Guideline Article

International Journal of
Dermatology and Venereology

OPEN

Guidelines for Diagnosis and Treatment of Atopic Dermatitis in China (2020)[#]

Atopic Dermatitis Working Group, Immunology Group, Chinese Society of Dermatology, Xu Yao[1], Zhi-Qiang Song[2], Wei Li[3], Yun-Sheng Liang[4], Yan Zhao[5], Hua Cao[6], Tao Chen[7], Xue Chen[5], Ai-Ping Feng[8], Song-Mei Geng[9], Heng Gu[1], Shu-Ping Guo[10], Yan-Ling He[11], Ye-Hong Kuang[12], Chun-Ying Li[13], Xiao-Hong Li[14], Zheng-Xiao Li[9], Jun-Qin Liang[15], Hong-Ye Liu[10], Ling-Ling Liu[16], Yu-Mei Liu[17], Zhi Liu[18], Hai Long[19], Qian-Jin Lu[19], Yan Lu[20], Xiao-Qun Luo[3], Xiao-Yan Lv[21], Lin Ma[22], Zhu Shen[23], Xin Shi[24], Zhong-Xiang Shi[25], Xiang-Yang Su[26], Qing Sun[27], Jian-Ping Tang[28], Ao-Xue Wang[29], Hui-Ping Wang[30], Jian-Qin Wang[17], Ming-Yue Wang[16], Zai-Xing Wang[31], Yu-Min Xia[9], Ting Xiao[32], Zhi-Qiang Xie[33], Huan Xing[22], Ying Xiong[34], Zi-Gang Xu[22], Bin Yang[4], Zhi-Rong Yao[35], Jian-Bin Yu[14], Nan Yu[36], Kang Zeng[37], Jian-Zhong Zhang[5], Jun-Ling Zhang[38,*], Hua Zhao[39], Zuo-Tao Zhao[16], Wei Zhu[40], Ying-Hua Zhu[41], Ying Zou[42]

[1] Hospital for Skin Diseases (Institute of Dermatology), Chinese Academy of Medical Sciences, Nanjing, Jiangsu 210042, China; [2] Southwest Hospital of Military Medical University, Chongqing 400038, China; [3] Huashan Hospital, Affiliated with Fudan University, Shanghai 200040, China; [4] Dermatology Hospital of Southern Medical University, Guangzhou, Guangdong 510091, China; [5] Peking University People's Hospital, Beijing 100044, China; [6] Ruijin Hospital, Affiliated with Shanghai Jiaotong University, Shanghai 310000, China; [7] Chengdu Second People's Hospital, Chengdu, Sichuan 610017, China; [8] Union Hospital Affiliated with Tongji Medical College of Huazhong University of Science and Technology, Wuhan, Hubei 430022, China; [9] The Second Affiliated Hospital of Xi'an Jiaotong University, Xi'an, Shaanxi 710004, China; [10] First Hospital of Shanxi Medical University, Taiyuan, Shanxi 030012, China; [11] Beijing Chao-Yang Hospital, Capital Medical University, Beijing 100027, China; [12] Xiangya Hospital, Central South University, Changsha, Hunan 410008, China; [13] Xijing Hospital, Fourth Military Medical University, Xi'an, Shaanxi 710032, China; [14] The First Affiliated Hospital of Zhengzhou University, Zhengzhou, Henan 450052, China; [15] People's Hospital of Xinjiang Uygur Autonomous Region, Wulumuqi, Xinjiang 830001, China; [16] Peking University First Hospital, Beijing 100034, China; [17] Guangzhou Institute of Dermatology, Guangzhou, Guangdong 510095, China; [18] The Affiliated Hospital of Guizhou Medical University, Guiyang, Guizhou 550004, China; [19] The Second Xiangya Hospital of Central South University, Changsha, Hunan 410011, China; [20] The First Affiliated Hospital of Nanjing Medical University, Nanjing, Jiangsu 210029, China; [21] West China Hospital, Sichuan University, Chengdu, Sichuan 610041, China; [22] Beijing Children's Hospital, Capital Medical University, Beijing 100045, China; [23] Sichuan Academy of Medical Sciences & Sichuan Provincial People's Hospital, Chengdu, Sichuan 610072, China; [24] The Second Affiliated Hospital of Soochow University, Suzhou, Jiangsu 215004, China; [25] Shandong Provincial Dermatology Hospital, Jinan, Shandong 250022, China; [26] The Third Affiliated Hospital of Sun Yat-sen University, Guangzhou, Guangdong 510630, China; [27] Qilu Hospital of Shandong University, Jinan, Shandong 250012, China; [28] Hunan Children Hospital, Changsha, Hunan 410007, China; [29] The Second Affiliated Hospital of Dalian Medical University, Dalian, Liaoning 116027, China; [30] General Hospital, Tianjin Medical University, Tianjin 300052, China; [31] First Affiliated Hospital of Anhui Medical University, Hefei, Anhui 230022, China; [32] The First Hospital of China Medical University, Shenyang, Liaoning 110001, China; [33] Peking University Third Hospital, Beijing 100191, China; [34] Linyi People's Hospital, Linyi, Shandong 276003, China; [35] Xinhua Hospital, Affiliated with Shanghai Jiaotong University School of Medicine, Shanghai 200092, China; [36] General Hospital of Ningxia Medical University, Yinchuan, Ningxia 750021, China; [37] Nanfang Hospital, Southern Medical University, Guangzhou, Guangdong 510515, China; [38] Tianjin Academy of Traditional Chinese Medicine Affiliated Hospital, Tianjin 300120, China; [39] The First Medical Center, Chinese PLA General Hospital, Beijing 100048, China; [40] Xuanwu Hospital, Capital Medical University, Beijing 100053, China; [41] Dalian Dermatosis Hospital, Dalian, Liaoning 116021, China; [42] Shanghai Dermatology Hospital, Shanghai 200443, China.

[#] *The Guidelines in Chinese were published on Chinese Journal of Dermatology, 2020,53(2): 81-88.*

* *Corresponding authors: Prof. Heng Gu, Hospital for Skin Diseases (Institute of Dermatology), Chinese Academy of Medical Sciences, Nanjing, Jiangsu 210042, China. E-mail: guheng@aliyun.com; Prof. Jian-Zhong Zhang, Peking University People's Hospital, Beijing 100044, China. E-mail: rmzjz@126.com*

Conflicts of interest: The authors reported no conflicts of interest.

International Journal of Dermatology and Venereology (2021) 4:1

Received: 10 September 2020, Accepted: 11 January 2021

doi: 10.1097/JD9.0000000000000143

Abstract
Atopic dermatitis (AD) is a common disease clinically characterized by chronic recurrent eczematous lesions, dry skin, and pruritus. AD can negatively impact patients' quality of life. The prevalence of AD in China has been increasing during the past few decades. Based on the most recent advances in the treatment of AD, we updated the 2014 version of the Guidelines for Diagnosis and Treatment of Atopic Dermatitis in China regarding the definition, epidemiology, pathogenesis, clinical classification, diagnosis, prevention, and treatment of AD.

Keywords: atopic dermatitis, diagnosis, therapy, guideline

Introduction

AD, also known as atopic eczema, is a chronic, recurrent, and inflammatory skin disease. AD is usually considered a systemic disease because it is often concomitant with other atopic diseases such as asthma or allergic rhinitis. As the clinical symptoms of AD are particularly characterized by intense pruritus, the disease can substantially impact patient's health-related quality of life. The prevalence of AD has been increasing globally in recent decades, and ranges from 10% to 20% among children in developed countries.[1] The prevalence of AD in China has also increased rapidly during the past 10 years, although this increase occurred later in China than in Japan,[2] Korea,[3] and western developed countries. The prevalence of AD diagnosed using the Williams criteria was 0.7% in adolescents (aged 6–20 years) in China in 1998.[4] The prevalence of AD among preschool children (aged 1–7 years) in 10 cities in mainland China was 2.78% in 2002,[5] and the prevalence of AD in children in Shanghai was 8.3% in 2012.[6] The most recent survey carried out in China in 2014 reported a clinical diagnosis-based prevalence of AD of 12.94% in children aged 1–7 years[7] and 30.48% in infants aged 1–12 months.[8]

To provide guidance for the diagnosis and treatment of AD in China, the Chinese Society of Dermatology Immunology Group developed the 1st and 2nd versions of the Guidelines for the Diagnosis and Treatment of Atopic Dermatitis in China in 2008 and 2014, respectively. Considering the rapid advances in the diagnosis and treatment AD in the past 6 years globally and in China, the Chinese Society of Dermatology Immunology Group and Collaborative Research Center of Atopic Dermatitis created an expert panel to develop this updated revision of the Guidelines for the Diagnosis and Treatment of Atopic Dermatitis in China. This updated version will help guide the clinical practice of doctors and medical staff working in the field of dermatology.

Etiology and pathogenesis

Genetic and environmental factors play important roles in the development of atopic dermatitis (AD).[9] A family history of atopic diseases is the strongest risk factor for AD,[7] while genetic factors primarily influence both the skin barrier function and the balance of the immune response. Skin barrier dysfunction in AD usually comprises filaggrin loss-of-function mutations.[10] Most patients with AD have multiple abnormal immunities that are based on the activation of T-helper type 2 (Th2) cells. Environmental factors associated with AD include climate changes, changes in lifestyle, inappropriate bathing, microbial infection, and allergen irritation.[11] The modern lifestyle (such as excessive hygiene practices and the consumption of western-style foods) and environmental exposure (to irritants such as air pollution and cigarette smoke) may be involved in the pathogenesis of AD by inducing dysfunction of the immune system and skin barrier function via epigenetic modification.[12-13] Moreover, psychological factors (such as stress, anxiety, and depression) also play a certain role in AD.[9,14]

Although the mechanism by which AD develops is not yet fully understood, current evidence suggests that the pathogenetic process of AD involves immune deviation, skin barrier dysfunction, and skin microbial dysbiosis. Th2-type inflammation is characteristic of AD. The important cytokines mediating the development of AD are interleukin (IL)-4 and IL-13,[15] which mainly originate from Th2 cells, as well as basophils and group 2 innate lymphoid cells. In the chronic phase of AD, the lesions contain a mixed infiltration of Th1, Th17, and Th22 cells.[16] Barrier dysfunction due to filaggrin loss-of-function mutations is conducive to the penetration of environmental antigens, which initiates skin inflammation in AD.[17] Langerhans cells and dermal dendritic cells also participate in transcutaneous sensitization, resulting in IgE production.[18–20] Th2 cytokines inhibit the expression of barrier-related proteins in keratinocytes, which further attenuates the skin barrier function.[21] The skin lesions or normal-appearing skin in patients with AD often show microbial dysbiosis characterized by an increased abundance of *Staphylococcus aureus* and a decrease in microbial diversity.[22] Abnormal metabolism due to skin microbiota further facilitates skin inflammation.[23] Repeat scratching also aggravates and prolongs the skin inflammation, as scratching not only stimulates keratinocytes to produce pro-inflammatory cytokines, but also releases self-antigens that induce production of the corresponding IgE antibody.[24] Moreover, the development of skin inflammation in AD involves non-immune factors, such as neuroendocrine factors.[9,14,25]

Clinical manifestations

AD usually begins in infancy, and more than 50% of patients with AD develop the disease in their first year of

life. However, adult patients with incipient AD are not rare. AD is a chronic inflammatory condition with varying manifestations that are primarily characterized by dry skin, chronic eczematous lesions, and intractable pruritus. Of the patients with AD in China, 74.6% are classified as having mild AD, 23.97% as having moderate AD, and 1.44% as having severe AD.[6] Based on the age of onset, AD can be divided into four stages, namely infantile (3 months–2 years), childhood (2–12 years), adolescent/adult (12–60 years), and older age (>60 years). Each stage has specific manifestations. In the infantile stage, lesions initially primarily present as acute eczematous plaques on the face and scalp, and then spread to the flexural surfaces of the extremities. Infantile AD can persist into childhood, but new-onset AD during childhood is not uncommon. Lesions in the childhood stage are characterized by subacute or chronic rashes (thickened, dry, and lichenoid plaques) mainly involving the cubital fossa, popliteal fossa, and the flexural surfaces of the legs. The adolescent/adult stage is similar to the childhood stage, as lesions primarily present as subacute or chronic rashes, and prurigo-like plaques and lesions are common. The older age stage is a recently recognized specific stage in which AD is characterized by generalized lesions or even erythroderma, more frequently affecting men than women.[26]

Based on the findings of laboratory examinations or the mechanism of inflammatory development, AD can be further categorized in two ways. First, AD can be categorized into extrinsic and intrinsic subtypes. Extrinsic AD is characterized primarily by a high level of IgE (>200 kU/L), a family history of atopic diseases, and an increase in levels of IgE specifically against certain foods and/or aeroallergens; intrinsic AD is characterized by a normal level of IgE (<200 kU/L), no history of atopic diseases, and no allergen-specific IgE.[27] Second, AD can be categorized into inflammatory models primarily initiated by Th2 cells, Th22 cells, Th17 cells, Th1 cells, or a mixture of these cell types. For example, both pediatric and adult patient populations harbor Th2-centered inflammation; pediatric AD shows significant Th17/Th22 cell involvement, but lacks the Th1 cell upregulation that is characteristic of adult AD. In Asian patients with AD, the inflammatory model comprises mixed Th2 and Th17 cells.[28]

The characteristic manifestations that are valuable for the diagnosis of AD include xerosis, ichthyosis, keratosis pilaris, palmar hyperlinearity, nonspecific hand-foot dermatitis, eczema papillae, cheilitis, recurrent conjunctivitis, Dennie Morgan infraorbital folds, infra-auricular fissures, periorbital shadows, pityriasis alba, pruritus during sweating, sensitivity to wool, excessive reaction to insect bites, and white scratches. Some patients with AD have concomitant allergic diseases, such as allergic asthma and allergic rhinoconjunctivitis. Data from studies performed in China indicate that 16.7% of patients with AD have a previous diagnosis of asthma, and 33.7% have concomitant allergic rhinoconjunctivitis. Moreover, the incidence of allergic diseases that affect organs other than the skin in patients with AD increase with age.[29] In addition, due to the long-term nature of the disease, patients with chronic AD are at high risk of developing mental/nervous disorders, inflammatory bowel disease, rheumatoid arthritis, cardiovascular disease, and lymphoma.[30–32]

Diagnosis

The diagnosis of AD should be considered for patients with eczematous lesions, and should be based on both clinical manifestations and the results of comprehensive physical examination. Further investigation may include the peripheral blood eosinophil count, serum total IgE level, allergen-specific IgE level, eosinophil cationic protein level, and patch testing when necessary. AD is a heterogeneous disease with various manifestations, and the diagnosis should be based on relevant diagnostic criteria.

The criteria widely used to diagnose AD are the Hanifin-Rajka criteria[33] and the U.K. Working Party's diagnostic criteria (also referred to as the Williams criteria). The Williams criteria include chronic skin pruritis (major criterion) plus three or more of the following minor criteria: (1) history of flexural dermatitis, including at the elbow, popliteal fossa, anterior ankle region, neck (including buccal rash in children younger than 10 years); (2) history of asthma or allergic rhinitis (or history of atopic diseases in first-degree relatives of children younger than 4 years); (3) history of generalized dry skin; (4) visible flexural eczema (eczema on the cheek/forehead and limbs of children younger than 4 years); (5) rash onset before the age of 2 years (for patients older than 4 years).[34]

Diagnostic criteria have also been proposed by the Chinese dermatologists Kefei Kang,[35] Jianzhong Zhang,[36] and Zhirong Yao.[8,27] The Chinese AD Diagnostic Criteria proposed by Zhang *et al*.[36] include the following items: (1) symmetrical eczema (dermatitis) for more than 6 months; (2) personal and/or family history of atopic diseases (including eczema, allergic rhinitis, asthma, and allergic conjunctivitis); (3) elevated total serum IgE level and/or allergen-specific IgE positivity and/or an increase in the peripheral blood eosinophil count. AD is diagnosed if the patient meets the first criterion, plus either of the second or third criteria. The sensitivity of Zhang's criteria is higher than that of the Hanifin-Rajka criteria and the Williams criteria for the diagnosis of AD in adolescents and adults.

The criteria for diagnosing AD in Chinese children proposed by Yao *et al*.[37] are: (1) pruritus; (2) typical morphology and distribution, or atypical morphology and distribution with xerosis; and (3) a chronic or chronically relapsing course. AD is diagnosed if the patient meets all three criteria. Typical morphology and distribution (flexural dermatitis) includes facial and extensor involvement in children. Atypical morphology and distribution includes: (1) typical eczematous lesions in non-flexural locations (such as scalp dermatitis, eyelid eczema, nipple eczema, vulvar eczema, nummular eczema, fingertip

eczema, non-specific hand or foot dermatitis/atopic winter feet, nail or perinail eczema, and eczematous lesions in other parts of the body); (2) atypical eczematous lesions, such as pityriasis alba, cheilitis, infra-auricular and retroauricular fissuring/infranasal fissuring, prurigo, pompholyx, and the papular lichenoid variant. The sensitivity of this diagnostic criteria for AD in children is higher than that of the Hanifin-Rajka criteria and the Williams criteria. The Williams criteria has been widely used in China during the past few years. The criteria proposed by Zhang *et al*.[36] are recommended for the diagnosis of adult/adolescent AD, while the criteria proposed by Yao *et al*.[37] are recommended for the diagnosis of childhood AD.

It is not difficult to diagnose AD in patients with typical manifestations. However, most patients do not have typical clinical manifestations. In such cases, the possibility of AD should be considered and careful medical history taking and comprehensive medical examinations, including laboratory examinations. Some patients also need long-term follow-up.

The differential diagnoses for AD include seborrheic dermatitis, contact dermatitis, psoriasis, ichthyosis, scabies, parapsoriasis, hypereosinophilic dermatitis, cutaneous T cell lymphoma, Netherton syndrome, hyperimmunoglobulin E syndrome, Langerhans cell histiocytosis, Wiskott-Aldrich syndrome, and AD-like graft-versus-host disease. There are many methods used to evaluate the severity of AD, such as the scoring of AD (SCORAD), eczema area and severity score index, investigators global assessment, and visual analog scale. The SCORAD value is used to classify the severity of AD as mild (SCORAD: 0–24), moderate (SCORAD: 25–50), and severe (SCORAD: >50).[38] An evaluation of the disease severity can be used as a reference for treatment.

Treatment

The goal of AD treatment is to alleviate or eliminate clinical symptoms, eradicate triggers and/or aggravating factors, reduce and prevent recurrence, mitigate comorbidities, and improve the patient's quality of life. With appropriate treatment and disease management, the symptoms of AD can be completely relieved or significantly improved, enabling the patient to lead a normal life.

Patient education

As AD is a chronic recurrent disease that requires long-term treatment, it is important to establish a good doctor-patient relationship and to obtain a good treatment effect by managing the disease properly. The physician should explain to the patient and their family the nature of the disease, its clinical features, and precautions that should be undertaken. A detailed analysis of the patient and their family should be made to identify etiological and aggravating factors (including nonspecific triggers and specific allergen triggers), and patients should avoid exposure to triggers and exogenous allergens. A comprehensive assessment of the patient's medical history, duration of illness, and the area and severity of lesions should be conducted to select the optimal therapeutic regimen to control the disease in the short-term. Clinicians should also explain how to use the medication, the expected efficacy, and possible adverse effects. During follow-up, clinicians should carefully evaluate the average condition to enable timely adjustments of the treatment and maintenance of the asymptomatic status for as long as possible by initiating proactive treatment to reduce recurrence.[39]

Basic treatment

Cleansing and bathing

The skin must be cleansed gently to get rid of crusts and bacterial contaminants in case of bacterial superinfection. Cleansers with non-irritant and low-allergen formulas are recommended, preferably with a pH close to the normal epidermal pH (about 6).[40] The water temperature should be (27–30)°C, and the bathing time should be limited to 5–10 minutes. Adding antiseptics such as sodium hypochlorite to the bathwater may be useful for the treatment of AD in patients with an infection tendency[41]; the suggested frequency is once daily or every other day.

Restoration and retention of the normal skin barrier

Emollients are the mainstay of AD management.[42–44] The use of emollients for dry skin reverses the reduction in the water content of the stratum corneum, thereby promoting recovery of the skin barrier function, preventing allergen invasion, relieving pruritus, and reducing the recurrence and severity of dermatitis.[45] Patients should select emollients based on their own skin condition, and sufficient and frequent use is necessary.[46] Emollients that are rich in lipids are a good choice during the dry and cold winter period. Emollients should be applied directly after a bath or a shower following gentle drying, when the skin is still slightly humid. Large quantities are usually required (up to 100 g per week for young children, and up to 250 g for adults).[47]

Environmental control

It is essential to avoid all kinds of mechanic and chemical irritants, such as scratching, friction, wool, acid, and bleaches. It is also important to refrain from over-drying and avoid high temperatures. The optimal ambient temperature is 18–22 °C. Sweat should be removed as soon as possible. Airborne allergens should be eliminated from the surroundings as much as possible.

Dietary intervention

Food allergy has been documented in approximately one-third of children with moderate to severe AD.[48] According to the recommendations of the National Institute of Allergy and Infectious Diseases, limited food allergy testing (of cow's milk, eggs, wheat, soy, and peanut) should be considered for children with moderate to severe AD who

are younger than 5 years.[49] Food allergy is less common in children older than 5 years; when suspected, the choice of food for testing should be based on the clinical history. Tree nuts, shellfish, and fish become relevant in subsequent childhood years. In older children, adolescents, and adults, pollen-related food allergy should be considered; for example, those with a birch pollen allergy may develop oral allergy syndrome upon exposure to apples, celery, carrots, and hazelnuts. If there is a consistent correlation of symptoms, the suspected food should be avoided during a diagnostic elimination diet for 4 to 6 weeks.[49] If the elimination diet does not result in improvement, the suspected food should not be avoided; this is especially important for children, as blind elimination of a food may lead to weight loss, poor growth, and calcium deficiency.

Avoidance of contact allergens

Allergic contact anaphylaxis is common in patients with AD, with a prevalence of about 6% to 60%. Common exposure allergens are nickel, neomycin, fragrances, formaldehyde, preservatives, lanolin, and rubber. Patients with AD are advised to avoid these allergens as much as possible.[50]

Topical treatment

Topical corticosteroids (TCS)

The application of TCS is the first-line therapy for mild-to-moderate AD. To effectively control inflammation and alleviate symptoms, different formulations and potencies of TCS should be chosen in accordance with the location, type, and area of lesions. TCS are generally classified into four grades: very potent (0.1% fluocinolone acetonide cream, 0.05% clobetasol cream), potent (0.05% halometasone cream, 0.05% betamethasone dipropionate cream, 0.1% betamethasone valerate cream, 0.05% betamethasone dipropionate cream, 0.1% betamethasone valerate cream, 0.25% desoximetasone ointment and cream), moderate (0.05% fluticasone propionate cream, 0.1% mometasone furoate, 0.1% hydrocortisone butyrate cream, 0.1% triamcinolone cream), and mild (hydrocortisone cream, 0.05% desonide cream/ointment).[51] It is crucial to administer appropriate TCS, promptly proceed with remission induction therapy to reduce inflammation within a few days, and switch to a less potent TCS or topical calcineurin inhibitor (TCI) once the inflammation is controlled. Mild or moderate TCS are recommended for short-term use in some special parts such as the face, neck, and skin folds. Occlusive dressings can be used for hypertrophic lesions.[52] For effective symptom control, short-term (usually 3 days, less than 14 days) wet wrap therapy is recommended for acute, generalized, severe, or refractory lesions, especially for children who are not suitable for systemic medication.[53-54] However, long-term extensive use of TCS may result in skin and systemic adverse reactions.

Patients with moderate-to-severe or relapse-prone AD should switch to long-term proactive treatment after all lesions have been successfully treated. This involves the application of TCS or a TCI twice a week to the previously affected skin areas, together with the use of emollients on the entire body, which is effective in reducing relapses and topical glucocorticoid usage.[55-56]

Many patients are overly concerned about the adverse effects of topical glucocorticosteroids, and may even refuse to use them. To reassure patients and improve medication compliance, clinicians should clearly explain the safety of standardized use, duration of treatment, and the medication adjustment method.

TCIs

TCIs are important anti-inflammatory drugs for the treatment of AD. TCIs are indicated for lesions on the face, neck, skin folds, breasts, and the anal and genital areas. In addition to controlling skin inflammation and pruritus, proactive treatment with TCIs reduces recurrence.[57] Patients with mild-to-moderate AD should use 1% pimecrolimus ointment,[58] while patients with moderate-to-severe AD should use 0.03% (for children) and 0.1% (for adults) tacrolimus ointment. Long-term usage of TCIs does not cause skin barrier disruption or skin atrophy. The common adverse reactions are burning sensation and stinging at the application site, which gradually disappears with prolonged use in most patients. Because of the irritation, it is recommended that TCS should be considered first to ameliorate acute symptoms before switching to TCI maintenance therapy.[59]

Other topical medications: Drugs such as zinc oxide oil (paste) or black bean distillation oil ointment are effective for AD. Normal saline and other wet compress drugs are also efficacious in controlling the oozing of acute AD lesions. Topical phosphodiesterase 4 inhibitor ointment is approved in the United States for the treatment of mild-to-moderate AD in patients older than 2 years.[60]

Systemic treatment

Oral antihistamines

Nonsedating, second-generation antihistamines are recommended as an adjuvant to relieve pruritus in patients with AD, especially those with allergic comorbidities like urticaria or allergic rhinitis. Increased doses are acceptable when necessary. First- or second-generation antihistamines are an option for patients with intense pruritus or sleep disturbance. Considering the adverse effects of first-generation antihistamines on sleep quality (delayed and reduced rapid eye movement) and learning and cognitive ability, long-term use of first-generation antihistamines is not recommended, particularly in children.[61]

Immunosuppressants

Immunosuppressants are recommended for patients with severe AD refractory to conventional regimens, and the recommended duration of immunosuppressant therapy is more than 6 months. The indications and contraindications of immunosuppressants should be considered, and patients should be closely monitored for adverse effects.[62]

Cyclosporine is the most commonly used immunosuppressant in the treatment of AD, and the initial dose is 3–5 $mg \cdot kg^{-1} \cdot d^{-1}$. Once the inflammation is under control, the dosage should be tapered down to a minimum dose (0.5–1 $mg \cdot kg^{-1} \cdot d^{-1}$) to maintain remission. The recommended course of treatment is no more than 2 years, and intermittent therapy is also feasible.[63] During treatment, the blood pressure, renal function, and blood concentration of cyclosporine should be monitored regularly. Phototherapy should be avoided during cyclosporine treatment.

Methotrexate should be taken at a dosage of 10–15 mg weekly, either as one dose or two divided doses. History of liver diseases and alcohol consumption should be assessed before starting treatment.

Azathioprine should be taken at a dosage of 50–100 mg per day, starting from a low dose. Genetic testing for thiopurine methyltransferase activity should be performed before prescribing azathioprine,[64] and close attention should be paid to routine blood tests during treatment. If leukopenia or anemia occur, azathioprine should be stopped immediately.

Oral glucocorticosteroids

In principle, it is recommended to avoid using oral glucocorticosteroids or to use them as little as possible. Short-term treatment with oral glucocorticosteroids can be used to treat an acute flare-up in patients with severe AD or AD refractory to other regimens. According to the 2014 American Academy of Dermatology guidelines for AD, the recommended dosage range is 0.5 to 1.0 $mg \cdot kg^{-1} \cdot d^{-1}$.[65] Considering the actual use of glucocorticosteroids in China, the recommended dosage is 0.5 $mg \cdot kg^{-1} \cdot d^{-1}$ (for methylprednisolone). Tapering and discontinuation is recommended once the condition improves. For some refractory cases, treatment with glucocorticosteroids followed by immunosuppressant or ultraviolet light (UV) therapy should be considered. Long-term glucocorticosteroid use should be avoided to prevent or minimize adverse effects.[62]

Biological agents

Dupilumab is a fully human monoclonal antibody against the alpha chain of the IL-4/13 receptor,[62] which blocks the biological effects of IL-4 and IL-13. Dupilumab has shown strong efficacy in adult patients with moderate-to-severe AD,[15] and has been approved for use in Europe and the United States. The first injection dosage is 600 mg subcutaneously, followed by 300 mg every other week, and efficacy is shown at 4–6 weeks. Dupilumab can be also used for long-term maintenance therapy in combination with topical medications and emollients. Conjunctivitis is a common adverse effect of dupilumab.[62]

Janus kinase (JAK) inhibitors

JAK inhibitors block a variety of signals involved in the immune response and inflammation. Both oral and topical JAK inhibitors have shown good efficacy. Baricitinib antagonizes JAK1 and JAK2. Adult patients with moderate-to-severe AD receiving baricitinib (4 mg/d) together with TCS for 16 weeks achieved a 61% reduction in the eczema area and severity score index 50.[66] Upadacitinib, a selective JAK1 inhibitor, has also been shown to be effective for moderate-to-severe AD in adults.[67] Four weeks of topical tofacitinib ointment (a selective JAK1 and JAK3 inhibitor) twice a day resulted in the resolution or near-resolution of mild-to-moderate AD lesions in 73% of patients.[68]

Others

In China, sodium thiosulfate and compound glycyrrhizin injections are used for symptom control during an acute flare-up of AD; however, high-quality evidence-based medical evidence is required to confirm the effectiveness of this treatment.

UV therapy

UV therapy is an effective treatment for chronic, lichenified lesions in adults with moderate-to-severe AD, pruritus control, and maintenance therapy. Narrow-spectrum medium-wave ultraviolet (NB-UVB) and medium-to-high-dose UVA1, combined with TCS and emollients, are preferable due to their safety and effectiveness. NB-UVB is not recommended in the acute stage of AD, while UVA1 is efficacious in managing AD flare-ups.[69] Emollients should be used after phototherapy. Phototherapy should not be used for children younger than 12 years and those whose symptoms are exacerbated by sunlight exposure. UV therapy should not be used in combination with TCIs.

Treatment of pruritus

Pruritus is the most significant symptom of AD. Pruritus may cause sleep disturbance or even physical and mental problems, markedly affecting the life quality of patients. In addition, the vicious "itch-scratch" cycle may induce and exacerbate AD, which makes pruritus control the main purpose of AD treatment. Pruritus is effectively managed with emollients, antihistamines, topical anti-inflammatory drugs, systemic anti-inflammatory drugs, biologics, and phototherapy. For chronic intractable pruritus (especially intense pruritus at night) that has a poor response to the abovementioned treatments, the use of systemic antipruritic agents such asmirtazapine, pregabalin, paroxetine, and naltrexone could be considered; however, these agents have potential adverse effects.[62,70]

Antimicrobial therapy

Antibacterial therapy

AD lesions are colonized extensively by *S. aureus*, and TCS, TCIs, and sodium hypochlorite 0.005% baths can reduce *S. aureus* colonization. Short-term systemic or topical antibiotics should be considered only when there is evident infection. Systemic antibiotics like penicillin or first-generation cephalosporins are chosen in accordance

with the results of drug sensitivity testing. The use of topical antibacterial drugs should be limited to 1–2 weeks, as long-term use may lead to drug resistance and sensitization.

Antiviral therapy

Patients with AD are prone to severe viral skin infections. Eczema herpeticum should be treated actively with antiretrovirals such as acyclovir and valacyclovir.

Antifungal therapy

Malassezia spp. may contribute to the pathogenesis of AD with lesions distributed on the head and neck, and AD in patients with detectable IgE-mediated sensitization against *Malassezia*. In such cases, treatment with topical or systemic azole antifungals may be effective.[71]

Allergen-specific immunotherapy

Despite the low level of evidence and the heterogeneity of studies, numerous studies have showed that dust mite allergen-specific immunotherapy effectively improves the condition, reduces the disease severity and the frequency of recurrence, and lowers the risk of airway allergy, especially for patients with severe AD and an allergy to dust mites.[72-73] The recommended treatment period is more than 3 years.

Traditional Chinese medicine

Treatment is based on clinical symptoms and signs. The adverse effects of drugs should also be considered.

Stepwise treatment approach for AD

Basic treatment

The optimal management of AD involves health education, use of emollients, and avoidance of triggering factors (eg, nonspecific factors, allergens).

Mild AD

Appropriate TCS/TCIs should be selected in accordance with the lesions and the affected body area. Oral antihistamines should be taken when necessary to control allergic comorbidities (eg, urticaria, allergic rhinitis) or relieve itching. Antimicrobial therapy should be started if the skin becomes infected.

Moderate AD

Appropriate TCS/TCIs should be selected in accordance with the lesions and the affected body area, and wet wrap therapy should be used to control acute flare-ups if necessary. Proactive maintenance treatment consists of TCS/TCI and NB-UVB/UVA1 treatment.

Severe AD

Patients with severe AD should be hospitalized and treated with systemic immunosuppressants (such as cyclosporine, methotrexate, azathioprine, and mycophenolate mofetil) plus short-term treatment with glucocorticosteroids (to control acute severe refractory lesions), dupilumab, or UVA1/NB-UVB therapy.

References

[1] Weidinger S, Novak N. Atopic dermatitis. Lancet 2016;387 (10023):1109–1122. doi:10.1016/S0140-6736(15)00149-X.

[2] Takeuchi S, Esaki H, Furue M. Epidemiology of atopic dermatitis in Japan. J Dermatol 2014;41(3):200–204. doi:10.1111/1346-8138.12331.

[3] Choi WJ, Ko JY, Kim JW, et al. Prevalence and risk factors for atopic dermatitis: a cross-sectional study of 6,453 Korean preschool children. Acta Derm Venereol 2012;92(5):467–471. doi:10.2340/00015555-1252.

[4] Gu H, Yan Y, Chen K, et al. Survey on atopic dermatitis in China. Chin J Dermatol 2000;33(6):379. doi:10.3760/j.issn:0412-4030.2000.06.001.

[5] Gu H, You L, Liu Y, et al. Survey on the prevalence of childhood atopic dermatitis in ten cities of China. Chin J Dermatol 2004;37(1):29–31. doi:10.3760/j.issn:0412-4030.2004.01.011.

[6] Xu F, Yan S, Li F, et al. Prevalence of childhood atopic dermatitis: an urban and rural community-based study in Shanghai, China. PLoS One 2012;7(5):e36174. doi:10.1371/journal.pone.0036174.

[7] Guo Y, Li P, Tang J, et al. Prevalence of atopic dermatitis in Chinese children aged 1-7 ys. Sci Rep 2016;6:29751. doi:10.1038/srep29751.

[8] Guo Y, Zhang H, Liu Q, et al. Phenotypic analysis of atopic dermatitis in children aged 1-12 months: elaboration of novel diagnostic criteria for infants in China and estimation of prevalence. J Eur Acad Dermatol Venereol 2019;33(8):1569–1576. doi:10.1111/jdv.15618.

[9] Brown S, Reynolds NJ. Atopic and non-atopic eczema. BMJ 2006;332 (7541):584–588. doi:10.1136/bmj.332.7541.584.

[10] Palmer CN, Irvine AD, Terron-Kwiatkowski A, et al. Common loss-of-function variants of the epidermal barrier protein filaggrin are a major predisposing factor for atopic dermatitis. Nat Genet 2006;38:441e6. doi:10.1038/ng1767.

[11] Kantor R, Silverberg JI. Environmental risk factors and their role in the management of atopic dermatitis. Expert Rev Clin Immunol 2017;13 (1):15–26. doi:10.1080/1744666X.2016.1212660.

[12] Liang Y, Chang C, Lu Q. The genetics and epigenetics of atopic dermatitis-filaggrin and other polymorphisms. Clin Rev Allergy Immunol 2016;51(3):315–328. doi:10.1007/s12016-015-8508-5.

[13] Bin L, Leung DY. Genetic and epigenetic studies of atopic dermatitis. Allergy Asthma Clin Immunol 2016;12:52. doi:10.1186/s13223-016-0158-5.

[14] Akdis CA, Akdis M, Bieber T, et al. Diagnosis and treatment of atopic dermatitis in children and adults: European Academy of Allergology and Clinical Immunology/American Academy of Allergy, Asthma and Immunology/PRACTALL Consensus Report. Allergy 2006;61(8):969–987. doi:10.1111/j.1398-9995.2006.01153.x.

[15] Han Y, Chen Y, Liu X, et al. Efficacy and safety of dupilumab for the treatment of adult atopic dermatitis: a meta-analysis of randomized clinical trials. J Allergy Clin Immunol 2017;140(3):888–891.e6. doi:10.1016/j.jaci.2017.04.015.

[16] Dainichi T, Kitoh A, Otsuka A, et al. The epithelial immune microenvironment (EIME) in atopic dermatitis and psoriasis. Nat Immunol 2018;19(12):1286–1298. doi:10.1038/s41590-018-0256-2.

[17] Brunner PM, Guttman-Yassky E, Leung DY. The immunology of atopic dermatitis and its reversibility with broad-spectrum and targeted therapies. J Allergy Clin Immunol 2017;139(4S):S65–S165. doi:10.1016/j.jaci.2017.01.011.

[18] Luo Y, Wang S, Liu X, et al. Langerhans cells mediate the skin-induced tolerance to ovalbumin via Langerin in a murine model. Allergy 2019;74 (9):1738–1747. doi:10.1111/all.13813.

[19] Liang Y, Wang P, Zhao M, et al. Demethylation of the FCER1G promoter leads to FcεRI overexpression on monocytes of patients with atopic dermatitis. Allergy 2012;67(3):424–430. doi:10.1111/j.1398-9995.2011.02760.x.

[20] Liang Y, Yu B, Chen J, et al. Thymic stromal lymphopoietin epigenetically upregulates Fc receptor γ subunit-related receptors on antigen-presenting cells and induces TH2/TH17 polarization through dectin-2. J Allergy Clin Immunol 2019;144(4):1025–1035.e7. doi:10.1016/j.jaci.2019.06.011.

[21] Thyssen JP, Kezic S. Causes of epidermal filaggrin reduction and their role in the pathogenesis of atopic dermatitis. J Allergy Clin Immunol 2014;134(4):792–799. doi:10.1016/j.jaci.2014.06.014.

[22] Li W, Xu X, Wen H, et al. Inverse association between the skin and oral microbiota in atopic dermatitis. J Invest Dermatol 2019;139(8):1779–1787.e12. doi:10.1016/j.jid.2019.02.009.
[23] Yu J, Luo Y, Zhu Z, et al. A tryptophan metabolite of the skin microbiota attenuates inflammation in patients with atopic dermatitis through the aryl hydrocarbon receptor. J Allergy Clin Immunol 2019;143(6):2108–2119.e12. doi:10.1016/j.jaci.2018.11.036.
[24] Su H, Luo Y, Sun J, et al. Transglutaminase 3 promotes skin inflammation in atopic dermatitis by activating monocyte-derived dendritic cells via DC-SIGN. J Invest Dermatol 2020;140(2):370–379.e8. doi:10.1016/j.jid.2019.07.703.
[25] Lipozencić J, Wolf R. Atopic dermatitis: an update and review of the literature. Dermatol Clin 2007;25(4):605–612. doi:10.1016/j.det.2007.06.009.
[26] Lv T, Wang H. Recognition and management of senile atopic dermatitis. Chin J Dermatovenereol 2019;33(8):949–954. doi:10.13735/j.cjdv.1001-7089.201810075.
[27] Suárez-Fariñas M, Dhingra N, Gittler J, et al. Intrinsic atopic dermatitis shows similar TH2 and higher TH17 immune activation compared with extrinsic atopic dermatitis. J Allergy Clin Immunol 2013;132(2):361–370. doi:10.1016/j.jaci.2013.04.046.
[28] Chan TC, Sanyal RD, Pavel AB, et al. Atopic dermatitis in Chinese patients shows TH2/TH17 skewing with psoriasiform features. J Allergy Clin Immunol 2018;142(3):1013–1017. doi:10.1016/j.jaci.2018.06.016.
[29] Shi M, Zhang H, Chen X, et al. Clinical features of atopic dermatitis in a hospital-based setting in China. J Eur Acad Dermatol Venereol 2011;25(10):1206–1212. doi:10.1111/j.1468-3083.2010.03953.x.
[30] Andersen YM, Egeberg A, Gislason GH, et al. Autoimmune diseases in adults with atopic dermatitis. J Am Acad Dermatol 2017;76(2):274–280.e1. doi:10.1016/j.jaad.2016.08.047.
[31] Schmitt J, Schwarz K, Baurecht H, et al. Atopic dermatitis is associated with an increased risk for rheumatoid arthritis and inflammatory bowel disease, and a decreased risk for type 1 diabetes. J Allergy Clin Immunol 2016;137(1):130–136. doi:10.1016/j.jaci.2015.06.029.
[32] Thyssen JP, Hamann CR, Linneberg A, et al. Atopic dermatitis is associated with anxiety, depression, and suicidal ideation, but not with psychiatric hospitalization or suicide. Allergy 2018;73(1):214–220. doi:10.1111/all.13231.
[33] Hanifin JM, Rajka G. Diagnostic features of atopic dermatitis. Acta Derm Venereol 1980;92(Suppl):44–47.
[34] Williams HC, Burney PG, Hay RJ, et al. The U. K. Working Party's Diagnostic Criteria for Atopic Dermatitis. I. Derivation of a minimum set of discriminators for atopic dermatitis. Br J Dermatol 1994;131(3):383–396. doi:10.1111/j.1365-2133.1994.tb08530.x.
[35] Kang K, Tian R. Discussion on clinical features and diagnostic criteria of genetic allergic dermatitis. J Clin Dermatol 1986;2:60–63. (in Chinese).
[36] Liu P, Zhao Y, Mu ZL, et al. Clinical features of adult/adolescent atopic dermatitis and chinese criteria for atopic dermatitis. Chin Med J (Engl) 2016;129(7):757–762. doi:10.4103/0366-6999.178960.
[37] Cheng R, Zhang H, Zong W, et al. Development and validation of new diagnostic criteria for atopic dermatitis in children of China. J Eur Acad Dermatol Venereol 2020;34(3):542–548. doi:10.1111/jdv.15979.
[38] Severity scoring of atopic dermatitis: the SCORAD index. Consensus Report of the European Task Force on Atopic Dermatitis. Dermatology 1993;186(1):23. doi:10.1159/000247298.
[39] Wang S, Ma L. Treatment of atopic dermatitis: challenges and coping strategies. Chin J Dermatol 2018;51(1):69–71. doi:10.3760/cma.j.issn.0412-4030.2018.01.024.
[40] Burkhart CG. Clinical assessment by atopic dermatitis patients of response to reduced soap bathing: pilot study. Int J Dermatol 2008;47(11):1216–1217. doi:10.1111/j.1365-4632.2008.03829.x.
[41] Wong SM, Ng TG, Baba R. Efficacy and safety of sodium hypochlorite (bleach) baths in patients with moderate to severe atopic dermatitis in Malaysia. J Dermatol 2013;40(11):874–880. doi:10.1111/1346-8138.12265.
[42] Grimalt R, Mengeaud V, Cambazard F, et al. The steroid-sparing effect of an emollient therapy in infants with atopic dermatitis: a randomized controlled study. Dermatology 2007;214(1):61–67. doi:10.1159/000096915.
[43] Szczepanowska J, Reich A, Szepietowski JC. Emollients improve treatment results with topical corticosteroids in childhood atopic dermatitis: a randomized comparative study. Pediatr Allergy Immunol 2008;19(7):614–618. doi:10.1111/j.1399-3038.2007.00706.x.
[44] Eberlein B, Eicke C, Reinhardt HW, et al. Adjuvant treatment of atopic eczema: assessment of an emollient containing N -palmitoylethanolamine (ATOPA study). J Eur Acad Dermatol Venereol 2008;22(1):73–82. doi:10.1111/j. 1468-3083.2007.02351.x.
[45] Ma L. The role of emollients and home care in the treatment of atopic dermatitis. J Pract Dermatol 2008;1(1):1. doi:10.3969/j.issn.1674-1293.2008.01.034.
[46] Williams HC. Clinical practice. Atopic dermatitis. N Engl J Med 2005;352(22):2314–2324. doi:10.1056/NEJMcp042803.
[47] Wollenberg A, Szepietowski J, Taieb A, et al. Corrigendum: consensus-based European guidelines for treatment of atopic eczema (atopic dermatitis) in adults and children: part I. J Eur Acad Dermatol Venereol 2019;33(7):1436. doi:10.1111/jdv.15719.
[48] Eigenmann PA, Sicherer SH, Borkowski TA, et al. Prevalence of IgE-mediated food allergy among children with atopic dermatitis. Pediatrics 1998;101:E8. doi:10.1542/peds.101.3.e8.
[49] Sidbury R, Tom WL, Bergman JN, et al. Guidelines of care for the management of atopic dermatitis: section 4. Prevention of disease flares and use of adjunctive therapies and approaches. J Am Acad Dermatol 2014;71(6):1218–1233. doi:10.1016/j.jaad.2014.08.038.
[50] Fonacier LS, Aquino MR. The role of contact allergy in atopic dermatitis. Immunol Allergy Clin North Am 2010;30(3):337–350. doi:10.1016/j.iac.2010.06.001.
[51] Zhang J. Dermatology Glucocorticoid Specification Application Manual. Shanghai Scientific & Technical Publishers; 2011:31. (In Chinese)
[52] Baron SE, Cohen SN, Archer CB, et al. Guidance on the diagnosis and clinical management of atopic eczema. Clin Exp Dermatol 2012;37(Suppl 1):7–12. doi:10.1111/j.1365-2230.2012.04336.x.
[53] González-López G, Ceballos-Rodríguez RM, González-López JJ, et al. Efficacy and safety of wet wrap therapy for patients with atopic dermatitis: a systematic review and meta-analysis. Br J Dermatol 2017;177(3):688–695. doi:10.1111/bjd.15165.
[54] Wang S, Ma L. Efficacy of wet-wrap treatment for 13 cases of severe childhood atopic dermatitis: a clinical observation. Chin J Dermatol 2017;50(11):832–834. doi:10.3760/cma.j.issn.0412-4030.2017.11.013. (in Chinese).
[55] Pariser D. Topical corticosteroids and topical calcineurin inhibitors in the treatment of atopic dermatitis: focus on percutaneous absorption. Am J Ther 2009;16(3):264–273. doi:10.1097/MJT.0b013e31818a975c.
[56] Wollenberg A, Ehmann LM. Long term treatment concepts and proactive therapy for atopic eczema. Ann Dermatol 2012;24(3):253–260. doi:10.5021/ad.2012.24.3.253.
[57] Liang Y, Liu L, Wang S, et al. Efficacy and safety of 0.03% tacrolimus ointment in the long-term intermittent maintenance treatment of atopic dermatitis in children: a multicenter randomized controlled clinical trial. Chin J Dermatol 2019;52(8):519–524. doi:10.3760/cma.j.issn.0412-4030.2019.08.001. (in Chinese).
[58] Nghiem P, Pearson G, Langley RG. Tacrolimus and pimecrolimus: from clever prokaryotes to inhibiting calcineurin and treating atopic dermatitis. J Am Acad Dermatol 2002;46(2):228–241. doi:10.1067/mjd.2002.120942.
[59] Wollenberg A, Barbarot S, Bieber T, et al. Consensus - based European guidelines for treatment of atopic eczema (atopic dermatitis) in adults and children: part I. J Eur Acad Dermatol Venereol 2018;32(5):657–682. doi:10.1111/jdv.14891.
[60] Paller AS, Tom WL, Lebwohl MG, et al. Efficacy and safety of crisaborole ointment, a novel, nonsteroidal phosphodiesterase 4 (PDE4) inhibitor for the topical treatment of atopic dermatitis (AD) in children and adults. J Am Acad Dermatol 2016;75(3):494–503.e6. doi:10.1016/j.jaad.2016.05.046.
[61] He A, Feldman SR, Fleischer ABJr. An assessment of the use of antihistamines in the management of atopic dermatitis. J Am Acad Dermatol 2018;79(1):92–96. doi:10.1016/j.jaad.2017.12.077.
[62] Wollenberg A, Barbarot S, Bieber T, et al. Consensus - based European guidelines for treatment of atopic eczema (atopic dermatitis) in adults and children: part II. J Eur Acad Dermatol Venereol 2018;32(6):850–878. doi:10.1111/jdv.14888.
[63] Garrido Colmenero C, Blasco Morente G, Tercedor Sánchez J. Oral cyclosporine weekend therapy: a new maintenance therapeutic option in patients with severe atopic dermatitis. Pediatr Dermatol 2015;32(4):551–552. doi:10.1111/pde.12592.
[64] Relling MV, Schwab M, Whirl-Carrillo M, et al. Clinical pharmacogenetics implementation consortium guideline for thiopurine dosing based on TPMT and NUDT15 genotypes: 2018 update. Clin Pharmacol Ther 2019;105(5):1095–1105. doi:10.1002/cpt.1304.
[65] Sidbury R, Davis DM, Cohen DE, et al. 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(2):327–349. doi:10.1016/j.jaad.2014.03.030.

[66] Guttman-Yassky E, Silverberg JI, Nemoto O, et al. Baricitinib in adult patients with moderate-to-severe atopic dermatitis: a phase 2 parallel, double-blinded, randomized placebo-controlled multiple-dose study. J Am Acad Dermatol 2019;80(4):913–921.e9. doi:10.1016/j.jaad.2018.01.018.

[67] Guttman-Yassky E, Thaçi D, Pangan AL, et al. Upadacitinib in adults with moderate to severe atopic dermatitis: 16-week results from a randomized, placebo-controlled trial. J Allergy Clin Immunol 2020;145(3):877–884. doi:10.1016/j.jaci.2019.11.025.

[68] Bissonnette R, Papp KA, Poulin Y, et al. Topical tofacitinib for atopic dermatitis: a phase IIa randomized trial. Br J Dermatol 2016;175(5):902–911. doi:10.1111/bjd.14871.

[69] Tzaneva S, Seeber A, Schwaiger M, et al. High-dose versus medium-dose UVA1 phototherapy for patients with severe generalized atopic dermatitis. J Am Acad Dermatol 2001;45(4):503–507. doi:10.1067/mjd.2001.114743.

[70] Pavlis J, Yosipovitch G. Management of itch in atopic dermatitis. Am J Clin Dermatol 2018;19(3):319–332. doi:10.1007/s40257-017-0335-4.

[71] Kaffenberger BH, Mathis J, Zirwas MJ. A retrospective descriptive study of oral azole antifungal agents in patients with patch test-negative head and neck predominant atopic dermatitis. J Am Acad Dermatol 2014;71(3):480–483. doi:10.1016/j.jaad.2014.04.045.

[72] Bae JM, Choi YY, Park CO, et al. Efficacy of allergen-specific immunotherapy for atopic dermatitis: a systematic review and meta-analysis of randomized controlled trials. J Allergy Clin Immunol 2013;132(1):110–117. doi:10.1016/j.jaci.2013.02.044.

[73] Zhong H, Deng X, Song Z, et al. Immunological changes after ASIT in AD allergen-specific immunotherapy and their potential correlation with clinical response in patients with atopic dermatitis patients sensitized to house dust mite. J Eur Acad Dermatol Venereol 2015;29(7):1318–1324. doi:10.1111/jdv.12813.