Invited Review Article

Recent developments and advances in atopic dermatitis and food allergy

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ABSTRACT

This review highlights recent advances in atopic dermatitis (AD) and food allergy (FA), particularly on molecular mechanisms and disease endotypes, recent developments in global strategies for the management of patients, pipeline for future treatments, primary and secondary prevention and psychosocial aspects. During the recent years, there has been major advances in personalized/precision medicine linked to better understanding of disease pathophysiology and precision treatment options of AD. A greater understanding of the molecular and cellular mechanisms of AD through substantial progress in epidemiology, genetics, skin immunology and psychological aspects resulted in advancements in the precision management of AD. However, the implementation of precision medicine in the management of AD still requires the validation of reliable biomarkers, which will provide more tailored management, starting from prevention strategies towards targeted therapies for more severe diseases. Cutaneous exposure to food via defective barriers is an important route of sensitization to food allergens. Studies on the role of the skin barrier genes demonstrated their association with the development of IgE-mediated FA, and suggest novel prevention and treatment strategies for type 2 diseases in general because of their link to barrier defects not only in AD and FA, but also in asthma, chronic rhinosinusitis, allergic rhinitis and inflammatory bowel disease. The development of more accurate diagnostic tools, biomarkers for early prediction, and innovative solutions require a better understanding of molecular mechanisms and the pathophysiology of FA. Based on these developments, this review provides an overview of novel developments and advances in AD and FA, which are reported particularly during the last two years.

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Introduction

There are remarkable recent developments understanding the mechanisms, diagnostic and therapeutic management of atopic dermatitis (AD) and food allergy (FA) and differences in the practice by dermatologists and pediatricians in different countries. AD is a chronic inflammatory pruritic skin disease that affects a large number of children and adults in industrialized countries. Its worldwide prevalence, ranges from 0.2% to 24.6%, with the highest prevalence of AD in childhood in Africa and Latin America. The onset of AD occurs during the first year of life in 60% of the children. The prevalence of AD in the first 2 years of life is 21.5%. 43.2% of these children have spontaneous outgrow of the disease, 38.3% persist with mild AD and mild rhinitis and 18.7% persist with severe disease and show an extensive atopic march including FA, asthma, and rhinitis. Only 16.8% of AD patients have onset after adolescence. AD and FA are extensively overlapping. The prevalence of FA has been suggested to increase in the last two decades and is in the range of 4% in food challenge tests in 1 year, which increases to 6–8% in questionnaire surveys. FA shows various different clinical presentations with respect to responsible allergens, age at presentation, timing of reaction, presence of comorbid atopic diseases, outgrow and resolution with time, and response to immunotherapy. This heterogeneity of clinical presentations of FA possess a challenge to successful management and treatment. Avoidance of allergenic foods and the use of epinephrine in case of a severe reaction triggered by accidental ingestion remain the standard of care, as there are currently no approved treatments for FA. Dysregulated immune response patterns and their heterogeneous and complex combination in chronic inflammation, immune cell and tissue cell hyperresponsiveness, microinflammation even at the...
healing stage and tissue remodeling in affected tissues define the complexity of FA and AD.

Modern healthcare is rapidly developing and staying away from the concept of including all of the patients in one basket to an individualized response with the combination of precision diagnosis and personalized treatment. An overarching medicinal concept is developing with better understanding of genotypes, phenotypes, endotypes, regiotypes, biomarkers and therapeutics of diseases that also fully include AD and FA. More than 100 years old allergen-specific management of allergic diseases has particularly contributed to the early awareness in precision medicine. Multi-omics, big data, and systems biology have demonstrated a profound complexity and dynamic variability in AD and FA between individuals, as well as between regions.

Basic research has intensified during the recent years to better understand the immune and inflammatory mechanisms in AD and FA. IgE sensitization, essential molecular pathways of type 2 response, mechanisms of disease outgrow and therapy response are important in both diseases. Mechanisms of desensitization, successful ways of treatment without side effects and short- and long-term tolerance mechanisms are key research areas in FA. This article highlights and summarizes key advances in AD and FA published during the last couple of years. Important ones from these achievements are summarized in Tables 1 and 2.

**Global strategies for the assessment and management of atopic dermatitis**

There is a consistent association of AD with other atopic diseases including asthma and FA. The concept of atopic march was developed to describe the progression of these atopic diseases in children. Although it most often starts in infancy, it is also highly prevalent in adults. Among the adult AD population, a multidimensional burden has been described not only including dermatologic symptoms, but also increased socioeconomic burden, sleep disorders, and reductions in health-related quality of life and work productivity. With increasing severity, the multidimensional burdens listed above also increase. International Classification of Diseases, 11th Revision (ICD-11) was provided, and ICD-9, clinical modification codes alone were found to be insufficient for identification of AD from healthcare databases, but incorporation of the diagnosis of asthma, hay fever, and FA improved the positive predictive value and specificity of these searches. The Harmonizing Outcomes Measures for Eczema (HOME) initiative is an evidence driven and evidence-generating outcomes research initiative that aims to develop standardization of a core set of outcome measurements of atopic eczema, which is also known as AD or eczema. Various instruments exist to measure symptoms in AD to assess safety and efficacy of therapies in clinical trials. Among 18 instruments, the pediatric Itch Severity Scale (ISS), Patient-Oriented Eczema Measure (POEM), Patient-Oriented SCOring Atopic Dermatitis (PO-SCORAD), Self-Administered Eczema Area and Severity Index (SA-EASI), and adapted SA-EASI are currently recommended for assessing symptoms of AD in future clinical trials. However, the use of simple patient-reported global AD severity scores is feasible for clinical practice and epidemiological research. A simple scoring system of mild, moderate, and severe patient-reported AD severity correlated well with objective AD assessments, objective SCORAD, and EASI. Patient-reported AD severity may be sufficiently valid for assessing AD severity. For the management of AD, patient’s increased adherence to topical medication is indispensable particularly with use of topical corticosteroids. The topical corticosteroid phobia (TOPICOP) score is available for the assessment of topical corticosteroid phobia based on 12 items. TOPICOP scorings can feasibly be applied internationally and can be used to obtain data from studies and to adapt patient education and treatment. The lifetime prevalence of atopic diseases is significantly increasing from adolescence to adulthood, particularly that of allergic rhinitis. Regarding the clinical course of AD, no significant difference in AD prevalence before and after childhood has been found by systemic review and meta-analysis of longitudinal

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clear that differing nomenclature of the disease has important clinical and epidemiological research, it is becoming increasingly manifest. These longitudinal circumstances, the EAACI Taskforce on Regulatory Aspects of Allergen Immunotherapy, as a part of the EAACI AIT Guidelines, analyzed how effective treatment. Products for allergen immunotherapy (AIT) have been approved by national authorities; however, different regulations exist worldwide. Although regulatory framework in the European Union (EU) has been developed in the field of AIT, it remains heterogeneous. New allergen products for AIT are being developed and placed an emphasis on medical products that promote health and safety, and efficacy of medical allergen products is required for an effective treatment. Products for allergen immunotherapy (AIT) have been approved by national authorities; however, different regulations exist worldwide. Although regulatory framework in the European Union (EU) has been developed in the field of AIT, it remains heterogeneous. New allergen products for AIT are being developed and manufactured each year. However, despite the increased number of medical products such as AIT, regulatory framework for quality parameters has not yet been reached. Thus, it is extremely complicated and challenging to develop a harmonized international approach to regulation. International pharmaceutical companies have recently placed an emphasis on medical products that promote health and supply local and neighboring markets as well as global markets. Therefore, it is quite important to understand the regulation of allergen products from a global perspective. From these kind of circumstances, the EAACI Taskforce on Regulatory Aspects of Allergen Immunotherapy, as a part of the EAACI AIT Guidelines, analyzed how products for the diagnosis of allergies and AIT are regulated in different countries and regions worldwide. They also provided an overview of how AIT products are regulated with respect to their manufacturing and quality in EU, and United States. They described similarities and differences in the regulation of allergen manufacturing and quality control between the EU and United States.

Prevention of atopic dermatitis

The development of AD in infancy and subsequent conditions such as FA, asthma, and allergic rhinitis has been observed as co-manifestation or occurring in sequence. These longitudinal associations have been known to lead to atopic march, and an association between AD and birch pollen allergy has also been reported. There has been controversy regarding whether atopic march is the primary causal factor in childhood allergic diseases. A recent study indicated that AD, asthma and allergic rhinitis partly coexist, because they share many genetic risk variants that dysregulate the expression of immune-related genes. Another study showed that the risk of developing asthma or allergic rhinitis was much higher in IgE-associated AD compared to nonallergic AD. Therefore, it has been argued that it is important to distinguish between eczema with and without IgE sensitization when considering the implications of allergic diseases in infancy.

Environmental factors, such as bacteria influence the human microbiome and immune system. Development of novel preventative approaches is important, and a recent review summarizes current evidence for the potential of bacteria and their metabolites in the prevention of allergic diseases. Environmental factors, such as bacteria can influence the human microbiome and immune system. Development of novel preventative approaches is important, and a recent review summarizes current evidence for the potential of bacteria and their metabolites in the prevention of allergic diseases.

However, the increased incidence of AD and the progression from AD to allergic rhinitis and asthma have highlighted the need for disease prevention. A recent article indicates that shorter duration or non-exclusive breastfeeding was associated with a weak overall increased risk of AD, but not sensitization. Concerning the influence of pregnancy-related and perinatal factors, children who are born by cesarean section and assisted-delivery showed significant associations with AD, asthma and atopic sensitization in childhood. Effect of food diversity in childhood has also been investigated. The consumption of cheese had a significant protective effect for AD. The effect on AD may be associated with the diversity of consumed cheese, including those rich in microbial diversity. It has to be noted here that cheese is an important provider of short chain fatty acids that are linked to prevention of AD in children and mouse models. Despite a preventative approach to decrease AD in early-childhood, some patients may have persistent disease into adulthood. However, the prevalence of comorbidities in patients with AD is not well characterized.

Recent studies have shown that patients with severe AD had a high prevalence of smoking, stroke, cardiovascular disease, inflammatory bowel disease, depression and anxiety. Several studies in AD prevalence by country, estimations of adult AD prevalence ranges from 2.1% to 4.9%. For international clinical and epidemiological research, it is becoming increasingly clear that differing nomenclature of the disease has important harmful or unwanted consequences. AD as well as the term atopic eczema describe clinically chronic relapsing pruritic inflammatory skin conditions. In this context, the International Eczema Council (IEC) noted that the term eczema is imprecise and confusing and recommended the use of AD or atopic eczema in all publications, presentations and discussions about the disorder.

Product-specific standardization is of critical importance for patients with suspected or proven allergy. Ensuring persistent quality, safety, and efficacy of medical allergen products is required for an effective treatment. Products for allergen immunotherapy (AIT) have been approved by national authorities; however, different regulations exist worldwide. Although regulatory framework in the European Union (EU) has been developed in the field of AIT, it remains heterogeneous. New allergen products for AIT are being developed and manufactured each year. However, despite the increased number of medical products such as AIT, regulatory framework for quality parameters has not yet been reached. Thus, it is extremely complicated and challenging to develop a harmonized international approach to regulation. International pharmaceutical companies have recently placed an emphasis on medical products that promote health and supply local and neighboring markets as well as global markets. Therefore, it is quite important to understand the regulation of allergen products from a global perspective. From these kind of circumstances, the EAACI Taskforce on Regulatory Aspects of Allergen Immunotherapy, as a part of the EAACI AIT Guidelines, analyzed how products for the diagnosis of allergies and AIT are regulated in different countries and regions worldwide. They also provided an overview of how AIT products are regulated with respect to their manufacturing and quality in EU, and United States. They described similarities and differences in the regulation of allergen manufacturing and quality control between the EU and United States.

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These comorbidities might represent targets for prevention and intervention of AD management.

**Psychological aspects of atopic dermatitis**

AD has been thought to carry an increased risk for mental disorders. However, few studies have reported the prevalence of psychiatric disorders among adults with AD. A recent study revealed that adolescents with AD from Korea are associated with a higher prevalence of depression symptoms and suicidal behaviors. A poor health-related quality of life is linked with depressive mood, depression, and suicidal ideation, which are, in turn, associated with AD. Therefore, improving poor health-related quality of life and managing psychological status in AD among adolescents are critical. From a population-based survey using large-scale observational data, association among depression, anxiety, and AD has been analyzed. The risk of hospitalization and suicide was also examined. They found a significant association between self-reported AD among adults and clinician-diagnosed psychiatric status, including depression and anxiety. Moreover, a recent study of the association between AD and suicidality suggests that patients with AD are at an increased risk of suicidal ideation and suicide attempts. However, depression, anxiety, and suicidal ideation do not lead to psychiatric consultations, hospitalization, or suicide. One study reported that improvement of AD appears to be reduced these psychiatric conditions.

Epidemiological studies using standardized diagnostic criteria suggest that 3%–6% of the child population may suffer from attention-deficit/hyperactivity disorder (ADHD) and more recently, a relevant association between AD and ADHD has been reported. Moreover, children with ADHD are more likely to have not only AD but asthma, allergic rhinitis, and allergic conjunctivitis than their counterparts. A Swedish birth cohort study found that preschool eczema was not associated with ADHD medication at school age. To shed more light on the comorbidity of AD and ADHD, Schmitt et al. hypothesized that children with AD, who do not meet the complete diagnostic criteria of AD frequently show features of ADHD and increased mental health problems. They concluded that even if the clinical diagnosis of ADHD is excluded, children with AD show increased levels of ADHD symptoms. Despite these findings, the underlying biological mechanisms still require further investigation. Therefore, prevention and effective treatment of AD represent unmet needs in children as well.

**Mechanisms and pathophysiology of atopic dermatitis**

Major mechanisms of AD include abnormalities in the terminal differentiation of keratinocytes that lead to a defective stratum corneum. A defective barrier in AD allows the penetration of allergens and microbes, leading to IgE sensitization and type 2 cytokine production that drives allergic inflammation. At least two AD subtypes can be distinguished: the first type is characterized by a strong type 2 mediated response with high levels of serum immunoglobulin E (IgE) and the second is a nonallergic type characterized with normal IgE levels. MicroRNAs (miRNAs) are short, single-stranded RNA molecules that regulate Th2 skewing and influence innate and adaptive immune responses. Among miRNAs, miRNA-146a is needed for the production of IgE and linked to the modulation of Th1/Th17 cell mediated responses in mice. A matricellular protein, periostin, is induced by Th2 cytokines IL-4 or IL-13 and plays an important role in barrier dysfunction. A recent study shows that IL-24, produced in keratinocytes downstream of periostin and IL-13, decrease flaggann expression that leads to barrier dysfunction in AD. In AD, Th2 cells as well as other T-cell subpopulations (Th1, Th17, and Th22) are detectable in the AD skin lesions. Figure 1 shows immune and inflammatory cells in AD. It is important to emphasize that the majority of T cells in AD skin lesions are cutaneous lymphocyte-associated antigen (CLA) memory T cells. Due to recirculation, peripheral CLA T cells have similar features characteristic of T cells present in AD skin lesions. Various skin T cells, such as CD4 Th1 cells, CD4 Th2, CD4 Th17, CD4 Th22, CD4 Treg, resident memory T cells, γδ T cells, CD8 Tc1, CD8 Tc2, Mucosal-associated invariant T cells (MAIT) are described in Table 3. One recent advancement in AD was evidence showing that circulating CLA T cells can be a reliable peripheral biomarker of inflammatory events occurring in the skin. There is conflicting literature regarding the diversity of T-cell receptor (TCR) repertoire in AD skin lesions and their relationship to nonlesional skin. In this context, Brunner et al. showed that nonlesional AD skin shares a TCR repertoire similar to lesional AD skin.

Other cell types, such as innate lymphoid cells (ILC), mast cells, eosinophils, basophils, and inflammatory dendritic cell populations can be detected in AD skin. In human skin mast cells, proteomic analysis identifies two novel mast cell proteins, LICAM/CD171 and DPP4/CD26, that are specifically associated with AD skin. Skin mast cell and sphingosine-1-phosphate (SIP) activation is a novel effector that initiates remodeling in AD. Several ILC-modulating factors are dysregulated in AD and the levels of IL-25, IL-33, TSLP, and PGD2 are elevated in AD skin. In addition, cell–cell interactions between ILC2s and keratinocytes lead to activation or suppression of ILC2s. Identification of surface molecules on these cells involved in type 2 immunity could provide new therapeutic targets for the treatment of AD. Blom et al. identified, for the first time, the expression of CD200R by cells such as ILC2, Th2, and basophils. Interleukin-31 (IL-31), preferentially produced from Th2 cells, binds to the IL-31 receptor (IL-31R) expressed on sensory nerves. IL-31/IL31R signaling has recently been shown to play a critical role in the development of pruritus in AD. In the skin, there exists at least three populations of antigen-presenting cells including Langerhans cells (LCS), monocyte-derived LC-like cells, and inflammatory dendritic epidermal cells (IDECs). IDECs and LC-like cells have been found to be present in both steady states and inflammatory states, and they are present in AD. LC and IDEC in AD skin do not respond to Toll-like receptor (TLR) 2 activation and may contribute to the inability to clear S. aureus infection. LC in patients with AD carry the high-affinity receptor for IgE, FcεRI, and are engaged in the pathogenesis of AD. The aryl hydrocarbon receptor mediates the anti-inflammatory feedback mechanism in FcεRI-expressing human LC.

**Future therapeutic targets and experimental models for the treatment of atopic dermatitis**

Although there are many available treatments for allergic diseases, AIT induces establishment of long-term clinical tolerance to allergens, resulting in the prevention of further development of allergic diseases and a role for primary prevention has also been suggested. Among currently investigated AIT routes in FA, oral immunotherapy (OIT) involves the oral administration of increasing amounts of allergens. The transcriptomic profiles of skin obtained from mice that were epicutaneously sensitized, but orally tolerated indicate that oral antigen administration provides protection against AD by the expression of genes regulating Th2 inflammatory responses and skin barrier function. In a relevant mouse model of AD, another study reported the efficacy of topical ivermectin, a drug used for scabies and rosacea, improved AD by inhibiting the priming and activation of allergen-specific T cells.

Several recent studies have shown promising results in the use of mesenchymal stem cells for the treatment of AD.
explored the clinical potential for superoxide dismutase 3-transduced mesenchymal stem cells in mice with AD. They showed that subcutaneously administrated superoxide dismutase 3-transduced mesenchymal stem cells suppress skin inflammation via the histamine H4 receptor/IL-4 receptor-dependent mechanism.\textsuperscript{81} Succinate is an intermediate of the citric acid cycle that binds to its specific receptor, SUCNR1/GPR91. In addition, it acts as an alarmin and is involved in tissue injury or inflammatory stimulus. Furthermore, GPR91, a metabolic control receptor for the binding of succinate, deficiency in mice leads to allergic contact dermatitis, suggesting that GPR91 is a therapeutic target for the treatment of allergic skin diseases.\textsuperscript{82}

In humans, Kopf–nagel et al. investigated the effect of RNase 7, a 14.5-kDa antimicrobial ribonuclease on isolated human T cells.\textsuperscript{83} They demonstrated that CD4\textsuperscript{+} T cells from AD patients showed a less pronounced downregulation of IL-13 in response to RNase 7 compared to healthy controls.\textsuperscript{83} Thus, RNase 7 has immunoregulatory functions on Th2 cells and reduces the production of Th2 cytokines in the skin.

Many receptors have been studied, such as CCR4, CCR10, and CCR8, for the recruitment of immune cells to the skin.\textsuperscript{84–86} Due to the complexity of AD, it would be interesting to target specific cells with cocktails of chemokine receptor antagonists administered as ointments on the skin.\textsuperscript{84} In a randomized clinical trial of neonatal...
BCG vaccination in the Danish population, BCG vaccination at birth was found to be associated with less AD among children with atopic predisposition, although more studies are needed to confirm these findings.87

Precision medicine for food allergy: diagnosis and the role of biomarkers in early prediction

Molecular mechanism-linked therapies can be defined as therapies tailored to the characteristics of each patient to obtain a better clinical outcome. These different therapeutic responses linked to individual patient’s biological mechanisms is known as precision medicine.88 Precision medicine consists of four main components including disease taxonomy, digital monitoring of patients and biomarkers, disease phenotypes and endotypes, and biomarker-and endotype-linked patient care and therapies.89 Three main pillars of precision medicine are endotypes, phenotypes, and biomarkers.90 Important concepts such as regiotypes and theratypies have been recently introduced. Both regiotypes (regional differences in phenotypes and endotypes as well as allergens affecting different parts of the world) and theratypies (treatment responses) represent important advancements for precision diagnosis and treatment.91 All of all allergic diseases, FA is particularly well-suited as a target for precision medicine. This is due to its pathophysiology, the modulation of which has resulted in better clinical outcomes, and additionally has been clearly associated with detectable biomarkers90,91. The consensus document of EAACI and American Academy of Allergy, Asthma and Immunology (AAAAI) has been recently published under the auspices of the PRACTALL collaboration platform.92 PRACTALL is an initiative of EAACI and AAAAI to harmonize the European and American approach to allergic diseases with regard to patient treatment and scientific progress.90 In the consensus document, special consideration was given to defining endotypes in order to assist in developing novel therapeutic approaches. The definition of endotypes in FA is necessary to develop novel therapeutic approaches. FA endotypes can be characterized into IgE-mediated endotypes, including alpha-gal allergy and oral allergy syndrome, and non-IgE-related and mixed endotypes such as food protein–induced gastrointestinal endotype and eosinophilic endotype.93-96 Diagnostic tools and biomarkers for accurate diagnosis, evaluation of prognosis, and efficacy of treatment are still under investigation, but basophil activation test and component-resolved diagnostics are promising tools.95,96 A recent systematic review showed that selected components of cow’s milk, hen’s egg, peanut, hazelnut, and shrimp allergen revealed high specificity for diagnosis of FA in component resolved diagnosis.97,98 In a multicenter study, the detection of Ana o 3-specific IgE provides a predictive value in the diagnosis in children with suspected cashew allergy.99 A combination of component-resolved diagnostics and other factors such as clinical background and extract-based serology has been proposed to predict severe reactions to hazelnut allergy.99 Several biomarkers have been associated with FA including skin prick tests, allergen specific IgE, IgG4, genetic, and epigenetic markers.90,103,104 A study of patients with meat allergy revealed that the IgG subclass distribution in these patients is distinct from natural IgG responses in nonallergic individuals.105 Due to a frequent co-sensitization to birch pollen allergens and profilins, diagnosis of lipid transfer proteins (LTPs) using plant extracts is difficult.106 In a study from a central European population, Pru p 3, peach LTP, can be used as an allergen marker for LTP sensitization.107 To identify diagnostic markers for anaphylaxis in food allergic patients, Wittenberg et al. found serum levels of apolipoproteins as a useful biomarker of anaphylaxis.108 Early prediction of the severity of FA is one of the key issues for the accurate diagnosis and improved management. The extent to which the severity of food allergic reactions can be predicted by clinical factors such as age, type of food, and eliciting dose is currently unknown.109 Several studies provided evidence that the eliciting dose contributes to the frequency of accidental reactions.10,110 Another study suggests that individuals have a threshold of reactivity for symptoms in general as well as a threshold for symptoms specifically of anaphylaxis.111 Additionally, a double-blind, placebo controlled study on patients with food challenge-confirmed FA to milk, egg, peanut, cashew, and/or hazelnut indicated that clinicians should not use the eliciting dose obtained from a graded food challenge.112 This is because eliciting dose only contributes to reaction severity. A successful diagnostic allergy work-up is required to tailor medical treatments to individual characteristics of each FA patient.111 Extensive immune and allergy workups are becoming more and more important for many diseases.113 For FA diagnosis, a comprehensive toolbox for improved documentation and decision-making using oral food challenges has been provided.114 With these tools, we hope to reduce the influence of subjective judgment of supervising physicians.115

Innovative solutions: allergen exposure chambers

Allergen exposure chambers have proven to be valuable tools for diagnosis and determining safety and efficacy of new therapeutics.116-119 This tool can help to develop further evidence for allergen immunotherapy as well as biological therapies, which can potentially control allergic diseases.120-122 Allergen exposure chambers also provide a new setting which has generated evidence that in patients with AD with grass pollen sensitization is linked to a worsening of cutaneous symptoms.123 Although facilities have been reported as technically validated, various technical setups and specifications are found in allergen exposure chamber facilities.124 Furthermore, several unmet needs require attention and evaluation before allergen exposure chambers can be used in allergen immunotherapy clinical trials.125 Thus, it is necessary to standardize allergen exposure chambers, and harmonize protocols for clinical and immunological research in order to improve data quality and facilitate better application of allergen exposure chambers. Currently, the EAACI position paper harmonizes current concepts of allergen exposure chambers with regard to standardization of the challenge procedure and assessments, pediatric issues, and regulatory issues.126 These relevant unmet needs and issues may be addressed before determining safety and efficacy of new therapeutics.125

Animal models in AD and FA

Animal models of human diseases are commonly utilized for the development of new drugs and the analysis of pathogenic research. Current animal research targets specific immune mechanisms involved in human atopic and allergic diseases.127 In AD, AIT has been recently reported in a randomized controlled trial and meta-analysis, especially in patients sensitized to the house dust mite antigen.128-130 However, there is still controversy about the role of AIT as a therapeutic intervention in AD. Several reasons exist for this, such as there is no relevant mouse model to investigate the mechanism and validate AIT in AD and primary end points were not achieved in several proof of concept clinical trials in AD. Shin et al. established an AIT model of AD using Dermatophagoides farinae treated NC/Nga mice and demonstrated clinical and histological improvement.131 They found that induction of Tregs and IL-10-producing NK cells is a possible source of IL-10 and this model may be a useful tool to analyze the efficacy of AIT modalities for the treatment of AD.131
Mechanisms and pathophysiology of food allergy

In food allergic patients, exposure to food antigens elicits a type 1 hypersensitivity reaction, which induces anaphylaxis. Atopic diseases are significantly associated with food induced anaphylaxis both in children and adults, but not with anaphylaxis induced by drug and venom. Oral tolerance is the mechanism by which we maintain a normal physiological response to food antigens, and the breakdown of oral tolerance is likely to be linked to sensitization to food allergens. In humans, early skin barrier disruption due to environmental allergens is in addition, little is known about the mechanisms of FA reactions in companion animals. In dogs, an allergen specific IgE response and CD8+ T cell phenotype have been studied for the mechanism of FA. Based on the current knowledge and the EAACI position paper, comparative studies of companion animals and humans suffering from FA may serve to fill knowledge gaps in this area.

Novel strategies for the treatment and management of food allergy

The current treatment approach of FA is strict avoidance of the offending food or foods and the use of rescue medication in the event of an allergic reaction. Therefore, a significant amount of research has been conducted on food AIT including OIT, sublingual immunotherapy (SLIT), and epicutaneous immunotherapy (EPIT). The aim of food AIT is to achieve clinical desensitization, sustained unresponsiveness, and oral tolerance, which are essential for emerging therapies for FA. The EAACI Task Force on Allergen Immunotherapy for IgE-mediated FA provided evidence-based recommendations for active treatment with AIT. Food AIT has shown the greatest promise for children 4–5 years of age with
symptoms suggestive of persistent IgE-mediated FA to cow’s milk, hen’s egg, or peanut.\textsuperscript{167} In addition to the improvement of symptoms, quality of life of patients with FA improves during OIT for allergy.\textsuperscript{168} In other words, a greater understanding of psychological mechanisms suppresses experimental FA in mice. Combination therapy with AIT.\textsuperscript{175} Encapsulation of allergens or DNA vaccines into nanomaterials may provide advantages compared to conventional AIT.\textsuperscript{176,177} Srivastava et al., investigated the efficacy and safety of peanut OIT using CpG-coated nanoparticles containing a peanut extract in a mouse model of peanut allergy.\textsuperscript{178} They found that mice treated with the nanoparticles were significantly protected from anaphylaxis.\textsuperscript{179} For the improvement of SLIT treatment, combination therapy with systemic administration of IL-2/anti-IL-2 complex suppresses experimental FA in mice. Combination therapy may represent a promising strategy for the treatment and management of FA.\textsuperscript{179} Another recent focus has turned to primary prevention of FA.\textsuperscript{180} Early peanut introduction is one way to prevent, but early peanut recommendations differ among countries with formal guidelines.\textsuperscript{181} Furthermore, there is evidence supporting that early egg introduction can decrease the risk of developing egg allergy.\textsuperscript{182}

Conclusion

In conclusion, we have reviewed the recent developments on AD and FA. An important feature of these recent developments is that the era of precision medicine brings novel strategies in the management and treatment of AD and FA. Development of a prevention strategy, early interventions and psychological disturbance are important aspects of patient care. The emergence of novel diagnostic tools, innovative solutions, and biomarkers as well as novel mechanisms of AD and FA can be used to accelerate the development of novel drugs and targeted therapies. Identifying treatment effects and looking at candidate biomarkers in both animal models and humans will provide evidence to promote the ability to practice personalized treatment.

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Conflict of interest

CAA reports employment/leadership/advisory role in Regeneron, Sanofi Aventis, and Scilbase. He has received research funding from Allergopharma, Novartis, Idorsia, SciBase, EU Horizon 2020 Cure, Swiss National Science Foundation, and Actelion. KS has no conflict of interest.


