Ann Dermatol Vol. 27, No. 4, 2015 http://dx.doi.org/10.5021/ad.2015.27.4.355

REVIEW ARTICLE

Personalized Immunomodulatory Therapy for Atopic Dermatitis: An Allergist's View

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The current standard medical therapy for atopic dermatitis (AD) mainly focuses on symptomatic relief by controlling skin inflammation with topical corticosteroids and/or topical calcineurin inhibitors. However, the clinical efficacy of pharmacological therapy is often disappointing to both patients and physicians. The terminology of AD contains a historical meaning of eczematous dermatitis caused by hypersensitivity reaction to environmental inhalant or food allergen. Complex interrelationships among genetic abnormalities, environmental triggers, skin barrier defects, and immune dysfunction resulting in a vicious domino-circle seem to be involved in the development and maintenance of AD. In the viewpoint of AD as an allergic disease, complete avoidance of clinically relevant allergen or induction of specific immune tolerance through administrations of allergen (allergen immunotherapy) can provide clinical remission by breaking the vicious domino-circle maintaining a chronic disease state. In recent clinical studies, monoclonal antibodies including the anti-interleukin-4 receptor antibody and anti-B cell antibody induced significant clinical improvements in patients with AD. The detailed characteristics of immune dysfunction are heterogeneous among patients with AD. Therefore, a personalized combination of immunomodulatory therapies to reduce hypersensitivity (allergen immunotherapy) and correct immune dysfunction (monoclonal antibody therapy) could be a reasonable therapeutic approach for patients with AD. Future immunomodulatory therapies for AD should be developed to achieve long-term treatment-free clinical remission by induction of immune tolerance. **(Ann Dermatol 27(4) 355～363, 2015)**

-Keywords-
Atopic dermatitis, Hypersensitivity, Immunomodulation, Allergens, Therapeutics

INTRODUCTION

Atopic dermatitis (AD) is a common chronic relapsing inflammatory skin disease characterized by itching, dry skin, inflammation, and exudation and is frequently associated with a personal or familial history of allergic diseases[1]. Hypersensitivity reaction to environmental agent has been suggested to be the pathogenetic mechanism responsible for the development and maintenance of chronic skin inflammation in AD patients[2]. However, the pathogenetic mechanism of AD seems to be more complexly associated with genetic abnormalities, environmental triggering factors, skin barrier defects, and immune dysfunction. In addition, the precise pathogenetic mechanism of AD is not yet completely understood[2,3].

The current standard medical therapies for AD, including the use of topical corticosteroids and/or topical calcineurin inhibitors, are focused mainly on symptomatic relief, and their clinical efficacies are often disappointing to both patients and physicians[1]. Although the condition of a considerable number of AD patients can be improved by systemic treatment with corticosteroid, cyclosporine, or mycophenolate mofetil, there is a possibility of toxicity from long-term treatment with these compounds[1]. Various approaches to modulate immune system using monoclonal antibodies have been attempted in patients with severe AD[4-7]. Recent clinical trials with monoclonal antibodies showed conflicting results in terms of clinical efficacies[4-7].

Received May 11, 2015, Accepted for publication May 12, 2015

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Positive clinical efficacy results have been reported in clinical trials with anti-interleukin (IL)-4 receptor antibody and anti-B cell antibody in AD patients[4,5]. Negative clinical efficacy results have been reported in clinical trials with anti-IgE antibody and anti-activated T cell antibody[6,7]. Further studies on the long-term clinical efficacy and safety of monoclonal antibody-based immunomodulatory therapies for AD are needed. Additionally, development of a new therapeutic modality for AD patients is required.
In this review, the rationale for a personalized immunomodulatory therapy as a therapeutic approach for AD will be discussed.

HISTORY OF THE TERMINOLOGY OF "ATOPIC DERMATITIS"

The term "atopy" was first coined by Coca and Cooke[8] in 1923 to describe a genetic predisposition toward the development of immediate-type hypersensitivity reaction (allergic reaction) against common environmental antigen, frequently manifested as hay fever (allergic rhinitis), bronchial asthma, eczematoid dermatitis, or food allergy. In 1933, Wise and Sulzberger proposed the name "atopic dermatitis" in place of the older traditional terms "neurodermatitis," "prurigo Besnier," and "allergic eczema" on the basis of their belief that hypersensitivity to food and airborne antigens was important in the development of eczematous skin lesions in a certain group of patients[9,10]. They also proposed the following 9 diagnostic criteria for AD: (1) atopic family history; (2) antecedent infantile eczema; (3) flexural localization; (4) gray-brown discoloration of the skin; (5) absence of vesicles; (6) vasomotor instability; (7) negative patch test reactions to contact irritants; (8) positive skin test reactions to various environmental and food antigens; and (9) the presence of reagins in the serum (presence of specific IgE antibodies to common allergens in the serum)[10]. Wise and Sulzberger stated that the logical therapy for AD was the avoidance of all foods and inhalants giving positive skin reactions, and they also advocated desensitization therapy with the most suspected substance[10,11]. Therefore, the term of AD originally referred to eczematous dermatitis caused by allergic reaction to inhalant or food allergens. In contrast to the belief of the earlier researchers who coined the term of AD, the pathogenetic significance of hypersensitivity reaction (allergic reaction) in the development of AD seems be currently underestimated, and therapy for AD tends to be focused on skin inflammation and skin barrier defect[11-13].

INCOMPLETENESS OF CURRENT PHARMACOLOGICAL THERAPIES FOR AD AND COMPLEMENTATION BY SYSTEMIC IMMUNOMODULATORY THERAPY TARGETING HYPERSENSITIVITY REACTION AND IMMUNE DYSFUNCTION

The majority of AD patients want a cure or long-term treatment-free clinical remission of AD. However, currently, AD patients and their families are generally informed that there is no curative treatment for AD and that this disease should be controlled by continuous medical management[14]. This mismatch between demand and supply in AD treatment seems to be the main reason for the current abundance of unconventional or alternative treatment approaches for AD by patients and their families seeking a cure for AD. This "AD problem" is resulting in substantial medicosocial problems and economical burdens in many developed countries[15].
The present author suggests that the incompleteness or inefficacy of the current standard medical therapies for AD and the overwhelming "AD problem" might partly be a result of the under-diagnosis and under-treatment of AD in the viewpoint of AD as an allergic disease (the absence of the "allergy concept" in the current treatment approaches). Besides pharmacological therapy, allergen-specific therapies including the avoidance of sensitized allergen and allergen immunotherapy are clinically effective in AD patients[16,17]. This review proposes that the active clinical application of the concept of AD as an allergic disease and the introduction of allergen-specific therapies could produce additional clinical improvements in AD patients and contribute to the resolution of the current "AD problem." Clinically relevant allergens should be screened by an allergy skin test or a serum allergen-specific IgE assay, and the clinical relevance of the sensitized allergen should be confirmed either by a careful history on the relationship between exposure to the allergen and triggering of clinical symptoms or by objective provocation tests (including the atopy patch test) in AD patients. Moreover, AD patients should be advised and educated about the methods for avoiding clinically relevant sensitized allergens (e.g., house dust mites, skin-colonizing fungi, and food allergens). However, avoidance of environmental triggering factors including allergens and irritants is often technically difficult and insufficient in AD patients. In these cases, allergen immunotherapy could be helpful[17]. Allergen immunotherapy is a treatment in which small amounts of sensitized allergens are repeatedly administered either subcutaneously or sublingually to induce allergen-specific immune tolerance in patients with allergic diseases[18].

Allergen immunotherapy has been shown to be clinically beneficial in AD patients sensitized to inhalant allergens such as house dust mites in a meta-analysis of multiple randomized clinical trials[19].

ONE-WAY VERTICAL FLOW PATHOGENESIS MODEL OF AD

AD is currently regarded as a multifactorial disorder caused by multiple pathogenetic elements including genetic predisposition, environmental trigger, immune dysfunction including hypersensitivity reaction, chronic skin inflammation, and skin barrier defect[2,3]. However, the precise inter-relationships between multiple pathogenetic elements involved in the development and maintenance of AD are not yet completely understood. Many complex models have described the interactions between the multiple pathogenetic elements in the development of AD[11-13,20]. The main controversy is regarding which event between skin barrier defect and immune dysfunction occurs first and is more important in AD development[13]. The present author proposes a one-way vertical flow pathogenesis model of AD showing the associations among multiple pathogenetic elements (Fig. 1). In this model, (1) environmental toxicants (e.g., volatile inorganic chemicals, air pollution, and food additives) absorbed through the respiratory mucosa, gastrointestinal mucosa, or skin induce immune dysfunction in genetically susceptible human subjects; (2) immune dysfunction induced by the toxicants produces hypersensitivity to environmental allergens and

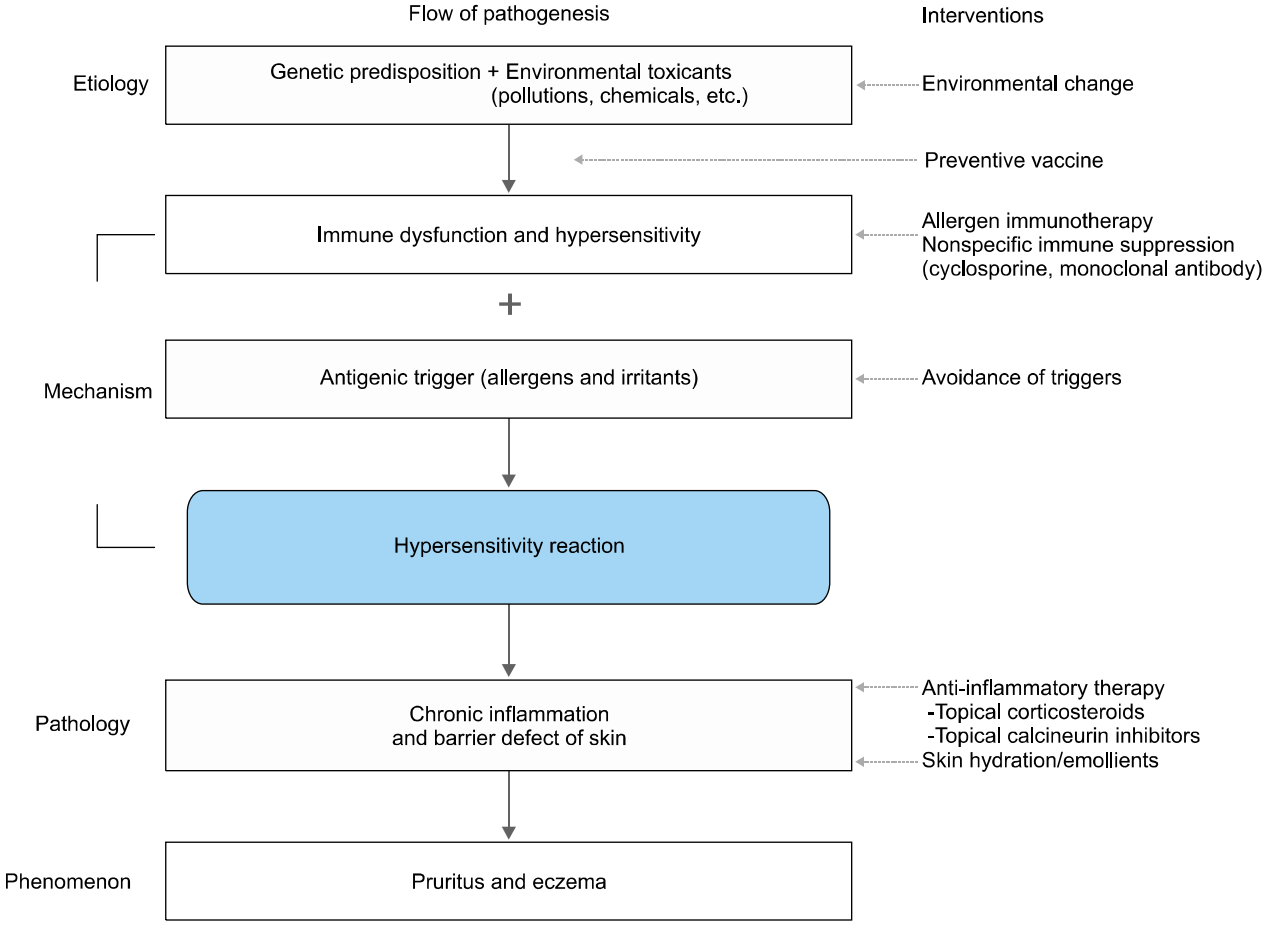

Fig. 1. One-way vertical flow pathogenesis model of atopic dermatitis. This vertical model suggests that (1) environmental toxicants (e.g., volatile inorganic chemicals, air pollution, and food additives) induce immune dysfunction and hypersensitivity in genetically susceptible human subjects by decreasing the threshold for developing hypersensitivity reaction to environmental allergens and irritants; and (2) exposure to the allergens and/or irritants induces hypersensitivity reaction, chronic skin inflammation, skin barrier defect, and clinical manifestations of atopic dermatitis (pruritus and eczema). In this model, multiple modalities could be introduced to block multiple elements in the pathogenetic pathway for the treatment of atopic dermatitis. In addition, blocking the upper stream of the pathogenetic pathway of this model might be a more effective and fundamental therapeutic approach than blocking the lower stream of the pathogenetic pathway.

irritants by decreasing the threshold for developing hypersensitivity reaction; and (3) exposure to the allergens and/or irritants induces hypersensitivity reaction, chronic inflammation, skin barrier defect, and the clinical manifestations of AD (pruritus and eczema), as suggested by an environmental scientist ("toxicant-induced loss of tolerance" theory)[21,22]. The present author proposes that multiple modalities could be introduced to stop the functioning of the pathogenetic pathway to prevent or treat AD in this one-way vertical flow pathogenesis model of AD (Fig. 1). In addition, blocking the upper stream of the pathogenetic pathway of this model might be a more effective and fundamental therapeutic approach than blocking the lower stream of the pathogenetic pathway (Fig. 1).

EVIDENCES SUPPORTING THE KEY ROLE OF HYPERSENSITIVITY REACTION (ALLERGIC REACTION) IN THE PATHOGENESIS OF AD

Hypersensitivity reaction (allergic reaction) to environmental allergen play a critical role in the development and maintenance of AD according to the following evidences.

1) Exposure to sensitized allergen (e.g., skin contact, inhalation) aggravates preexisting eczematous skin lesions or induces new eczematous skin lesions in AD patients[23,24].
2) Avoidance of sensitized allergen induces clinical improvement in AD patients[16,25].
3) Allergen immunotherapy including the repeated administrations of small amounts of sensitized allergen to induce allergen-specific immune tolerance results in clinical improvement in AD patients sensitized to inhalant allergen[17-19].
4) The majority of AD patients (80%～90%) show allergic sensitization to common inhalants or food allergens[26].
5) Serum IgE concentrations are increased in the majority of AD patients[27].
6) AD patients frequently have coexisting other allergic diseases (e.g., allergic rhinitis, allergic keratoconjunctivitis, and bronchial asthma)[28].
7) Children with AD frequently outgrow AD before puberty and progress to bronchial asthma and/or allergic rhinitis (allergic march)[28].

These evidences support that hypersensitivity reaction play a key role in the pathogenesis of AD, and allergen-specific therapies including the avoidance of sensitized allergen and allergen immunotherapy should be introduced for the treatment of AD patients.

EVIDENCES SUPPORTING THE IMMUNE DYSFUNCTION AS A MAJOR THERAPEUTIC TARGET FOR AD

Immune dysfunction could be an ideal therapeutic target to induce long-term treatment-free clinical remission in AD patients according to the following evidences[4,5,29-33].

1) Significant clinical improvement of AD can be induced by immunosuppressive drugs (e.g., cyclosporine, mycophenolate)[29,30].
2) Significant clinical improvement of AD can be induced by monoclonal antibodies to specific immune components (anti-IL-4 receptor antibody or anti-B cell antibody)[4,5].
3) Immunoadsorption to remove circulating immunoglobulins (IgG, IgA, IgM, and IgE) from plasma by using an anti-immunoglobulin antibody column induced significant clinical improvements in severe AD patients[31].
4) The majority of children with AD experience natural clinical remission before puberty[32].
5) Passive transfer of food allergy and subsequent development of AD occurred in a recipient following bone marrow transplantation from a donor with food allergy[33].

These evidences suggest that immune dysfunction plays a key role in the pathogenesis of AD and is a useful therapeutic target. Clinical remission might be achieved by the correction of immune dysfunction in AD patients. The present author believes that an increased exposure to environmental toxicants is the most important factor responsible for the recent substantial increase in the prevalence of AD in developed countries as suggested (Fig. 1)[21]. Current medical therapies focus on controlling skin inflammation by using topical corticosteroids and/or topical calcineurin inhibitors[1]. However, immune dysfunction and hypersensitivity reaction in the upstream of the pathogenetic pathway might be more useful therapeutic targets than control of skin inflammation for long-term clinical remission in AD patients (Fig. 1).

PREVIOUS REPORTS ON THERAPEUTIC INTERVENTIONS INDUCING LONG-TERM TREATMENT-FREE CLINICAL REMISSION OF AD

Previous reports suggest that long-term treatment-free clinical remission of AD could be achieved by a complete change in the living environment, allergen immunotherapy, or natural remission in children with AD (Table 1).

Climatotherapy or heliotherapy involving complete changes in the living environment of AD patients has been re-

Table 1. Treatment methods that have been reported to produce long-term clinical remission in patients with atopic dermatitis

1. Complete change in living environment (climatotherapy or heliotherapy)
2. Allergen immunotherapy with house dust mite allergen
3. Allergen and allergen-specific antibody immune complex therapy
4. Natural remission in children with atopic dermatitis

ported to produce long-term treatment-free clinical remission of AD in the majority of severe AD patients[34,35]. However, the clinical remission usually disappeared after the patients returned to their previous living environments[34,35]. These findings suggest that environmental factors are critical in the development and maintenance of AD. However, it is also suggested that the endogenous tendency of AD patients (immune dysfunction and hypersensitivity) prone to develop a chronic skin inflammation is not completely corrected by substantial change in the environmental factor alone.

Another important treatment modality that has been reported to produce long-term treatment-free clinical remission in AD patients is an allergen immunotherapy[36]. Observational studies reported long-term treatment-free clinical remission in AD patients after allergen immunotherapy or treatment by allergen-antibody complexes[36-38].

An interesting puzzle on the nature of AD is that a significant number of children with AD (up to 70%) experience natural remission of their disease before puberty[26]. The remission of AD in children seems to be due to a natural induction of immune tolerance. However, the exact mechanism inducing natural remission of AD in children has not yet been determined. If the mechanism is identified, then its application in the treatment of AD might be the most promising therapeutic approach in the future.

EVIDENCES AGAINST THE CRITICAL ROLE OF SKIN BARRIER DEFECT IN THE PATHOGENESIS OF AD

The evidences supporting the importance of immune dysfunction and hypersensitivity in the pathogenesis of AD argue against the hypothesis that defect in the gene for the skin barrier protein (i.e., filaggrin) is a primary cause of AD[12,13,39,40]. If the mutation of the filaggrin gene is a critical and essential pathogenetic component responsible for the development of AD, how can we explain the marked clinical improvements of AD frequently observed by complete changes in the environment (climatotherapy), allergen immunotherapy, or the interesting finding of natural remission observed in children with AD?

CRITICISM AGAINST THE CRITICAL ROLE OF HYPERSENSITIVITY REACTION TO ENVIRONMENTAL ANTIGEN IN THE PATHOGENESIS OF AD

There has been criticism regarding the importance of hypersensitivity reaction to environmental antigen in the pathogenesis of AD. The rationales supporting this criticism are as follows.

1) A certain number of AD patients have no evidence of allergic sensitization to environmental antigen, known as the "intrinsic type of AD" (about 10%～20% of adult AD patients)[41-43].
2) Avoidance of the sensitized house dust mite allergen was effective in children with AD but not in adult AD patients in randomized controlled studies[25,44].
3) The autoreactivity to self-protein (auto-allergy) seems to play a role in the development of chronicity of AD[45].
4) Although a systematic review on allergen immunotherapy for AD showed a positive evidence of clinical efficacy, relatively few well-designed clinical trials have studied the clinical efficacy of allergen immunotherapy, and further clinical trials are needed to obtain a strong evidence[19,46].

The relative importance of hypersensitivity reaction to environmental antigen in the pathogenesis of AD could be variable among patients[43]. In addition, a chemical or metal, rather than a protein, could act as an antigen causing chronic skin inflammation, as suggested in the intrinsic type of AD[42]. However, the importance of immune dysfunction and hypersensitivity reaction (not confined to IgE-mediated type I hypersensitivity reaction) in the pathogenesis of AD could be supported by the above mentioned evidences.

REASONS FOR THE CLINICAL EFFICACY OF MULTIPLE DIFFERENT THERAPEUTIC APPROACHES FOR AD ("DOMINO THEORY")

It is unclear how both climatotherapy and allergen immunotherapy can induce long-term clinical remission in AD patients although these 2 approaches target different pathogenetic elements of AD. The present author suggests that a vicious domino-circle formed from the negative interactions among multiple pathogenetic elements is essential for the development and maintenance of AD based on the personal clinical experiences obtained during the treatment of AD patients ("domino theory"). If one specific pathogenetic factor (e.g., environmental trigger, immune dysfunction, skin inflammation, or skin barrier defect) can be sufficiently controlled to break the vicious domino-cir-

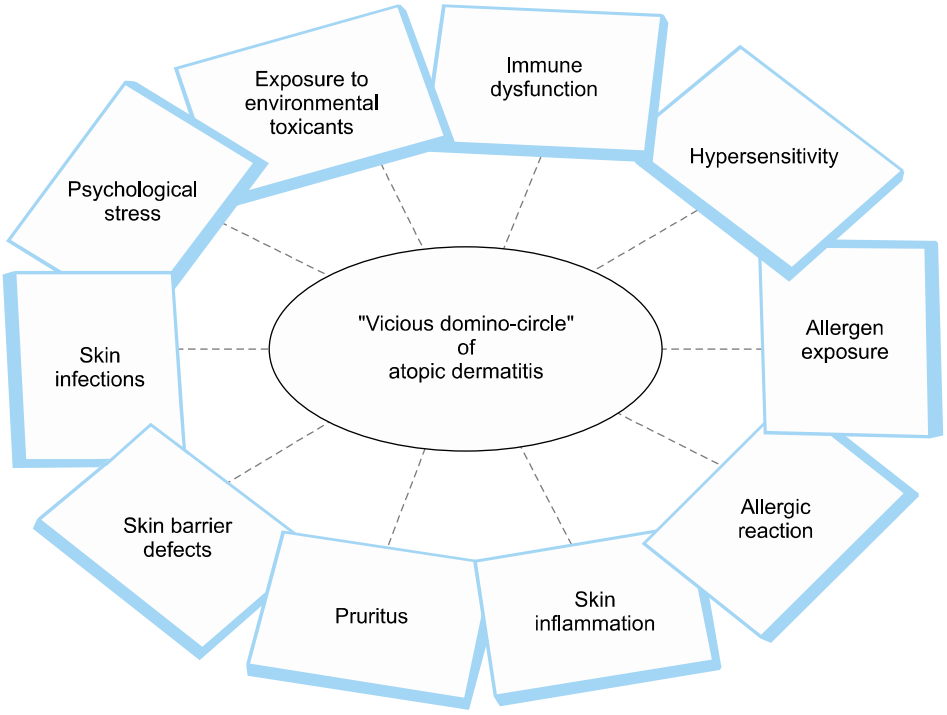

Fig. 2. "Domino theory".
A vicious domino-circle formed from negative interactions among multiple pathogenetic elements is essential for the development and maintenance of atopic dermatitis, and if one of the pathogenetic elements (e.g., environmental triggers, immune dysfunction, skin inflammation, or skin barrier defects) can be sufficiently controlled to break the vicious domino-circle, then clinical remission of atopic dermatitis could be possible.

cle, clinical remission of AD could be possible (Fig. 2). This theory can also explain the long-term clinical remission observed in AD patients induced by various types of therapeutic interventions including climatotherapy, allergen immunotherapy, diet change, nutritional supplementation, and lifestyle change. Therefore, the "domino theory" of AD supports a therapeutic concept that multiple different therapeutic approaches can produce clinical improvements and even induce long-term treatment-free clinical remission in AD patients. In addition, this concept supports that a multidisciplinary therapeutic approach including environmental control, psychological support, and patient education should be attempted to achieve maximal clinical improvements in AD patients.

REGULATORY T CELL AS A CRITICAL TARGET FOR THE TREATMENT OF AD

Regulatory T cell plays a critical role in maintaining immune tolerance including the suppression of autoimmunity (immune tolerance to self antigens) and hypersensitivity (immune tolerance to non-self antigens)[47]. Deficiency of regulatory T cell function has been suggested to be a key immune dysfunction responsible for the development of autoimmune and allergic diseases, as observed in animal experiments[48]. Allergen immunotherapy decreases allergic inflammation (T helper type2 cell activation and IgE-mediated reaction) and induces clinical improvement in patients with allergic diseases possibly through an activation of regulatory T cell[49]. Lactobacillus or vitamin D supplementation has also been shown to activate regulatory T cell in animal models[50,51]. There have been reports on the positive clinical efficacy of lactobacillus or vitamin D supplementation in AD patients[52-55]. Therefore, combinations of various approaches to activate regulatory T cell, including allergen immunotherapy, vitamin D supplementation, and lactobacillus supplementation, might provide maximal clinical improvements in AD patients by the induction of immune tolerance[51].

RATIONALE FOR A PERSONALIZED COMBINATION OF MULTIPLE THERAPIES TARGETING DIFFERENT STEPS IN THE PATHOGENETIC PATHWAY OF AD

The pathogenetic mechanisms involved in the development of AD seem to be variable among AD patients. Because of this heterogeneity in the pathogenetic mechanism, the clinical efficacy of a single type of therapy can be insufficient and unpredictable in AD patients. In real clinical practice, many physicians apply various combinations of pharmacological therapies targeting skin inflammation (use of topical corticosteroid and/or topical calcineurin) and immune dysfunction (use of immunosuppressant drugs including cyclosporine) and provide advices regarding the avoidance of environmental triggers (allergens

and irritants) in the treatment of AD patients. For the achievement of maximal clinical improvement, a personalized combination of immunomodulatory therapies including allergen immunotherapy and monoclonal antibody therapy (e.g., anti-IgE or anti-IL4 receptor antibody) should be tried and personalized according to the characteristics of immune dysfunction and hypersensitivity in individual AD patients in order to achieve a maximal clinical improvement.

PRESENT AND FUTURE OF IMMUNOMODULATORY THERAPY FOR AD

Current immunomodulatory therapies for AD using immunosuppressive drugs and monoclonal antibodies are directed to a nonspecific suppression of immune function, and this approach could be harmful in AD patients because of the possible increase in the risk of infection and/or malignancy. Therefore, future development of immunomodulatory therapy for AD should be directed to the normalization of immune dysfunction without immune suppression. The duration of the clinical efficacy of the current immunomodulatory therapies for AD is relatively short, and regular maintenance therapy is essential for long-term clinical improvement. Future immunomodulatory therapy for AD should aim for long-term clinical remission without the need for maintenance therapy (Table 2). Currently, none of the available immunomodulatory therapies has proven to modify the disease course of AD. Future immunomodulatory therapies should aim for the modification of the long-term disease course and ultimately the long-term treatment-free clinical remission and cure of AD. Unfortunately, no definite tool is currently available for the primary prevention of AD. Future studies should also focus on the development of preventive vaccines for AD.

Induction of immune tolerance mimicking the immunological mechanism responsible for the natural remission of AD in children would be an ideal method to achieve clinical remission in AD patients. Induction of an anti-idiotypic immune response (immune response to the antigen-binding site of an antibody) has been suggested as a mechanism responsible for the development of immune tolerance in animal studies[56]. However, limited clinical data supporting anti-idiotypic immunomodulatory therapy in human subjects with allergic diseases are available. Recently, the clinical efficacy of recombinant idiotype vaccines resulting in the prolongation of disease-free survival was demonstrated in patients with B-cell lymphoma in a randomized placebo-controlled clinical trial[57]. This result suggests that anti-idiotypic immunomodulatory therapy could be also clinically effective in patients with allergic diseases. The present author hypothesized that repeated intramuscular injections of autologous immunoglobulin could induce clinical improvements in AD patients by stimulating active immune responses to the antigen-binding sites of pathogenic antibodies, thereby correcting immune dysfunction. Repeated intramuscular injections of autologous immunoglobulin (mainly IgG) purified from autologous plasma using Protein A (autologous immunoglobulin therapy) induced significant long-term clinical improvements in 2 of 3 patients with severe recalcitrant AD[58]. Autologous immunoglobulin therapy also significantly decreased the clinical severity scores and serum IgE concentrations in 17 adult patients with severe AD[59]. Future immunomodulatory therapies for AD should be personalized to specifically correct the immune dysfunction and hypersensitivity in individual patients.

CONCLUSION

Immune dysfunction and hypersensitivity reaction play key roles in the pathogenesis of AD. Systemic immunomodulatory therapies with allergen immunotherapy or monoclonal antibodies to specific immune components could be effective in AD patients. However, the clinical efficacy of current immunomodulatory therapy is often unpredictable or insufficient in some AD patients due to the heterogeneity of the pathogenetic mechanisms among AD patients. Therefore, a personalized combination of immunomodulatory therapies to reduce hypersensitivity

Table 2. Present and future of immunomodulatory therapy for atopic dermatitis

Present	Future
· Transient symptomatic treatment	· Long-term clinical remission
· Pharmacological therapy	· Biological therapy
· Non-specific immune suppression	· Induction of immune tolerance. Correction of immune dysfunction and hypersensitivity.
· Monotherapy with single immunomodulatory modality	· Combinations of multiple antigen-specific and non-specific immunomodulatory modalities
· Treatment of patients with atopic dermatitis	· Prevention of development of atopic dermatitis in high risk subjects

(allergen immunotherapy) and correct immune dysfunction (monoclonal antibody therapy) could be a reasonable therapeutic approach for patients with AD. Future immunomodulatory therapies for AD should be developed to achieve long-term treatment-free clinical remission by induction of immune tolerance.

ACKNOWLEDGMENT

This work was supported by the National Research Foundation of Korea (NRF) grant funded by the Korea government (MSIP) (No. 2014R1A2A1A11049386).

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