exacerbating factors. Diagnostic criteria for AD by the Japanese Dermatological Association (JDA) were formulated in 1994,[1] and the severity classification of AD was formulated in 2001 through the interim report of 1998.[2,3] JDA guidelines for AD therapy were first formulated in 2000 and revised in 2003 and 2004.[4–6] In 2008, we formulated new guidelines for the management of AD, integrating diagnostic criteria, severity classification and guidelines for AD therapy.[7] A new treatment (oral cyclosporine) for AD has been added to Japanese health insurance, leading to the current revision. This guideline is basically designed for dermatologists who care for patients from the stage of primary care to the stage in which a high level of specialization is required in the treatment of AD.

In a national multicenter cross-sectional survey of dermatological patients conducted in 2007 by the JDA, the age distribution of patients with the disease showed a bimodal pattern with peak incidences at the ages of 0–5 and 21–25 years. Moreover, patients aged 46 years or older accounted for 9.64%. These results indicate that patients of many ages are subjected to daily examination and treatment. It is recommended to respect the discretion of dermatologists, consider patients' wishes and select the most appropriate therapy for each patient with reference to this guideline.

PATHOGENESIS

Atopic dermatitis is a chronic relapsing eczematous skin disease characterized by pruritus and inflammation and caused by the intervention of various unspecific stimulation and specific allergens. It is accompanied by the cutaneous physiological dysfunction of dry and barrier-disrupted skin due to abnormalities of the epidermis, especially the horny cell layers. Most patients have atopic diathesis, defined as: (i) a personal or family history (one or more of asthma, allergic rhinitis/conjunctivitis, and AD); and/or (ii) a predisposition to overproduction of immunoglobulin (Ig)E antibodies.

Although AD generally follows a chronic or chronically relapsing course, spontaneous remission may be expected when the symptoms are controlled well and continuously by appropriate treatments.

DIAGNOSIS

Diagnostic criteria

Based on "Definition and diagnostic criteria for AD" established by the JDA in 1994 (and revised in 2008), the definitive diagnosis of AD requires the presence of all three features: (i) pruritus; (ii) typical morphology and distribution; and (iii) chronic and chronically relapsing course, without any consideration of severity. Cases not meeting these criteria should be evaluated on the basis of age and clinical course with the tentative diagnosis of acute or chronic, non-specific eczema.[1] An English translation of these diagnostic criteria was published in 1995.[8] Cutaneous lymphoma, psoriasis, immune deficiency diseases, collagen diseases (systemic lupus erythematosus, dermatomyositis) and Netherton's syndrome have been newly added as exclusionary conditions in 2008 (Table 1). It is necessary to be able to distinguish these exclusionary conditions and to understand well the significant complications.

Reference

The diagnostic criteria defined by Hanifin and Rajka in 1980 are frequently used worldwide.[9] One of the differences between Hanifin & Rajka's criteria and the JDA criteria is that a personal or family history of atopic diseases (asthma, allergic rhinitis/conjunctivitis and AD) is defined as a basic feature in the former and as a diagnostic aid in the latter. However, atopic diathesis is clearly addressed in the definition of AD by the JDA (Table 1). The 23 minor features listed in the Hanifin and Rajka's criteria are characteristic for AD and often observed in this disease. However, their

Table 1. Definition and diagnostic criteria for atopic dermatitis by the Japanese Dermatological Association

Definition
Atopic dermatitis is a pruritic, eczematous dermatitis; its symptoms chronically fluctuate with remissions and relapses.
Most individuals with atopic dermatitis have atopic diathesis.
Atopic diathesis: (i) personal or family history (asthma, allergic rhinitis and/or conjunctivitis, and atopic dermatitis); and/or (ii) predisposition to overproduction of immunoglobulin E (IgE) antibodies.
Diagnostic criteria for atopic dermatitis
1. Pruritus
2. Typical morphology and distribution
(1) Eczematous dermatitis
• Acute lesions: erythema, exudation, papules, vesiculopapules, scales, crusts
• Chronic lesions: infiltrated erythema, lichenification, prurigo, scales, crusts
(2) Distribution
• Symmetrical
Predilection sites; forehead, periorbital area, perioral area, lips, periauricular area, neck, joint areas of limbs, trunk
• Age-related characteristics
Infantile phase: starts on the scalp and face, often spreads to the trunk and extremities
Childhood phase: neck, the flexural surfaces of the arms and legs
Adolescent and adult phase: tendency to be severe on the upper half of body (face, neck, anterior chest and back)
3. Chronic or chronically relapsing course (usually coexistence of old and new lesions)
• More than 2 months in infancy
• More than 6 months in childhood, adolescence, and adulthood
Definitive diagnosis of atopic dermatitis requires the presence of all three features without any consideration of severity.
Other cases should be evaluated on the basis of the age and clinical course with the tentative diagnosis of acute or chronic, non-specific eczema.
Differential diagnosis (association may occur)
Contact dermatitis, seborrheic dermatitis, prurigo simplex, scabies, miliaria, ichthyosis, xerotic eczema, hand dermatitis (non-atopic), cutaneous lymphoma, psoriasis, immune deficiency diseases, collagen diseases (systemic lupus erythematosus, dermatomyositis), Netherton's syndrome
Diagnostic aids
Family history (bronchial asthma, allergic rhinitis and/or conjunctivitis, atopic dermatitis), personal history (bronchial asthma, allergic rhinitis and/or conjunctivitis), follicular papules (goose-skin), elevated serum IgE level
Clinical types (not applicable to the infantile phase)
Flexural surface type, extensor surface type, dry form in childhood, head/face/neck/upper chest/back type, prurigo type, erythroderma type, combinations of various types are common
Significant complications
Ocular complication (cataract and/or retinal detachment): especially in patients with severe facial lesions, Kaposi's varicelliform eruption, molluscum contagiosum, impetigo contagiosa

Cited from Tagami,[8] with modification.

frequencies of development vary, and discrete expressions are used for some of the features; therefore, they are excluded from the diagnostic criteria by the JDA, although some of them are referred to as diagnostic aids, clinical types or significant complications (Table 1). Subsequently, an "abridged edition of Hanifin & Rajka's diagnostic criteria" was published in 2003.[10]

Diagnostic criteria in health checkups

"Definitions and diagnostic criteria for AD" by the JDA can be used routinely. In health checkups of infants, for whom the reliability of subjective symptoms and answers about clinical course cannot be expected, the diagnosis can be performed mainly by "typical morphology and distribution". This point needs to be clearly addressed when publishing.

Reference: nationwide investigation by inquiry/questionnaire

A questionnaire for AD diagnosis was developed in 1994 by the UK Working Party, and it has been used worldwide.[11] Its Japanese translation version has proven to be useful.[12] Furthermore, based on the questionnaire developed by the International Study of Asthma and Allergies in Childhood (ISAAC), global epidemiological surveys about eczema, including AD, have been conducted

periodically (http://isaac.auckland.ac.nz/Index.html).[13] Its Japanese translation version is used for epidemiological surveys.[14,15]

SEVERITY CLASSIFICATION

A severity classification useful for clinical trials

The statistical reliability and adequacy of the severity classification of AD developed by the advisory committee of AD severity classification of JDA have been verified, so it can be used for clinical trials (Fig. 1).[3] For the severity classification, three elements of eruption (erythema/acute papules, exudation/crusts and chronic papules/nodules/lichenification) are evaluated in the most severely affected part of each of the five body regions (head/neck, anterior trunk, posterior trunk, upper limbs and lower limbs). The areas of eruption on the five body regions are also evaluated, and both scores are totaled (maximum 60 points) (Fig. 1). A simple method for the severity classification has also been proposed by this committee.[2] In this method, the entire body is divided into the same five regions, severity is evaluated globally for each region and the total is calculated (maximum 20 points) (Fig. 2).

Reference

As an even simpler and easier method, other measures of severity have been proposed by the Research Group granted by the Ministry of Health, Labor and Welfare (Table A1). In the world, the Severity Scoring of Atopic Dermatitis (SCORAD) produced by the European Task Force on Atopic Dermatitis (maximum 103 points) or the Eczema Area and

This severity classification can be adopted only for the cases that are definitely diagnosed as atopic dermatitis.

Three elements of eruption are evaluated in the most severely affected part of each of the five body regions (15 times in total).

The areas of eruption on the five body regions are also evaluated (5 times in total). Both scores are totalized (20 times in total).

For evaluation of severity of eruption on each region, the severest part is selected for each element.

Evaluation of the area of eruption should be done considering all three elements for all five body regions.

The highest possible score is 60 points.

	Head/neck	Anterior trunk	Posterior trunk	Upper limbs	Lower limbs	Total
Erythema/acute papules						
Exudation/crusts						
Chronic papules/nodules/lichenification						
Area of eruption						

Total score

Evaluation method

I. Evaluation criteria for three elements of eruption

0 = absent, 1 = mild, 2 = moderate, 3 = severe

*Explanation of three elements of eruption

Erythema: All the redness, flushing and edema are included, acute papules: Papules not affected by scratching.

Exudation/crusts: Erosion by scratching is included.

Chronic papules: Papules affected by scratching. Nodules/lichenification: Eruption in which chronic papules progressed further.

II. Evaluation criteria for area of eruption

0 = no eruption, 1 ≤ 1/3, 2 = 1/3 ~ 2/3, 3 ≥ 2/3

(Cited from ref. 3 with modification).

Figure 1. Severity classification of atopic dermatitis by the Japanese Dermatological Association.

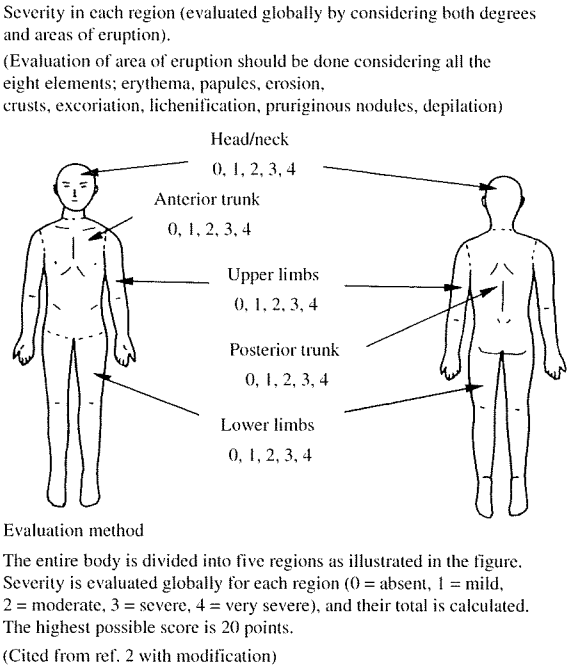

Figure 2. Severity classification of atopic dermatitis by the Japanese Dermatological Association (simple method).

Severity Index (EASI) developed by the EASI Evaluator Group (maximum 72 points) are frequently used.[16,17]

Reference: severity classification considering clinical course

As a severity classification considering the clinical course, the system of grading of the severity of AD published by Rajka and Langeland is frequently used.[18] Additionally, in the above-mentioned ISAAC questionnaire, the question "In the last 12 months, how often, on average, have you (has your child) been kept awake at night by this itchy rash?" diagnoses patients as severe when they answer "1 or more nights per week".[13–15]

Reference: evaluation of pruritus

A Visual Analog Scale (VAS) is useful for evaluation of pruritus.[19] In VAS, the patient places a mark on a 10-cm segment on the basis of the degree of pruritus. On the segment, 0 at the left end of the scale indicates "no pruritus" and 100 at the right end of that indicates "the severest pruritus". The distance from the left end to the marked point (mm) is used as a scale value for the pruritus. As described in SCORAD (evaluated by the scale of 0–10 in SCORAD), VAS can also be used for sleep loss. Table A2 shows the evaluation criteria for the degree of pruritus by behavioral rating scores. These were used for clinical trials with an evidence level over 2.[20,21]

Reference: evaluation of quality of life (QOL)

Both Skindex-16 and the Dermatology Life Quality Index (DLQI) have been analyzed statistically in detail[22–25] and are available in Japanese translations.[26–28]

Reference: disease markers of AD

Disease markers of AD which reflect the severity or disease activity include measurements of peripheral blood eosinophil count, serum total IgE, lactate dehydrogenase, and thymus and activation-regulated chemokine (TARC) levels. With regards to short-term markers, TARC has been shown to reflect the disease activity more sensitively than other laboratory markers.[29]

Severity of eruption

Selections of topical medications, which are key for treatment, should be determined in each region by "severity of eruption" (Table 2). In other words, a sufficiently intensive topical application should be selected for a severe eruption even when the lesion is small, while on the other hand, intensive topical applications are not necessary for mild eruptions even when the lesion is large. Therefore, for selections of topical medications, "severity of eruption" is the most important aspect. Severity of eruption must be determined by a physician with sufficient dermatological skill to predict the treatment effect (Table 2).

TREATMENT

Objective of the treatment

The objective of the treatment is to let the patient reach the following states.

1 There are no symptoms or minor symptoms, and the patient's daily life is not disturbed by the disease. Moreover, drug treatments are not much needed.
2 Even if slight or mild symptoms last, the disease rarely shows acute or intense exacerbations; they are not protracted, if any.

Table 2. Severity of eruption and topical corticosteroid application

Severity	Eruption	Topical corticosteroid application
Severe	Primarily severe swelling/edema/infiltration or erythema with lichenification, multiple papules, severe scales, crusts, vesicles, erosion, multiple excoriations and pruriginous nodules	Use of very strong or strong rank topical corticosteroids is the first-line treatment. Strongest rank topical corticosteroids are also available for refractory pruriginous nodules if sufficient effects are not achieved by applying very strong rank topical corticosteroids.
Moderate	Primarily moderate erythema, scales, a few papules and excoriations	Use of strong or medium rank topical corticosteroids is the first-line treatment
Mild	Primarily dryness, mild erythema and scales	Use of medium or weak rank topical corticosteroids is the first-line treatment
Slight	Primarily dryness with negligible inflammation	Topical application of medicines other than corticosteroids (emollients)

Cited from Kawashima *et al.*,[4] with modification.

Drug treatment

Atopic dermatitis is a pluricausal disease with related genetic factors and there are no drug treatments that can completely heal the disease. Therefore, treatment basically focuses on symptomatic relief.

Topical treatment for inflammation

At present, the drugs that can sedate the inflammation of AD sufficiently and whose effectiveness and safeness are proved scientifically are topical corticosteroids and tacrolimus ointment (topical calcineurin inhibitor). Another topical calcineurin inhibitor widely used elsewhere in the world, pimecrolimus cream, is not available in Japanese health insurance. The anti-inflammatory effect of topical non-steroid anti-inflammatory drugs (NSAIDs) is extremely weak, and they sometimes cause contact dermatitis; therefore, they are not well suited for topical treatment of AD.

Tacrolimus is a drug that inhibits calcineurin and controls inflammation by a different mechanism from that of topical corticosteroids. There are two kinds of tacrolimus ointments: 0.1% for an adult and 0.03% for a child. Tacrolimus ointment is recognized as a drug that is highly suited for eruptions on the face and neck. However, tacrolimus ointment is different from topical corticosteroids in that it cannot be used for erosions and ulcers and there is a limit to the strength of the drug efficacy. This drug is premised on use by a physician with sufficient dermatological skills to understand critical matters such as the patient's age, contraindications and careful administration.[30]

It is fundamental for treatment to consider how to select and combine topical corticosteroids and tacrolimus ointment that have been sufficiently evaluated as topical drugs which can sedate skin inflammation of AD consistently and immediately. Applying different kinds of topical corticosteroids on the right or left side each separately can be effective, as can applying topical corticosteroid and another kind of topical drug without corticosteroid on the right or left side separately, in order to determine effective drugs for a specific patient.

Topical corticosteroids

- Rank of topical corticosteroids (Table 3): In general, the effectiveness of topical corticosteroids and the occurrence rate of topical side effects parallel each other; therefore it is important to select drugs at ranks appropriate for the "severity of eruption" without selecting unnecessarily strong topical corticosteroids (Table 2).
- Bases of topical corticosteroids: Bases such as ointment, cream, lotion, and tapes must be selected according to the condition and site of skin lesion.
- Application times of topical corticosteroids: It is usual to apply these drugs twice a day in an acute exacerbation (morning and evening/after bathing). However, when using topical corticosteroids of lower ranks or changing to drugs without corticosteroids, it is necessary to confirm that there is no recurrence by changing to an intermittent pattern such as alternate-day or once-a-day application. With regards to topical corticosteroids at the rank higher than the strong class, there is not a significant difference between twice-a-day application and once-a-day application in curative effects after 3 weeks (evidence level II: by one or more

Table 3. Rank of topical corticosteroids

Strongest, %	
0.05	Clobetasol propionate
0.05	Diflorasone diacetate
Very strong, %	
0.1	Mometasone furoate
0.05	Betamethasone butyrate propionate
0.05	Fluocinonide
0.064	Betamethasone dipropionate
0.05	Difluprednate
0.1	Amcinonide
0.1	Diflucortolone valerate
0.1	Hydrocortisone butyrate propionate
Strong, %	
0.3	Deprodone propionate
0.1	Dexamethasone propionate
0.12	Dexamethasone valerate
0.1	Halcinonide
0.12	Betamethasone valerate
0.025	Beclometasone dipropionate
0.025	Fluocinolone acetonide
Medium, %	
0.3	Prednisolone valerate acetate
0.1	Triamcinolone acetonide
0.1	Alclometasone dipropionate
0.05	Clobetasone butyrate
0.1	Hydrocortisone butyrate
0.1	Dexamethasone
Weak, %	
0.5	Prednisolone

As of April 2009. Cited from Kawashima *et al.*,[4] with modification.

randomized controlled trials).[31,32] Considering the fact that side-effects diminish as the application times decrease, it is preferable to apply twice a day in an acute exacerbation to sedate the inflammation quickly and to apply once a day after improvement of the eruption (recommendation grade A: strongly recommended to perform). However, when using medium rank topical corticosteroids, twice-a-day application is more effective than once-a-day application (evidence level II).[33]

- Application amount of topical corticosteroids: A finger-tip unit (FTU) is the amount of ointment expressed from a tube with a 5-mm diameter nozzle and measured from the distal skin-crease to the tip of the index finger (~0.5 g); this is an adequate amount for application to two adult hand areas, which is approximately 2% of an adult body surface area.[34,35]

Long usage test results of the topical corticosteroids of the very strong rank have disclosed that, if the treatment begins with 5 g or 10 g a day, which is sufficient for an ordinary adult patient, as an initial amount (though it depends on the area of the eruption), and the amount is decreased gradually as the symptoms subside, no irreversible systemic side-effects occur during 3 months of use (though transient and reversible adrenal function suppression may occur). It is extremely rare to use topical corticosteroids of 5 g or 10 g a day for more than 3 months. However, in such cases, it is necessary to check for systemic effects regularly and to reconsider appropriate topical treatment for affected patients to reduce the amount of topical corticosteroids. For infants and children, treatment by topical corticosteroids should begin with volumes converted from the amount used for an adult based on their body-weight.

- Discontinuation of application: When topical corticosteroids are discontinued after inflammation is settled, it is important to discontinue them gradually while observing the symptoms, for example, to apply them intermittently instead of discontinuing suddenly. However, this principle does not apply when side-effects of topical corticosteroids are apparent.
- Infants and children: In principle, when the eruption is severe or moderate, topical corticosteroids one rank lower than those shown in Table 2 should be used. However, when sufficient effects are not obtained, higher rank topical corticosteroids should be used under careful supervision.
- Face: Considering the high absorption rate of drugs on the face, topical corticosteroids of medium or weak rank should be used in principle. Even in such cases, twice-a-day application should be limited for approximately 1 week and then the treatment should be changed to intermittent application. Discontinuation periods must be set for this type of treatment. Most of the facial erythematous lesions often found in adult patients in recent years are caused by factors other than topical corticosteroids, including scratching. However, the face is a region for which it is necessary to be alert to the occurrence of topical side-effects; therefore, careful examination is needed before prescribing.

In addition, the face is a region to which tacrolimus ointment is highly adapted; therefore, it is worthwhile to actively consider using it in accordance with the guidance.[30]

- Compliance: Because of misunderstandings about topical corticosteroids (mostly confusion with the side-effects of systemic corticosteroids and/or confusion between exacerbation of the AD itself and the side-effects of topical corticosteroids), fears and evasions arise about topical corticosteroids and a decrease in compliance is often seen. To correct such misunderstandings, it is necessary to take enough time to explain about the drugs and to instruct patients on their use. This influences treatment effects.
- Side-effects of topical corticosteroids: It is reported that the daily amounts that may cause adrenal function suppression are 10 g of 0.12% betamethasone valerate ointment (strong rank) in an occlusive dressing technique and 20 g as a simple application.[36,37] However, it is extremely rare to use such large amounts of topical drugs continuously in daily medical care. If topical corticosteroids are used properly, systemic side-effects such as adrenal insufficiency, diabetes mellitus and moon face, all caused by systemic corticosteroids, will not occur with normal consumption. Among topical side-effects, steroid acne, steroid flushing, skin atrophy, hypertrichosis and bacterial/fungal/viral skin infections occur occasionally; however, affected patients recover with discontinuation or appropriate treatments. Pigmentation can arise after the use of topical corticosteroids; however, this is postinflammatory pigmentation and not a side-effect of topical corticosteroids. Allergic contact dermatitis can rarely occur in response to topical corticosteroids; however, it is also necessary to be alert to contact dermatitis caused by base or additives of these drugs.

Tacrolimus ointment. Tacrolimus suppresses the functions of T lymphocytes by a mechanism which is distinct from that of corticosteroids. Tacrolimus ointment can be expected to show a high level of effectiveness against AD that is difficult to treat with topical corticosteroids. However, the effectiveness of this medicine depends on absorbance of the drugs and is affected by the region of application and the condition of the barrier function. It cannot be used for infants under 2 years of age because its safety has not been proven. In addition, it cannot be used on pregnant or breast-feeding women.

- Application amount of tacrolimus ointment: When tacrolimus ointment is used, the maximum amount of application per use is 5 g for 0.1% ointment for adults, 1 g for 0.03% ointment for children aged 2–5 years (below 20 kg of bodyweight), 2–4 g for children aged of 6–12 years (>20 kg and <50 kg) and 5 g for children aged 13 years and older (≥50 kg). In addition, the number of application times is limited to twice a day. One gram per use can be applied to four adult hand areas. When it is used over wide areas, physicians need to devise a method such as using topical corticosteroids together in accordance with the degree of eruption; however, it is not recommendable to apply the mixture of tacrolimus ointment and topical corticosteroids, or to put one upon another on the same site at the same time.
- Application method for tacrolimus ointment: This drug often causes stimulation symptoms such as transient burning sensations and hot flashes in the applied regions. However, these tend to disappear with remission of the eruption; therefore, it is necessary to explain this effect to the patient beforehand. Tacrolimus ointment is quite effective on the face and neck, which show good percutaneous absorption. When the effects of existing treatments such as topical corticosteroids are insufficient or the physician hesitates to administer these drugs due to their topical side-effects, tacrolimus ointment can frequently be employed. In addition, the effectiveness of this drug (0.1% for adults) on the trunk and extremities is approximately equivalent to that of topical corticosteroids of the strong rank (evidence level II).[38] When it is used on a region with a severe eruption that requires strong drug effects, it is recommended to initially attempt to improve the eruption by topical corticosteroids of the very strong or strongest rank and then shift to the use of tacrolimus ointment. In many cases, consumption of topical corticosteroids can be reduced by using this drug in combination. If improvement is seen in the eruption with this drug, the amount of the drug per use should be reduced appropriately or the application interval should be extended.

For patients with ichthyosiform erythroderma (e.g. Netherton's syndrome), tacrolimus ointment cannot be used, because side-effects such as renal

disturbances may develop due to high percutaneous absorption and the resultant increase in the blood concentration of this drug.

Long-term use of tacrolimus ointment, that is, for more than 3 years, has not been found to cause serious systemic adverse events.[39–41] Although we need to pay attention to the transient skin stimulation which has been reported in most clinical studies, tacrolimus ointment is basically considered a safe drug. A number of reports have also shown a lack of association between exposure to topical tacrolimus and lymphoma or skin cancers.[42,43] Guidelines in the USA and Europe recommend the use of tacrolimus ointment as maintenance therapy as well as induction therapy.[44] Recent studies reported the effectiveness of intermittent therapy for flare prevention with two- or three-times weekly applications of tacrolimus in stabilized AD (proactive therapy).[45,46]

Topical treatment for skin physiological dysfunction/ skin care

For the purpose of improving dry skin with decreased barrier functions and preventing recurrence of inflammation, it is necessary to care for such skin by applying topical emollients/protective agents that do not contain corticosteroids or tacrolimus. In other words, it is necessary to use some moisturizers continuously even for slight skin eruptions. When this is neglected, the inflammation recurs easily and leads to a decrease in the effectiveness of topical corticosteroids and tacrolimus ointment. It was reported that applying moisturizers (heparinoid preparation) twice daily significantly reduced the inflammation relapse of AD compared with the untreated control group (evidence level II, recommendation grade A).[47] It is standard to use them twice a day. When it is confirmed there is no recurrence, the treatment shall shift to once-a-day or intermittent application. It is necessary to be alert for the occurrence of contact dermatitis as a side effect, which should be distinguished from the recurrence of AD. If recurrence of AD is seen during maintenance treatment by skin care, physicians shall return to treatments with topical corticosteroids or tacrolimus ointment in the affected region to achieve early sedation in accordance with the degree of inflammation and then return to the maintenance treatments again.

Systemic treatment

Atopic dermatitis is characterized by pruritus as a subjective symptom. Drugs with antihistaminic effects (so-called antihistamines, the first-generation antihistamines, or anti-allergic drugs with antihistaminic effects, the second generation antihistamines) are used for the purpose of suppressing pruritus and preventing exacerbation due to scratching (Table 4). It has already been clarified that an addition of antihistamine to a topical corticosteroid reduces the pruritus associated with AD (evidence level II).[20] Moreover, a large-scale investigation has revealed that the effects of suppressing pruritus obtained by continuous administrations of antihistamines are higher than those obtained by intermittent administration during 12-week maintenance treatment.[48] It is also indicated that antihistamines should be

Table 4. Antihistamines and anti-allergic drugs used for atopic dermatitis

The first-generation antihistamines
Diphenylpyraline hydrochloride
Diphenhydramine hydrochloride
Cyproheptadine hydrochloride
Triprolidine hydrochloride
Hydroxyzine hydrochloride
Promethazine hydrochloride
Homochlorcyclizine hydrochloride
Alimezine tartrate
Diphenhydramine tannate
dl-Chlorpheniramine maleate
d-Chlorpheniramine maleate
Diphenylpyraline teoclate
Hydroxyzine pamoate
Clemastine fumarate
The second-generation antihistamines
Ebastine
Azelastine hydrochloride
Epinastine hydrochloride
Olopatadine hydrochloride
Cetirizine hydrochloride
Fexofenadine hydrochloride
Oxatomide
Emedastine difumarate
Ketotifen fumarate
Bepotastine besilate
Mequitazine
Loratadine
Anti-allergic drugs without antihistamine effect
Sodium cromoglicate
Tranilast
Suplatast tosilate

As of April 2009. Cited from Hide *et al.*,[50] with modification.

Table 5. Classification of antihistamines by sedative effect

Non-sedative
Fexofenadine hydrochloride (120 mg)
Epinastine hydrochloride (20 mg)
Ebastine (10 mg)
Cetirizine hydrochloride (10 mg)
Olopatadine hydrochloride (5 mg)
Bepotastine besilate (10 mg)
Less sedative
Azelastine hydrochloride (1 mg)
Mequitazine (3 mg)
Cetirizine hydrochloride (20 mg)
Sedative
d-Chlorpheniramine maleate (2 mg)
Oxatomide (30 mg)
Diphenhydramine tannate (30 mg)
Ketotifen fumarate (1 mg)
d-Chlorpheniramine maleate (5 mg/i.v.)

Cited from Yanai *et al.*,[49] with modification.

classified into three groups – non-sedative, less-sedative and sedative – according to the analysis of histamine H1 receptor occupancy in human brains (Table 5).[49] When concerned about the incidence rate of side-effects such as sleepiness and dullness, physicians should select non-sedative or less-sedative second-generation antihistamines initially and consider additional administration of other antihistamines while observing both side-effects and the suppressing effects against pruritus (Table 4).[50,51] Effects such as suppression of release of chemical mediators that anti-allergic drugs, including the second-generation antihistamines, have are expected to function as an adjuvant therapy for topical treatments (Table 4), but the inflammation of AD cannot be suppressed by anti-allergic drugs alone.

Although there have been no double-blind comparative studies, corticosteroids are sometimes administered p.o. to severe AD patients as induction therapy and are known to be effective from experience. Considering the systemic side-effects, short-term administration should be recommended.

Cyclosporine for the treatment of AD has been covered by health insurance since October 2008 in Japan. Cyclosporine can be administered p.o. to adult patients with severe and recalcitrant AD. According to the guidance, the use of cyclosporine can be repeated intermittently; however, it is necessary to discontinue it within the first 3 months of initial use (or resuming use). For details, refer to "Guidance for the use of Cyclosporin MEPC for atopic dermatitis", which is published elsewhere.[52]

Patients with AD are likely to develop complications such as skin bacterial infections caused by *Staphylococcus* or hemolytic *Streptococcus* and Kaposi's varicelliform eruption caused by herpes simplex virus. If patients are suspected of having these infections during treatment, appropriate antibiotics or antiviral drugs should be administrated p.o. immediately.

Considering evidence-based medicine, most reports on herbal medicine for AD are case accumulation studies with tens of cases. "Randomized, double-blind, placebo-controlled trials" have been conducted only in four studies of "Zemaphite" or "Hochu-ekki-to". Although the effectiveness of Zemaphite has been reported,[53,54] a negative result was also reported by another group.[55] It was reported that additional use of Hochu-ekki-to can reduce the dose of topical corticosteroids.[56] Overall, a number of studies include pediatric patients, in whom spontaneous remission must be taken into consideration. Therefore, it seems necessary to conduct careful examinations by selecting the appropriate subject cases, conducting larger-scale studies and collecting results of double-blind randomized comparisons from multiple facilities.

Avoidance of exacerbating factors

Remedial goals are achieved in many cases if a confidential relationship is built between the patient and a physician and the above-mentioned drug treatments are utilized sufficiently. However, exacerbating factors peculiar to the individual patient in social and daily life are seen in many cases; therefore, it is extremely important to detect such exacerbating factors and avoid them. Responses to food allergens can be found in infants. After infancy, environmental allergens such as mites and house dust are likely to be involved, and contact allergens including topical drugs, and mental stress can be exacerbating factors for all age groups.

Physicians should determine the involvement of allergens after removing them or running challenge tests of them (if possible) while referring to medical histories and the results of skin and blood tests. Allergens should not be determined only by observing clinical symptoms or blood test results alone.

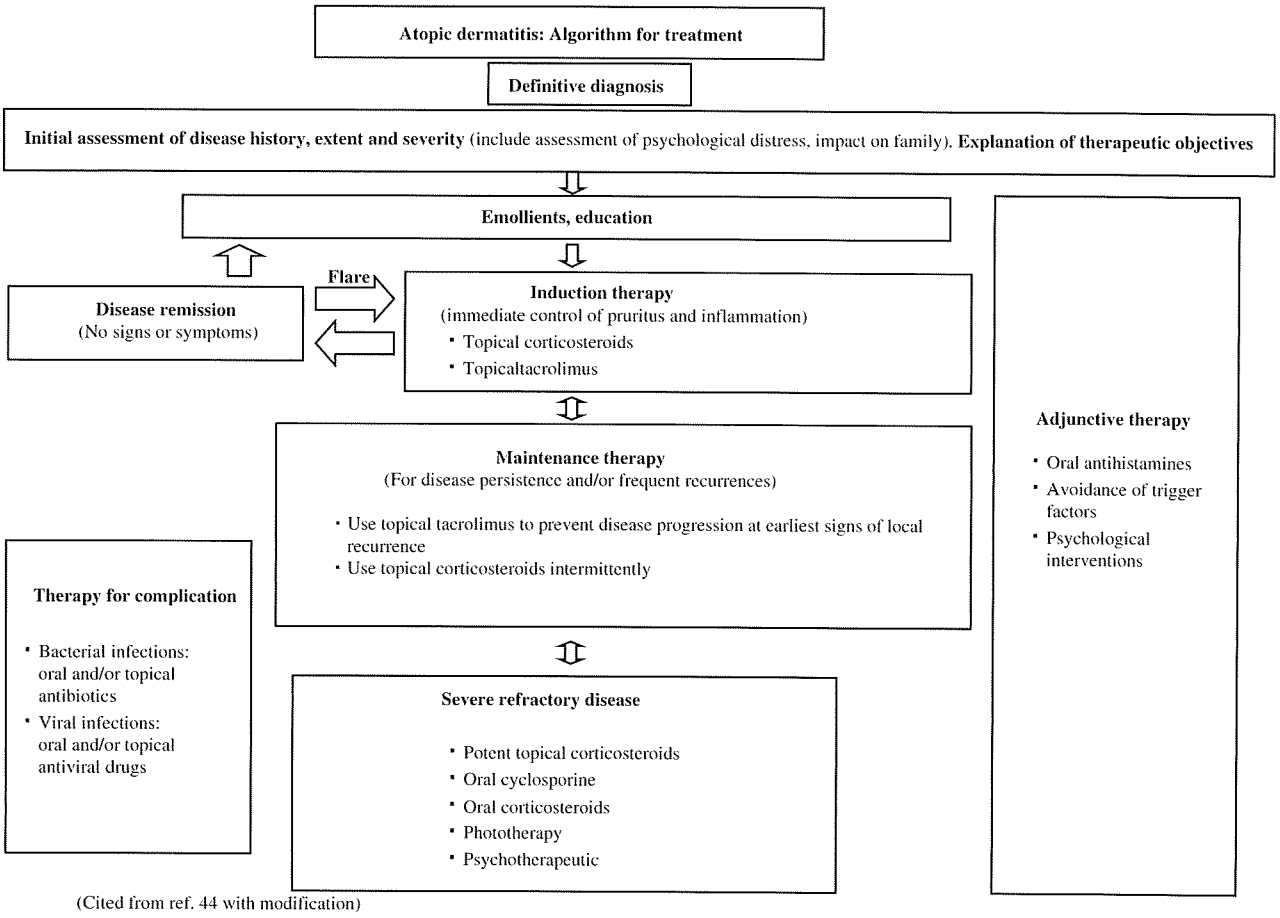

Figure 3. Algorithm for treatment of atopic dermatitis.

Moreover, it must be understood that even when allergens can be clarified, AD is a pluricausal disease, and allergen removal is only an adjuvant treatment for drug treatments. Patients cannot recover only by using these adjuvant treatments.

Psychosomatic approach

In some severe cases of adult patients with AD, psychosocial stresses such as human relations, pressure of work, worries about career and anxieties for independence may be involved. Such patients tend to have a habitual scratching behavior, which should be called "addictive scratching" or "scratch dependence"; this behavior worsens their eruption.[57] Furthermore, some child AD patients tend to have a similar habitual scratching behavior because they feel unloved. In such cases, it is necessary to employ both physical and mental treatments. Moreover, in some cases, team medical treatment with psychiatrists may be required.

Advice about daily life/complication

Generally, the following advice about daily life is useful for AD patients.

- Keep the skin clean by bathing or showering.
- Keep the room clean and create an environment with appropriate temperature and humidity.
- Regulate daily life and avoid overdrinking/overeating.
- Wear clothes with little stimulation.
- Cut fingernails to avoid skin damage by scratching.
- In cases with severe facial eruptions, the physician should make the patient consult an ophthalmologist regularly. It must be noted that ocular complications (cataract, retinal break and retinal detachment) are not caused by the use of topical

Table 6. Criteria for levels of evidence and grades of recommendation

Levels of evidence	
I	Systematic review or meta-analysis
II	One or more randomized controlled trials
III	Controlled study without randomization
IV	Analytical epidemiological study (cohort study or case–control study)
V	Descriptive study (case report or case accumulation study)
VI	Expert committee reports or opinions from specialist individual
Grades of recommendation	
A	Strongly recommended to perform (there should be at least one level I or II evidence that indicates effectiveness)
B	Recommended to perform (there should be at least one level II evidence of low quality, level III of good quality or level IV of extremely good quality that indicates effectiveness)
C1	Can be considered for use, but there is insufficient evidence (level III–IV evidence of low quality, plural level V of good quality or level IV approved by the committee)
C2	Not recommended for use because there is no evidence (there is no evidence that indicates effectiveness or there is evidence that indicates no effects)
D	Recommended to avoid (there is good evidence that indicates no effect or harmful effects)

Cited from Saida *et al.*,[66] with modification.

corticosteroids but by scratching and tapping the skin around the eyes.

- Bacterial/fungal/viral skin infections arise easily; therefore, it is necessary to maintain a good condition of the skin.

Reference: AD and cataract

Physicians should pay special attention to the ocular complications of AD such as cataract and retinal detachment. Ocular complications tend to occur in cases with severe face eruptions which are mainly due to an eyeball being pressed mechanically by scratching. An association of cataract with AD was reported for the first time in 1921. In 1936, Brunsting clarified that juvenile cataract arose in approximately 10% of AD patients.[58] Cataract tends to occur in AD patients at the age of 10–20 years; in many cases, eye operations are necessary and sometimes the condition progresses to blindness. The association of cataract with AD is sometimes misdiagnosed as a side-effect of topical corticosteroids without careful consideration. In 1952, topical corticosteroids were first introduced for the treatment of skin diseases. The prevalence of cataract complication in AD has not increased greatly since topical corticosteroids were introduced; therefore, it is necessary to treat atopic cataract as a completely independent disease. Because atopic cataract relates to the severity of face eruptions, the necessity of improving face eruption as early as possible has been pointed out.[59,60] However, it is also necessary to pay attention to the glaucoma caused by application of topical corticosteroids to eyelids.

Other treatments

With regards to other non-standard treatments, their effectiveness is claimed only in some facilities, and most of their effectiveness has not been proved scientifically; therefore, the authors do not introduce them in this guideline, which outlines basic treatments for AD. Furthermore, it is necessary to pay attention to the health injury that they may cause.[61]

Ultraviolet (UV) therapy is one of the alternative (or additional) therapies for AD. Psoralen and ultraviolet A therapy (PUVA), UV-A1, UV-B, narrow-band UV-B, UV-A plus UV-B and UV-A1 plus narrow-band UV-B therapies have been reported to be effective for AD.[62,63] In Japan, UV therapy is expected to be effective, particularly for AD patients resistant to topical corticosteroids or patients with side-effects to traditional therapies. There are various protocols such as UV therapy in combination with topical or short-term oral corticosteroids. Each institute has its own variation on the protocols to achieve better therapeutic effects. Moreover, there are many types of treatment applicators and fluorescent tubes; therefore, it is necessary to use them carefully.

Although some guidelines in the USA and Europe consider UV therapy as a second-line treatment, technical problems make it difficult to conduct a double-blind test or a half-side test precisely to obtain good evidence. UV therapy must be conducted carefully by dermatologists who fully understand its mechanism and know how to apply it to patients, and how to cope with its side-effects.[64,65]

Algorithm for treatment

Finally, algorithm for the treatment of AD is shown in Figure 3. It is important to combine appropriate

treatments considering the patients' skin condition after a definitive diagnosis and assessment of severity.

Levels of evidence and grades of recommendation

Evidence levels and recommendation grades mentioned in this guideline were determined by the "Criteria for levels of evidence and grades of recommendation" (Table 6) established by the Skin Cancer Group.[66]

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