Management of Atopic Dermatitis in Japan

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The guidelines for the treatment of atopic dermatitis (AD) issued by the Japanese Dermatological Association (JDA), which are basically designed for dermatologists, were first prepared in 2000 and revised in 2016. The guidelines for AD of the Japanese Society of Allergology (JSA), which are basically designed for allergologists, including internists, otorhinolaryngologists, ophthalmologists, and dermatologists, were first prepared in 2009 and revised in 2014. In this article, I review the definition, pathophysiology, etiology, epidemiology, diagnosis, severity classification, examination for diagnosis and severity assessment, and treatments for AD in Japan according to these two guidelines for AD (JDA and JSA).

Based on the definition and diagnostic criteria for AD of the JDA, patients meeting three basic criteria, 1) pruritus, 2) typical morphology and distribution of the eczema, and 3) chronic or chronically relapsing course, are regarded as having AD. Treatment measures for AD basically consist of drug therapy, skin care, and elimination of exacerbating factors. Drugs that potently reduce AD-related inflammation in the skin are topical corticosteroids and tacrolimus. It is most important to promptly and accurately reduce inflammation related to AD by using these topical anti-inflammatory drugs. Proactive therapy refers to a treatment method in which, after inducing remission, a topical corticosteroid or tacrolimus ointment is intermittently applied to the skin in addition to skin care with moisturizers in order to maintain remission. (J Nippon Med Sch 2017; 84: 2–11)

Key words: atopic dermatitis, Japanese guidelines, diagnostic criteria, topical corticosteroids, tacrolimus ointment

Introduction

The guidelines for the treatment of atopic dermatitis (AD) issued by the Japanese Dermatological Association (JDA) were first prepared in 2000 and basically designed for dermatologists. In 2008, guidelines for the management of AD in which diagnostic criteria for AD, severity classification, and treatment guidelines were integrated were prepared and partially revised. They were translated into English in 2009. The clinical practice guidelines for the management of AD 2016 of the JDA were prepared as a regular revision applying to all patients from children to adults with all severities of AD in 2016. The guidelines for AD of the Japanese Society of Allergology (JSA), which are basically designed for allergologists, including internists, otorhinolaryngologists, ophthalmologists, and dermatologists, were first prepared in 2009 and revised in 2014. In this article, I review the definition, pathophysiology, etiology, epidemiology, diagnosis, severity classification, examination for diagnosis and severity assessment, and treatments for AD in Japan according to these two guidelines for AD (JDA and JSA).

Definition

The definition of AD by the JDA is as follows. AD is a pruritic, eczematous dermatitis; its symptoms chronically fluctuate with remissions and relapses. Most individuals with AD have atopic diathesis. Atopic diathesis: (i) personal or family history (asthma, allergic rhinitis and /or conjunctivitis, and AD) and /or (ii) a predisposition to overproduction of immunoglobulin E (IgE) antibodies (Table 1).

Pathophysiology

A. Inflammatory Mechanism

AD is an inflammatory skin disease that belongs to the eczema/dermatitis group. The dominant mechanisms of
AD are controlled by T-helper (Th)2 cell-related cytokines such as interleukin (IL)-4 and IL-13, and Th2 chemokines such as thymus and activation regulated chemokine (TARC)/CCL17 and macrophage-derived chemokine (MDC)/CCL22. These chemokines are chemotactic for Th2 cells, which express the chemokine receptor CCR4, and are usually observed in lesional AD skin. We have demonstrated that serum TARC levels reflect the disease severity of AD patients. We also showed that serum TARC levels were useful as a short-term disease marker for AD, and the test began to be covered by health insurance in Japan in 2008. IL-4 and IL-13 derived from Th2 cells stimulate fibroblasts to produce peristatin, which induces production of proinflammatory cytokines, including thymus stromal lymphopoetin (TSLP), by keratinocytes. TSLP activates dendritic cells (DCs) and induces production of Th2 chemokines such as TARC and MDC. TSLP-activated DCs prime naïve T cells to produce Th2 cytokines such as IL-4 and IL-13. TSLP is highly expressed by keratinocytes of AD patients.

In the chronic stage, Th1 cells producing interferon (IFN)-γ and IL-12 also play an important role in the pathogenesis of AD. The number of Th17 cells is increased in the peripheral blood and acute lesional skin of AD. Interestingly, the Asian AD phenotype including Japanese presents a blended phenotype between that of European American patients with AD and those with psoriasis, which is known to be a Th17 dominant skin disease, including increased hyperplasia, parakeratosis, higher Th17 activation, and a strong Th2...
Fig. 1  Serum TARC levels reflect the disease severity of patients with atop dermatitis. Reprinted from the article by Tamaki K et al. published in Journal of Dermatol 2006.6

component6.

B. Skin Dysfunction

In AD patients the skin barrier function is reduced and skin irritability to nonspecific stimuli is enhanced, frequently causing inflammation. A recent study reported that filaggrin gene mutations were involved in the pathogenesis of AD3. Filaggrin aggregates keratin fibers and, when decomposed, contributes to water retention in the cornified layer as a natural moisturizing factor. Therefore, the skin of patients with AD in whom filaggrin levels are decreased tends to be dry. A reduction in the skin barrier function leads to antigen (allergen) invasiveness in the skin. Allergens such as mites and pollen function as protein antigens, and induce Th2-type immune responses that are mediated by the proteases contained in them5. The effects of histamine H1 receptor antagonists (antihistamines) on AD-related pruritus vary among patients, and the presence of a mediator other than histamine has been suggested. IL-31, a cytokine produced by Th2 cells, is significantly overexpressed in pruritic skin of AD patients compared with nonpruritic skin of psoriasis patients8. Staphylococcal superantigens markedly enhance IL-31 production. IL-31 receptor-bearing cells include keratinocytes, dendritic cells, and periphery sensory neurons, which might mediate pruritic signals to the central nervous system. IL-31 links T cells and pruritus in atopic skin inflammation15. Epidermal innervation is thought to be regulated by the balance between nerve elongation factors like nerve growth factor (NGF) and nerve repulsion factors like semaphorin 3A (Sema3A). Sema3A has been shown to inhibit NGF-induced sprouting of sensory nerves, and epidermal Sema3A levels are lower in AD patients, concomitant with an increase in epidermal nerve density that leads to hypersensitivity to pruritus26.

Etiology

AD is caused by a combination of genetic and environmental factors6.

A. Genetic Factors

Association studies in populations of diverse ancestry, meta-analysis of studies and genome-wide association study (GWAS) have shown that mutation in FLG (encoding filaggrin) is strongly associated with AD17–20. In addition to FLG, recent GWAS of European and Chinese populations for AD and a meta-analysis of GWAS have reported six susceptibility loci at a genome-wide level of significance: C11orf30-LRRC32, TMEM232-SLC25A46, TNFRS6B-ZGPAT, OVAL1, ACTL9, and KIF3A-IL1318–20. On the basis of data from a GWAS and a validation study comprising a total of 3,328 AD patients and 14,992 controls in the Japanese population, we reported eight new susceptibility loci: IL1RL1-IL18R1-IL18RAP, the major histocompatibility complex (MHC) region, OR10A3-NLRP10, GLB1, CCDC80, CARD11, ZNF365-EG2, and CYP24A1-PFDN421. We also replicated the association of the six above-mentioned susceptibility loci and FLG. Candidate
genes at these loci indicate roles for epidermal barrier functions (FLG and OVAL1), adaptive immunity (TNFR56B, IL13, and CARD11), IL-1 family signaling (IL1RL1, IL18R1, and IL18RAP), negative regulation of apoptosis and the inflammatory response (NLRP10), regulatory T cells (LRRC32 and EGR2), and the vitamin D pathway (CYP24A1) in the pathogenesis of AD. In addition, the associated region at chromosome 3p21.33 (GLB1 loci) is located adjacent to the CCR4 gene, which encodes a Th2-associated chemokine receptor for TARC and MDC.

B. Etiological and Exacerbating Factors
Numerous of etiological and exacerbating factors have been proposed, with the importance level of each varying among age groups and individual patients. These factors include foods, sweat, physical irritation including scratching, environmental factors, microbes/fungi, contact allergens, and stress. It is commonly experienced that sweat induces itch, leading to the aggravation of AD. Clinically, psychological stress is well known to exacerbate AD symptoms, especially from the second half of childhood to adulthood.

Epidemiology

A. Global Prevalence of AD
An epidemiological survey (Phase I) was performed from 1994 to 1996 by the International Study of Asthma and Allergies in Childhood (ISAAC). The global prevalence in children 6 to 7 years old ranged from 1.1% in Iran to 18.4% in Sweden, and was 7.3% on average. That in those 13 to 14 years old ranged from 0.8% in Albania to 17.7% in Nigeria and was 7.4% on average. Higher prevalence of AD was seen mostly in industrialized nations, including Sweden, Finland, the United Kingdom (UK), Japan, Australia, and New Zealand. In the epidemiological survey (Phase III) performed from 2001 to 2003 by the ISAAC, few nations showed a significant decrease in the prevalence in children 6 to 7 years old compared with the prevalence in the phase I study. For children 13 to 14 years old, the AD prevalence decreased in some previously high-prevalence centers in the industrialized world such as the UK and New Zealand.

B. Epidemiological Survey in Japan
A nationwide prevalence survey was performed in Japan from 2000 to 2008 using the medical examination data from public health centers, elementary schools, and universities. Figure 2 depicts the prevalence by age
and 82.8% of the cases were classified as mild women, respectively. The prevalence decreased with age was 6.9% overall, and 5.7% and 8.1% for men and 787 women) were examined and the prevalence of AD on clinical examinations of adults in central Victoria, 1999, Plunkett et al. reported the prevalence of AD based rerate, severe, and very severe groups, respectively. In 27,719), ranging from 7.4% (Iwate) to 15.0% (Fukuoka) in the eight areas. Seventy-four percent, 24%, 1.6%, and 0.3% of those affected were in the mild, moderate, severe, and very severe groups, respectively. Overall, the prevalence of first graders was slightly higher than that of six graders (11.8% vs. 10.6%, p<0.01). There was no apparent difference in prevalence between boys and girls. The prevalence of AD in Japanese elementary school children was about 10%, with three-quarters of those being mildly affected.

We also conducted a prevalence survey on adult AD using the medical examination results for 2,943 (1,759 men and 1,184 women) workers of two universities in Tokyo and Osaka in 2004 and 2007, respectively. The prevalence of AD was 6.3% overall, and 9.4%, 8.3%, 4.8%, and 2.5% for those in their 20s, 30s, 40s, and 50s/60s (Fig. 2), respectively. The prevalence for those in their 30s was significantly higher than for those in their 40s. The prevalence was significantly higher for women than for men (8.4% vs. 4.8%). Overall, 78.9%, 17.3%, 2.7%, and 1.1% of those affected were in the mild, moderate, severe, and very severe groups, respectively. In 1999, Plunkett et al. reported the prevalence of AD based on clinical examinations of adults in central Victoria, Australia. Interestingly, their results and ours suggested the same tendency. A total of 1,457 people (670 men and 787 women) were examined and the prevalence of AD was 6.9% overall, and 5.7% and 8.1% for men and women, respectively. The prevalence decreased with age and 82.8% of the cases were classified as mild.

**Diagnosis**

A. Diagnostic Criteria of the JDA

Based on the “Definition and Diagnostic Criteria for AD” (revised in 2008) prepared by the JDA in 1994, patients meeting three basic criteria: 1) pruritus, 2) typical morphology and distribution of eczema, and 3) chronic or chronically relapsing course, are regarded as having AD (Table 1). Eruption is symmetrically distributed, and frequently develops on the forehead, periorbital area, perioral area, lips, periauricular area, neck, joint areas of limbs, and trunk. Its distribution is characterized by age. During infancy, eruptions initially appears on the scalp and face, often expanding to the trunk and limbs. They appear in AD-specific sites during childhood, such as the neck, and the flexural surfaces of the arms and legs. During adolescence/adulthood, they become marked on the upper body, including the face.

B. Diagnostic Criteria of Hanifin and Rajka

The diagnostic criteria defined by Hanifin and Rajka in 1980 are frequently used worldwide. One of the differences between their criteria and the JDA criteria is that a personal or family history of atopic diseases 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).

**Severity Classification**

A. Severity Classification for the Whole Body

The classification of the severity of AD prepared by the Severity Classification-Reviewing Committee of the JDA is available for clinical studies because its statistical reliability and usefulness have been verified (Fig. 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 five body sites (head/neck, anterior trunk, posterior trunk, upper limbs, and lower limbs). The areas of eruption in the five body sites are also evaluated, and both scores are totalized (Fig. 3). Internationally, the Severity Scoring of AD (SCORAD) established by the European Task Force on AD and the Eczema Area and Severity Index (EASI) in the USA are widely used.

B. Severity of Eruption

The primary treatment, application of a topical corticosteroid, should be determined based on “the severity of each eruption” (Table 2). Briefly, potent topical therapy is selected to treat severe eruption even when its extent is narrow. However, it is not required for patients with mild eruption even when its area is extensive. Therefore, “the severity of each eruption” is the most important factor to consider when selecting topical therapy.

**Examination for Diagnosis and Severity Assessment**

A. Serum IgE Level

Total serum IgE levels are high in about 80% of AD.
patients. This parameter is useful for diagnosis. The total serum IgE level reflects the long-term severity and activity of AD, but not its short-term changes. IgE antibodies may be produced in AD patients in response to several allergens such as mites, house dust, pollen, fungi, and foods.

B. Peripheral Blood Eosinophil Counts, Serum Lactate Dehydrogenase (LDH) Levels, and TARC Levels

The parameters of the short-term severity and activity of AD include the peripheral blood eosinophil count, serum Lactate Dehydrogenase (LDH) Levels, and TARC Levels.
rum LDH level, and TARC level. The serum TARC level more sensitively reflects AD activity than the serum IgE level, LDH level, and peripheral blood eosinophil count. It may also be possible to review patient education and treatments by using the serum TARC level as a parameter.

Treatments

A. Goal of Treatment

The goal of treatment is to reach and maintain a state in which symptoms are absent or mild without daily activities being disturbed by AD and drug therapy not being required. Even when this level is not reached, the objective is to maintain a state in which the symptoms are mild without rapid exacerbations that afflict daily activities.

B. Treatment Measures

Treatment measures for AD basically consist of drug therapy, skin care, and elimination of exacerbating factors. These measures are important, and should be adequately combined for individual patients.

C. Drug Treatment

Drugs that potently reduce AD-related inflammation in the skin are topical corticosteroids and tacrolimus. It is most important to promptly and accurately reduce inflammation related to AD by using these topical anti-inflammatory drugs. Topical corticosteroids are classified into five ranks: strongest, very strong, strong, medium, and weak. It is important to adequately select drugs at a rank that matches the severity of each eruption (Table 2). Generally, in infants/children, topical corticosteroids one rank lower than that presented in Table 2 should be used when the severity of eruption is evaluated as severe or moderate. Tacrolimus ointment is available at the following concentrations: 0.1% for adults and 0.03% for children. The efficacy of 0.1% tacrolimus ointment is similar to that of strong topical corticosteroids. Irritative symptoms such as a transient burning sensation often appear at the site of application. However, most of these symptoms disappear with amelioration of the eruption. Tacrolimus ointment is frequently indicated for the face and neck. There is increasing evidence to show that the use of tacrolimus ointment does not increase the risk of skin cancer or lymphoma. Proactive therapy refers to a treatment method in which, after inducing remission, topical corticosteroids or tacrolimus ointment is intermittently applied to the skin in addition to skin care with moisturizers in order to maintain remission.

Histamine H1 receptor antagonists (antihistamines) are widely used to treat AD-related pruritus; however, their effects vary among patients. The oral administration of antihistamines is recommended as adjuvant therapy. The use of non-sedative second-generation antihistamines rather than sedative first-generation antihistamines is recommended because no differences have been reported in treatment responses, and the incidences of adverse reactions, such as sleepiness, malaise, and impaired performance, are low.

In 2008, the use of cyclosporine was approved for severe adult AD patients who do not respond to conventional treatments and have eruptions with marked inflammation involving 30% or more of the body surface area. The initial dose of this drug is 3 mg/kg/day and its administration should be completed in 8 to 12 weeks. It is important to promptly switch cyclosporine therapy to conventional topical anti-inflammatory drugs after the improvement of symptoms. Intermittent administration involving a 2-week or much longer period of discontinuation should be conducted if long-term administration is necessary.

D. Skin Care

The water content of the stratum corneum is reduced in AD patients, leading to dry skin and reduced skin barrier function. The use of moisturizers for the dry skin reverses the reduction in the water content of the stratum corneum, promoting recovery of the skin barrier function, preventing the recurrence of dermatitis, and inhibiting pruritus.

E. Elimination of Exacerbating Factors

Daily/social life-related exacerbating factors specific to individual patients exist in most cases. It is important to investigate and eliminate such factors. For example, contact allergies to topical drugs, cosmetics, perfumes, metals, and shampoos may exacerbate skin eruptions. It is necessary to establish whether eruptions subside by avoiding contact with suspected substances, make a definitive diagnosis based on patch tests, and avoid them.

F. Ultraviolet (UV) Therapy

Ultraviolet (UV) therapy is considered for patients with severe AD who do not respond to treatments with topical anti-inflammatory drugs, antihistamines, and moisturizers. In Japan, irradiation systems for narrow-band UVB therapy with a peak of 311 nm have been installed in an increasing number of hospitals and clinics. This therapy may be applied further because of its safety and the lack of a need for post-treatment light shielding.

G. Hospital Care/Education

Hospital care is indicated for some severe cases in
which the area of eruption is extensive. Such care may make it possible to thoroughly conduct intensive topical therapy with isolation from the daily environment, establish a healthcare professional-patient relationship of mutual trust, and review exacerbating factors. In AD patients, insufficient understanding of their condition and anxiety often lead to inappropriate treatments. Previous studies have indicated that several sessions of a multioccupational patient population education program involving physicians and nurses can markedly ameliorate the severity of eruption.

H. Adherence

In medical care for AD, it is important for patients and their families to understand the significance of treatments, positively participate in the selection of therapeutic strategies, accomplish treatments, and improve the will to continue treatments, that is, adherence to treatments. Health care professionals should explain the necessity of drug therapy and skin care to patients and motivate them.

I. Treatment Procedures

Treatment procedures for AD are shown in Figure 4. After making an accurate diagnosis and evaluating the disease severity, appropriate treatment methods should be presented to patients in accordance with the state of eruption.

J. Treatments in the Future

Finally, new treatments that are now undergoing clinical trials and will possibly be available in the future will be mentioned. Dupilumab is a monoclonal antibody against IL-4 receptor α and inhibits signaling of IL-4 and IL-13. Simpson et al. reported the results of two identically designed phase 3 trials of dupilumab monotherapy in adult patients with moderate-to-severe AD. Duplimab clearly improved the signs and symptoms of AD, including pruritus, symptoms of anxiety and depression, and quality of life compared with a placebo. CIM331 is an anti-human IL-31 receptor A antibody. Nemoto et al. reported that a single subcutaneous administration of CIM331 decreased pruritus, sleep disturbance and topical use of hydrocortisone in AD patients. OPA-15406 is a novel topical phosphodiesterase-4 (PDE4) inhibitor, and is expected to reduce AD-related inflammation because peripheral leukocytes of AD patients have elevated PDE4 activity. Hanifin et al. demonstrated that OPA-15406 provided rapid and sustained relief of patient-reported pru-
ritus and significant overall improvement of mild-to-moderate AD\textsuperscript{12}. Tofacitinib is a small molecule Janus kinase (JAK) inhibitor that has been shown to inhibit cytokines such as IL-4, Bissonne et al. reported that topical tofacitinib showed significantly greater efficacy vs. vehicle across end points, with early onset of its effect and safety comparable to a vehicle in patients with mild-to-moderate AD\textsuperscript{12}.

**Conflict of Interest:** The author declare no conflict of interest.

**References**


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29. European Task Force on Atopic Dermatitis: Severity scor-