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Literature Review
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Update Management of Atopic Dermatitis

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ABSTRACT
Background: Atopic dermatitis (AD) is a chronic recurrent skin disease that is very complex due to impaired skin barrier function in the form of xerosis, chronic eczematous lesions, and itching, commonly found in infants and children. Pathogenesis is thought to be the interaction of genetic factors, immune dysfunction, epidermal barrier dysfunction, and the role of the environment and infectious agents. Approach the disease by performing etiopathogenesis algorithms, clinical manifestations, diagnosis, and treatment. Based on the 2013 Asia-Pacific consensus, AD management guidelines using the 5-pillar principle have long been used. Currently, the European consensus in 2018 has developed new guidelines for AD management. **Purpose:** To provide an updated treatment for AD. **Review:** The ethiopathogenesis of AD is influenced by genetics, skin barrier disorders, and immune response disorders. Updated management of the European consensus in 2018 includes education, avoidance of precipitating factors, psychosomatic counseling, optimization of skin barrier function with moisturizers, anti-inflammatory and antimicrobial administration, allergen-specific immunotherapy, complementary and alternative drugs, phototherapy, and controlling the itch-scratch cycle with anti-itch in pediatric and adult AD patients. AD may affect patients' quality of self-esteem. In general, patients expect higher. **Conclusion:** AD affects the psychosocial aspects of patients. Updated management of AD adequately improves the quality of life.

Keywords: Atopic Dermatitis, Treatment, Mechanism.

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BACKGROUND

Atopic dermatitis (AD) is a chronic skin inflammation in children and adults with recurrent eczema lesions accompanied by itching that can affect the quality of life and is associated with other atopic diseases.[1] The prevalence of AD globally tends to increase in the last decade, in infants and children in the range of 10-20%, while in adults it ranges from 3-7%.[2] The prevalence of AD in Asia ranges from 0.96-22.6% in children and from 1.2% in adults.[3] Data on AD in Indonesia is not known with certainty. Based on data from AD patient visits at the Dermatology and Venereology Polyclinic, Allergy-Immunology Division, Dr. Mohammad Hoesin Central General Hospital (DV RSUPMH) Palembang in 2016-2020 found 287 of 3,607 visits (7.95%), 14.28% aged 0-5 years, 4.87% aged 6-11 years, 80.82% aged ≥ 12 years.

The ethiopathogenesis of AD is influenced by various factors, namely genetics, skin barrier disorders, and immune response disorders. Genetic factors in the form of filaggrin mutations (FLG) occur in most AD patients. Disruption of the skin barrier in the form of increased transepidermal water loss (TEWL) and bacterial colonization of AD lesions. Impaired immune response in the form of activation of T helper-2 (Th2) cytokines releases pro-inflammatory cytokines. Itching as a symptom of AD exacerbation triggers an itch-scratch cycle that exacerbates AD conditions. The treatment options for AD are aimed at restoring the skin barrier and suppressing the activation of cytokines that trigger inflammation.[2,4]

Based on the 2013 Asia-Pacific consensus, AD management guidelines using the 5-pillar principle have long been used. However, as new drug findings

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are currently reported in the form of various biologic and alternative agents for AD, the European consensus in 2018 developed new guidelines, including education, avoidance of precipitating factors, psychosomatic counseling, optimization of skin barrier function with moisturizers, anti-inflammatory and antimicrobial administration, allergen-specific immunotherapy, complementary and alternative drugs, phototherapy and controlling the itch-scratch cycle with anti-itch in pediatric and adult AD patients.[2,5]

This literature review will review the current management so that clinicians are expected to be able to adequately manage AD to improve the quality of life of AD patients. Hopefully, this review can be part of the consideration for choosing a new better treatment.

REVIEW

Atopic dermatitis is a multifactorial disease caused by a complex interaction of genetic factors, skin barrier disorders, and impaired immune responses to allergens. Genetic factors play an important role in the formation of an optimal skin barrier. More than 80 genetic mutations are known to be associated with the pathogenesis of AD. One of these genetic mutations is FLG (chromosome locus 1q21) which is a predisposing factor for AD in the range of 20-50% population of white Europeans and Asians. Serine protease inhibitor Kazal-type 5 gene (SPINK5) and lymphoepithelial Kazal-type trypsin inhibitor (LEKT1) as an inhibitor of the stratum corneum (SC) serine protease enzyme.[2]

The epidermis provides a protective/defensive function mediated by the stratum corneum (SC). These functions include a permeability barrier, which inhibits transcutaneous water evaporation, leading to adaptability in a dry external environment, and an antimicrobial barrier that promotes colonization of nonpathogenic normal flora and inhibits the growth of pathogenic microbes.

The water retention process in SK depends on the extracellular lipid matrix and FLG. These two components work to keep water-soluble substances out of the SK. Most AD patients have FLG mutations that cause an increase in transepidermal water loss (TEWL).[2,6] An increase in TEWL reduces the water content in SK so that the function of enzymes needed.

An increase in TEWL reduces the water content in SK so that the function of enzymes needed for the desquamation process is disrupted, adhesion occurs and the accumulation of corneocytes occurs, ultimately causing dry and rough skin.[2] Disruption of the antimicrobial barrier leads to bacterial colonization, commonly caused by *Staphylococcus aureus*. Colonization of *S. aureus* that produces superantigens further worsens the condition of severe AD, characterized by increased production of total IgE and specific IgE against *S. aureus* exotoxins.[2,6,7]

Disruption of the skin barrier causes allergens to penetrate the SK, causing inflammation and itching. Inflammation of the skin is due to innate and adaptive immune responses.[2] In the acute phase of AD, it is mainly due to the activation of Th2 cytokines, but in the chronic phase, there are changes in Th1 and Th22 activation. Th17 cytokines are found in both acute and chronic phases. In the acute phase, there is dysregulation of interleukin-4 (IL-4), IL-5, and IL-13, activation of eosinophils and mast cells, and production of IgE. Cytokines IL-1, thymic stromal lymphopoietin (TSLP), IL-25, IL-17E, and IL-33 activate Th2. Th2 cytokines inhibit the expression of the major differentiation proteins, such as loricrin, filaggrin, and involucrin.[8]

The clinical manifestations of AD can be acute, subacute, or chronic, and there are differences in the distribution of lesions in children and adults. In infants (<2 years of age), it is generally acute and found on the face, scalp, trunk, and extensor extremities. The clinical picture is dry skin with papules. Exudative erythema in the intertriginous areas, including the neck, axilla, cubital fossa, and popliteal fossa. In children aged 2-12 years, eruptions are found on the neck, axillae, cubital fossa, popliteal fossa, inguinal region, wrists, and feet. In severe AD, a chronic form is found in the form of lichenification and the location of the lesion in the flexor extremities. In adults, lesions are found on the face, neck, chest, and back. In severe AD, erythroderma may occur.[2,9]

The diagnosis of AD was established by the diagnostic criteria. Until now, what has been considered the gold standard for the diagnosis of AD is the Hanifin-Rajka criteria, which are 3 out of 4 major criteria and 3 out of 23 minor criteria. However, until now, there have been many other diagnostic criteria, namely the United Kingdom Working Party Criteria (UKC) and the criteria of the American Academy of Dermatology.[2]

Evaluation of AD severity uses several assessments, including SCORAD (SCORing Atopic Dermatitis), EASI (Eczema Area and Severity Index), and POEM (Patient-Oriented Eczema Measure).[2,8,10] In the SCORAD assessment, the severity is grouped into light (< 25), moderate (25-50), and heavy (> 50).[10]

The management of AD is divided into non-pharmacological and pharmacotherapy interventions. Pharmacological interventions include topical and

systemic drugs. The current management of AD according to the European consensus includes non-pharmacotherapeutic interventions, namely education, avoiding precipitating factors, and psychosomatic counseling. Pharmacotherapeutic interventions include optimization of the skin barrier with moisturizers, topical anti-inflammatory, antimicrobial, systemic anti-inflammatory, allergen-specific immunotherapy, complementary and alternative drugs, phototherapy and controlling the itch-scratch cycle with anti-itch.[5]

DISCUSSION

The success of AD treatment is indicated by the fact that the symptoms of AD disappear or are lighter and do not interfere with daily activities.[9] Patient education is the cornerstone of management in pediatric and adult AD patients (Figures 1 and 2). Patients have explained the disease, symptoms, causes, precipitating factors, drugs, and disease prognosis.[10] Take a 5-10 minute bath with warm water at 27-30^{0}C using a soap containing a moisturizer with a pH of 4-5, hypoallergenic, has a mild surfactant, and does not contain fragrances and dyes. Moisturizer is applied immediately after bathing.[5] Use moisturizer 2-3 times a day, or more if needed.[10] Wear soft, absorbent clothing. Prevent trigger factors, avoid trigger foods, and avoid stress. Patients have explained the type of drug given, the potency of the drug (especially corticosteroids), the method, and frequency of drug application. Patients were explained the time of drug administration (morning and evening after bathing), starting time, duration, and stopping time of the drug. Patients are also given information on the actions to be taken if they relapse.

The causes of atopic dermatitis are multifactorial. Allergens from the environment should be avoided. Prevention of trigger factors, such as irritants, allergens, extreme heat or cold temperatures, and trigger foods. Irritants that trigger AD include wool, irritant soaps, and perfumes. The use of clothes made of silk and cotton can reduce friction, causing good sweat absorption, so that the hydrolipidic layer on the skin is maintained and reduces skin irritation. Allergens include house dust mites, pets, and vehicle pollutants (nitrogen oxide). Patients with food allergies, especially cow's milk products, eggs, nuts, soy, wheat, and fish, are considered to have increased IgE as an extrinsic trigger factor for AD. A low-egg diet is thought to be beneficial in infants with egg-reactive IgE.[10] This is evaluated based on the history, clinical manifestations, and allergy testing performed.[7] Climate change can also trigger AD. In winter, exposure to high temperatures in the house and the environment will increase sweating and the evaporation of water from the skin, resulting in the exacerbation of dry and irritated skin. Using a humidifier during extreme heat or cold can help reduce AD symptoms.[10] Treatment of itching begins with avoiding triggers (dry skin and allergens) as well as topical and systemic medications. Skin hyperinnovation in AD affects peripheral itch sensitization due to the higher epidermal nerve fiber density in the damaged skin barrier due to dry skin.[10]

The psychotherapeutic intervention was performed in patients with severe AD. Psychological and emotional factors of patients affect the clinical picture of AD. Stress can cause an exacerbation of AD lesions. In schoolchildren, stressors in the form of exams and sleep disturbances can trigger AD. The itch-scratch cycle causes psychological disturbances due to the tendency to scratch continuously. Psychosomatic diseases cause anxiety and depression, which are comorbid factors for AD. Stress management by a psychiatrist, accompanied by family support, behavior modification, and relaxation exercises, can help cope with AD.[10]

Moisturizer is an emulsion consisting of active oil ingredients that are applied to the skin and used for rehydrating or regenerating dry, rough, and scaly skin due to xerosis, irritation, or other causes. Moisturizers based on function, nature, and mechanism of action are grouped as occlusive, humectant and emollient.[5] Occlusive moisturizers work to limit water loss from the skin's surface and maintain skin barrier lipid levels. The substance in occlusive moisturizers is hydrophobic, thus forming a protective layer on the skin, which will reduce TEWL by preventing water evaporation. Lanolin, olive oil and petrolatum are occlusives used to inhibit skin evaporation, thereby reducing itching.[5,10] Humectants work by pulling water into the skin. Hydration of the stratum corneum will restore the normality of the extracellular lipid matrix and the natural desquamation process according to its nature works like a natural hydrophilic. Urea, glycerin, hyaluronic acid, sorbitol, and alpha-hydroxy acid (AHA) are humectants that increase skin hydration and affect the formation of collagen and dermal mucopolysaccharides so that they can improve skin barrier function.[10] Urea can cause irritation and kidney disorders in infants, so it is not recommended.

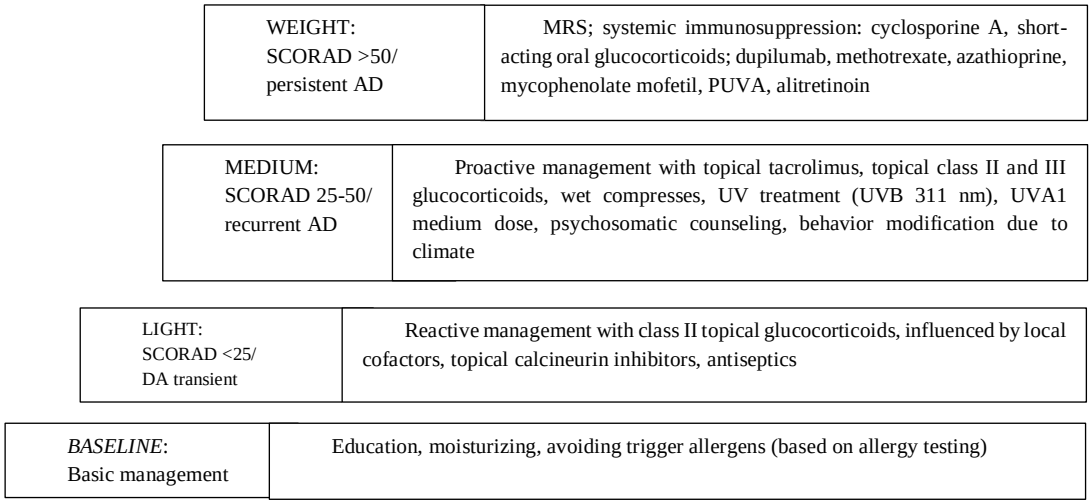

Figure 1. AD management chart in adults[10].

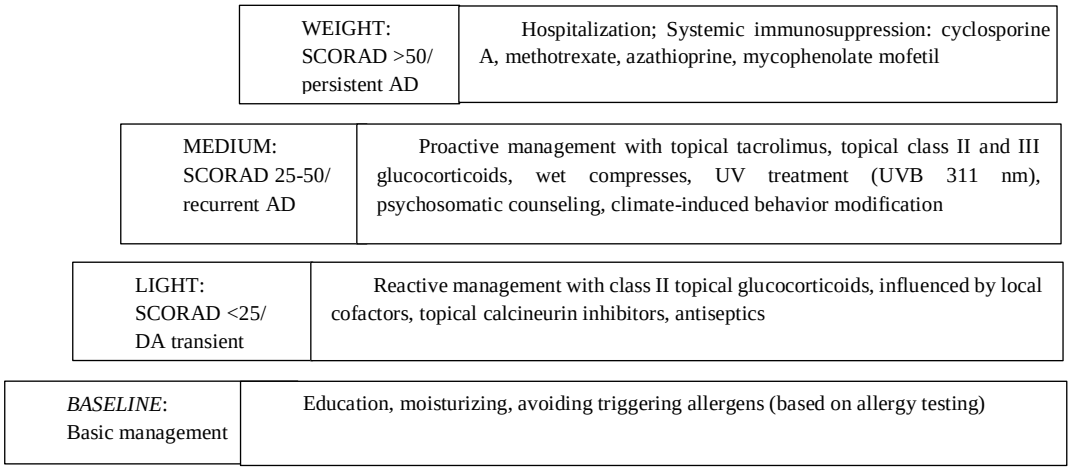

Figure 2. AD management chart in children[10].

Emollients work to fill and coat the outermost layer of the skin, functioning to make the skin softer and smoother but not reducing the water content in the epidermis layer. Emollient options include stearic acid, isopropyl palmitate collagen, elastin, and shea butter. Emollients containing ceramides are used for recurrent AD patients. In a study of 24 children with recurrent AD who were given emollients containing ceramides, 22 children experienced repair of lesions for 3 weeks.[10]

Topical drugs for anti-inflammatory consist of corticosteroids, calcineurin inhibitors, and crisaborole (Table 1).[10,11] Corticosteroids suppress the expression of activated leukocytes, cytokine production, T cell, mast cell, and macrophage production, eosinophil activation/degranulation, antigen presentation of Langerhans cells, activation of epidermal keratinocytes, and itching by preventing the release of cytokines associated to sensory nerves (IL-4, IL-13, and IL-31).[12] Topical corticosteroid administration should consider local transdermal absorption,

especially in the mucosal area. Selection is based on potency, frequency, duration of administration. Potent steroids are not used in pediatric AD patients.[11,13] In adults, moderate-potency corticosteroids are effective in treating recurrent atopic dermatitis of the trunk and extremities. Maintenance dose with a low-potency corticosteroid twice daily. In an open-label of 68 AD patients who were given mometasone furoate cream twice a day for 6 months, there was up to 90% remission of lesions, but 1 patient had skin atrophy.[12,14]

Topical calcineurin inhibitors (CI) include 0.03% and 0.1% tacrolimus, and 1% pimecrolimus. The mechanism of action of CI against AD is to suppress T cell activation and mast cell degranulation, suppress eosinophil activation, suppress Langerhans cell antigen presentation, inhibit releasing of sensory

neurotransmitters, and suppress the production of IL-31 and IL-33.[12,14] In children aged 2-5 years with body weight (BB) < 20 kilograms, the one-time dose of 0.03% CI does not exceed 1 gram. In children aged 2-4 years with a weight of 20-50 kilograms, the CI dose is 2-4 grams. In children > 13 years of age with a body weight > 50 kilograms, the dose does not exceed 5 grams. After AD symptoms have subsided, maintenance doses are given 2-3 times per week at sites of recurrent AD. Local side effects are generally irritation in the form of burning sensation, as well as bacterial and viral infections. Calcineurin inhibitors are not recommended for erythroderma.[11-13]

Wet-wrap action using corticosteroids, CI, or a combination of both are considered effective for the treatment of moderate and severe AD, aiming to reduce itching and inflammation by cooling the skin and increasing drug absorption. This procedure is applied over 2 weeks for the treatment of severe AD or resistant lesions before starting systemic drugs.[11] Wet-wraps are applied to the face, trunk, and extremities. The procedure begins with applying topical medication to the skin, then covering it with a layer of gauze or cotton moistened with warm water, then covering it again with a dry gauze bandage and leaving it for about 8 hours. Generally, this action is performed before bedtime to reduce sleep disturbances. Side effects are maceration, folliculitis, and secondary infection.[11]

Crisaborole is the latest AD drug that has been started in the US but has not yet received approval in Europe.[5] Crisaborole is a phosphodiesterase 4 (PDE4) inhibitor used as a topical drug for mild-moderate AD at > 2 years of age. PDE4 inhibitors decrease the production of pro-inflammatory cytokines. In the phase 3 clinical trial, two groups of AD patients given 2% crisaborole ointment and controls. AD lesions went into remission in 31.4% of the group given 2% crisaborole ointment, while remission was found in 18% of the control group. A side effect of burning sensation was reported by 4% of patients.[2,5]

Antimicrobial treatment is given if a clinical infection is found. Bleach baths can reduce current *S. aureus* colonization and infection. The use of mupirocin cream, topical anti-inflammatory drugs, and moisturizers in combination with a bleach bath was reported to be effective in AD patients with S. aureus skin infections. A randomized clinical trial by Huang et al. on 31 patients with moderate-severe AD treated with a bleach bath and mupirocin for 3 months showed clinical improvement in AD severity compared to regular bathing

Table 1. *Level of evidence* for topical medication in atopic dermatitis[15]

Drug	Power of recommendation	*Level of evidence*
Moisturizer	A	I
Wet-wrap action	B	II
Topical Corticosteroids	A	I
Topical calcineurin inhibitors	A	I
Combination of corticosteroids and calcineurin inhibitor	B	II
Bleach bath and mupirocin	B	II

*I: prospective control trials, II: large sample case series or retrospective trials, III: individual case reports

Table 2. *Level of evidence* for systemic medication in atopic dermatitis[8,11,15]

Drug	Power of recommendation	*Level of evidence*
Cyclosporine	A	I
Methotrexate	B	I-II
Mycophenolate Mofetil	B	I-II
Azathioprine	A	I
Systemic corticosteroids	B	II
Interferon-gamma	B	I
Dupilumab	A	I
Omalizumab	B	II
NB-UVB, UVA-UVB, UVA1	B	I-III
Vitamin D	B	I
Sedating antihistamines	B	I
Non-sedating antihistamines	C	I

*I: prospective control trials, II: large sample case series or retrospective trials, III: individual case report

Systemic anti-inflammatory drugs are used in patients with moderate-to-severe AD that cannot be fully controlled with topical medications. Systemic anti-inflammatory agents for AD include cyclosporine (CsA), methotrexate (MTX), mycophenolate mofetil (MMF) and azathioprine (AZA), corticosteroids, and interferon-gamma (IFN-γ) (Table 2).[11,12,14]

Cyclosporine (CsA) is an immunomodulator that affects T cell differentiation and IL-2. In AD, CsA works to inhibit cytokines that induce itching, including IL-4, IL-13, and IL-31. This drug is well-tolerated, effective, and safe for children aged 2-16 years with severe AD and who are resistant to topical drugs.[11] The maximum limit for the use of CsA as an AD drug is 1 year.[12] Side effects that have been reported include impaired renal function, hypertension, headache, malignancy, and elevated serum creatinine.[14] Saricaoglu et al. reported administration of CsA 2.5-5 mg/kg/day in 43 pediatric patients with severe AD, showing 17 patients (39.5%) experienced clinically significant improvement in 3-14 months.[12,14]

Methotrexate (MTX) is given in moderate-to-severe AD that is resistant to topical drugs. The mechanism of action of MTX is to block the synthesis of DNA, RNA, and purines, thereby inhibiting T cell function.[11] Side effects include abnormal liver function in 5.9% of patients and gastrointestinal disturbances in 3.9% of patients.[16] Methotrexate also causes bone-marrow suppression and pulmonary fibrosis. Folic acid supplementation reduces hematological toxicity. Both male and female patients must use contraception during MTX administration and for at least 3 months after the drug is given.[14,17] Lee et al. reported that in 102 patients with moderate-to-severe AD, the initial dose of 5-15 mg per week (age 0-5 years at 5 mg dose, age 6-10 years at 1.5-10 mg) was responding. They increased the dose by 2,5-5 mg for 2-4 weeks up to a maximum dose of 22.5 mg. After 6-10 weeks of drug administration, 60.8% experienced complete remission, and 39.2% showed little or no response to the drug.[16]

Mofetil mycophenolate (MMF) is an immunosuppressive that selectively affects B cells and T cells because it has a direct mechanism for treating inflammatory disorders. The MMF dose is 0.5-3 g/day.[14] Side effects such as nausea, vomiting, abdominal cramps, hematological and genitourinary disorders were reported.[2,14] Mycophenolate mofetil can be used as monotherapy in pediatric patients aged 2 years and over with severe AD.[14] Phan et al. reported that 140 AD patients who were given MMF had complete and partial remission in 77.6% of patients, recurrence in 8.2% of patients, and a decrease in SCORAD scores of 18 points from baseline. A side effect of herpes infection was found in patients with a duration of drug administration of 1 year.[14]

Azathioprine (AZA) is an imidazole derivative of 6-mercaptopurine and a purine analog that inhibits cellular proliferation, so this drug is more considered for inflammatory diseases with high proliferation rates. This drug affects B and T lymphocytes. AZA dosage is 1-3 mg/kg/day. Remission can occur more than 12 weeks after drug administration, and then AZA is tapped off or discontinued.[11] AZA side effects include nausea, vomiting, headaches, hypersensitivity reactions, elevated liver enzyme levels, leukopenia, an increased risk of infection, lymphoma, and non-melanoma skin cancer. Ideally, before administering AZA, a thiopurine methyltransferase (TPMT) test is performed.[18] Fuggle et al. reported 82 pediatric AD patients at a dose of 2-3.5 mg/kg/day. Side effects of impaired complete blood counts in 41% of patients. Clinical disturbances in the form of viral infection, nausea, lethargy and headaches in 20% of patients.[18]

Corticosteroids are used to achieve rapid clinical improvement by inhibiting the release of inflammatory cytokines and reducing local inflammation. The most commonly used preparations are intramuscular prednisolone and triamcinolone acetonide tablets. The dosage of oral prednisolone is 0.5-1 mg/kg/day.[11] A systematic review by Aljebab et al. regarding the administration of oral corticosteroids in children aged 28 days-18 years for 15 days showed side effects of 21.1% weight gain, 18.1% growth retardation, and Cushing's syndrome 19.4% in 6,817 children.[17]

Interferon-gamma (IFN-γ) works to induce the production of natural killer cells and increase macrophage oxidation. Interferon-gamma is considered an alternative in patients with drug-resistant or severe AD.[11] There is no recommended optimal dose. Generally given three times a week. The main side effects are fatigue, fever, nausea, vomiting, and muscle aches. Investigations before starting drug administration include a complete blood count, examination of kidney and liver function, and urinalysis.[11] Steven et al. observed 24 AD patients given a subcutaneous injection of IFN-γ at a dose of 50 g/m2/day. Clinical improvement and reduction in itching occurred after 12 weeks of drug administration. The side effect of malaise was found in one patient.[7]

Biological agents are current drugs that work based on the natural process of antibody formation, and having specific targets for inflammatory cells and mediators. Biological agents that can be used for AD include dupilumab, and omalizumab. Dupilumab (anti-

IL-4) is a human monoclonal antibody that binds to the -subunit of the IL-4 and IL-13 receptors, thereby inhibiting the mediation of chronic itch on Janus kinase (JAK). Dupilumab is the first and only biologic agent to be approved by the FDA as an AD drug. Minimal side effects include conjunctivitis and local reactions at the injection site. This drug is recommended for severe AD and is unresponsive to other drugs.[11,13] Ferrucci et al. reported 117 patients with severe AD who were given an injection of dupilumab 300 mg subcutaneously weekly and evaluated after 4 weeks and 16 weeks. Clinical improvement in EASI75 occurred in 72.7% of patients after 16 weeks. Quality of life improved with decreased anxiety, depression, itching and sleep disturbances compared to baseline.[19]

Omalizumab is a recombinant monoclonal antibody that binds to soluble IgE and B cell surface membrane-bound IgE. It is currently FDA-approved as an asthma drug. Omalizumab binds to the high-affinity IgE receptor (FceRI), thereby preventing IgE from binding to the surface of mast cells and basophils, causing mast cell degranulation blocks, and inhibiting the release of inflammatory mediators. Administration of subcutaneous omalizumab 0.016 mg/kg every 4 weeks in 20 AD patients for 16 weeks did not give clinically significant remission, despite a decrease in serum IgE.

Table 3. Comparison of conventional and current AD drugs[23]

Drug	CsA	MTX	AZA	MMF	Oral CS	Dupilumb
Recommended use	Acute episode, maintenance	Maintenance	Maintenance	Maintenance	Acute episode	Long-term maintenance
Laboratory test	Blood pressure, renal functions, serum lipids, electrolytes	Complete blood count, hepatic-renal functions	Complete blood count, hepatic-renal functions	Blood pressure, renal functions, serum lipids, electrolytes	Blood pressure, blood sugar, electrolytes, hepatic-renal	Not recommended
Time to response	1-2 weeks	8-12 weeks	8-12 weeks	4-8 weeks	Day 5	Day 2-4 weeks
Time to relapse	N/A	N/A	N/A	N/A	Fast	N/A
Starting dose	3-5 mg/kg/day	7.5-25 mg/week in adults, 0.2-0.5 mg/kg/week in children	Start at a dose of 50 mg/ day	1-2 g/day	Methylprednisolone 0.5 mg/kg/day Is reduced basedon response	600 mg 400 mg
Maintenance dose	0.5-1 mg/ kg every two weeks.	Same as the initial dose	1-3 mg/kg/day	In remission, the dose may be reduced	Not recommended for maintenance	> 60 kg: 300 mg/ week; < 60 kg: 200 mg/ week
Use in hepaic and renal failure	Not use if high creatinine level	Do not use	-	-	-	No dose adjustment
Pregnancy	Usable	Contraindicated	Low doses	Contraindicated	Usable	Unavailable data

N/A = not available

A placebo-controlled trial was compared with omalizumab (150-365 mg subcutaneously every 2-4 weeks for 24 weeks) in eight children with severe AD, recurrent, and high serum IgE levels. A 20-50% reduction in SCORAD in patients treated with omalizumab, whereas in placebo, it was 45-80%.[11,13]

Various complementary and alternative medicines are believed to be able to treat AD, including vitamin D3, vitamin E, and Chinese herbs. The meta-analysis by Hattangdi-Haridas et al. reported 25-dihydroxy vitamin D levels in pediatric AD patients compared to healthy controls. In AD patients, vitamin D deficiency was found to be 16 nmol/L.[20]

Jaffary et al. reported that 65 AD patients aged 10-50 years who were given oral vitamin E at 400 IU/day compared to placebo for 4 months showed a decrease in SCORAD values, itching, and lesion higher in patients given vitamin E.[21] Liu et al. reported that 275 AD patients aged 5-25 years who were given a 9-herb formula (radix pseudostellariae, forsythia, ramulus, medulla juci, lophatheri, semen coicis, rhizome, concha and radix glycyrrhizae) showed a decrease the severity and an increase the quality of life of patients with moderate-severe AD.[22] Chinese herbal medicine still requires further research in vivo and in vitro.

The length of time between a lesion's response to treatment and its recurrence are taken into account with systemic drugs for AD. The comparison between conventional dan current drugs are shown in Table 3.[23]

Narrowband (NB)-UVB (311 nm), UVA1 (340-400 nm), and UVA combined UVB (280-400 nm) phototherapy showed clinical improvement of lesions and itching. Phototherapy works to induce T cell apoptosis, reduce dendritic cells, and decrease the expression of Th2 cytokines including IL-5, IL-13, and IL-31. Chronic AD lesions are treated with NB-UVB and UVA1, while UVA1 is recommended for acute lesions. Phototherapy is performed as a second-line treatment in case of failure of the first-line consisting of moisturizers, topical corticosteroids, and topical CI.[8] The use of NB-UVB (311-313 nm) as first-line

treatment for children and adolescents because it is safe and effective. [11] Jorge et al. reported 14 pediatric AD patients who were treated with NB-UVB, a mean of 48 sessions with a cumulative dose of 34.9 J/cm3, and found that 87.5% of patients experienced clinical improvement. Side effects include mild erythema in 16% of patients.[24] The mechanism of itching in AD is complex and not fully understood. Several factors that influence itching include histamine in the form of proteases, neuropeptides, cytokines, lipids, opioids, protease activation receptors, mast cell receptors associated with G protein, and potential receptor pathways.[11] First-generation sedative H1 antihistamines can improve sleep quality in AD patients. Second-generation H1 antihistamines are less effective. The dose of oral antihistamines can be increased up to four times. Side effects such as sedation, dry mouth, blurred vision, and tachycardia. Giving cetirizine to 817 infants with AD for 18 months can reduce itching and reduce the use of topical corticosteroids.[11,14]

The approach to AD management with psychosomatic counseling, accompanied by the latest pharmacotherapy using new drugs of crisaborole and biologic agents, completes the long-standing principles of the 5 pillars of AD management. In addition, biologic agents are used as the last line of current AD treatment algorithms. Ideally, optimal therapy requires adherence because AD is chronic and recurrent.

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