NEWS AND COMMENTARIES

Global Allergy Forum and 3rd Davos Declaration 2015
Atopic dermatitis/Eczema: challenges and opportunities toward precision medicine

DOI:10.1111/all.12857

Atopic dermatitis/eczema (AD) is a highly complex disease showing a clear increase in its incidence across all continents during the last decades (1, 2). It is the most common skin disease and has, almost other allergic diseases, a substantial socioeconomic impact (3). The complexity of the underlying mechanisms explains the wide spectrum of the clinical phenotype such as the age of onset, natural history, range of sensitization, provocation factors, clinical appearance, severity, and therapeutic response. Moreover, progress in the last years (4) has also highlighted the potential role of the skin microbiome, neuro-immunological signals, and epigenetic regulation in the modulation of the disease, adding another level of complexity. This situation calls for a more differentiated approach in our efforts to understand the pathophysiology and to develop new preventative and therapeutic strategies better tailored for the subsets of this complex phenotype. This is particularly true when we consider the infantile and childhood onsets of AD, which are currently regarded as the first step of the feared atopic march including allergic rhinitis and/or asthma (5, 6). Thus, AD should more be considered as a systemic disease with a number of relevant comorbidities (7, 8), which will greatly benefit from new developments in the era of precision medicine (9).

In July 2015, a group of 63 scientists and clinicians from 13 countries gathered under the auspices of the Christine Kühne – Center for Allergy Research and Education (CK-CARE) for the 3rd Global Allergy Forum in Davos, Switzerland. As in the past, the scientists intensely discussed key issues relevant in the field of allergy and AD (10, 11). The aim of the Think Tank meeting in 2015 was to define and discuss new strategies in research and education in AD, which will pave the way for the precision medicine pathways in AD. This document is not meant to be a comprehensive list of research areas but rather summarizes the main results of the working groups in charge of the six most important fields considered for this meeting.

Epidemiology/standardization

Although AD is the most common skin disease, there are a number of critical issues with substantial consequences for our understanding of the global epidemiology of the disease (12–14). Simple issues such as the lack of consensus on the criteria for its diagnosis linked to the absence of standardized data and outcomes sets represent important hurdles for comparable data for current prevalence of AD in most regions. Hence, there is an underestimation of disease burden and the comorbidities (15, 16). No comparable data for treatments and prevention used in AD are available (17).

Key questions to be addressed as follows:

- A global consensual definition of AD valid for epidemiology, genetics and clinical research (fix the issue of extrinsic *vs* intrinsic AD).
- A validated methodology for measuring the severity of AD.
- Establish comprehensive and standardized registries for epidemiological studies in AD.
- The role of prenatal factors for the emergence of AD.
- Global epidemiology of AD and related disorders/comorbities in the different regions.
- Impact of AD on the quality of life at different ages and in different countries.
- Subtypes of AD according to the regions worldwide and the healthcare profiles.
- A better understanding of the different ages of onset, particularly in elderly.
- Different preventive and therapeutic approaches worldwide.

Skin barrier

Since the demonstration of functionally relevant mutations of the *filaggrin* (FLG) gene in AD, the role of the epidermal barrier function in the pathophysiology has been well established. Its significance for the sensitization toward food and environmental allergens has been shown in animal models and more recently in human (18, 19). However, a number of other mutations and/or variants affecting epidermal structures have been reported, which may have some functional relevance for our understanding of the disturbed epidermal barrier function and its consequences in AD (20, 21).

Key questions to be addressed as follows:

- A clearer definition of what exactly barrier function is.
- Functional genomics of candidate genes involved in the barrier function.
- Developing better tools for assessing the barrier function.
- Biomarkers discovery in the field of barrier function.
- Stratification of the phenotype 'barrier dysfunction' into more precise subgroups with appropriate biomarkers.

- Understanding the acquired and epigenetic regulation of the barrier function
- Need of proof of concept studies for improving the barrier function (e.g., pharmacologically induced increase of FLG expression).
- Better characterize the dynamic interaction between the stratum corneum and tight junctions.
- Impact of the individual microbiota on the barrier function.
- Impact of systemic and targeted therapies on the barrier function.
- Development of more biomarker-based and tailored moisturizers for early intervention in newborns.
- Improving the education of patients and parents for prevention and therapy approach.

Immune deviation

There is an overall agreement that, besides the barrier function, a deviation of the immune system represents the second important pillar in the pathophysiology of AD. Although substantial progress has been made in the last years, recent reports strongly suggest that we are far from understanding the pivotal mechanisms, which seem to be more complex than the initial Th2/Th1 dogma (22–24).

Key questions to be addressed as follows:

- Cooperative research activities on immune response in AD worldwide, for example, on micro-inflammation in nonlesional skin, immunology of comorbidities, recently discovered subsets of T cells, B cells, innate lymphoid cells, and epigenetic regulation.
- Immunological treatment *vs* cure of AD: Development of trials on the induction of immune tolerance in AD patients.
- Development of combined scores (biomarkers combined with clinical scores—algorithm) for diagnosis and endotypes.
- Development of better *in vitro* diagnostic (T-cell-related tests) and/or algorithm of diagnostic skin tests (skin prick test—atopy patch test) for AD.
- Development of studies on combined therapies (e.g., topic plus systemic, two biologicals, allergen specific immunotherapy plus dupilumab, imitation of real life scenario).
- Development and study of efficient antipruritic/anti-inflammatory drugs (thymic stroma lymphopoietin, IL-31, and histamine receptor type 4).
- The investigation of immune tolerance to relevant antigens/allergens by specific immunotherapy for the prevention of AD: subcutaneous immunotherapy, sublingual immunotherapy, and epicutaneous immunotherapy.
- Defining immunological target mechanism for primary/secondary prevention by learning from studies of outgrowth of disease 'window of opportunity'.

Environment/microbiome

Environment in the context of diseases is defined as the sum of exposure to physical, chemical, microbial, and psychosocial factors. AD is strongly influenced by the environment (25), and protective as well as aggravating factors have been described. One factor that has been extensively studied recently is the microbiome, which could also be considered as a part of the human body (26). Recent findings substantiated the role of host body-microorganisms interactions in the development and maintenance of AD (27). Further research should aim at elucidating the principles that govern the assembly, dynamics and impact of the microbiota on the skin barrier in AD (28). The results may open new research windows toward personalized microbiome-based intervention.

Key questions to be addressed as follows:

- Difference between 'healthy' microbiota and dysbiosis data from various populations, for example with different lifestyles and geographical or ethnical origins. Analysis of different skin layers, that is the stratum corneum and layers beneath.
- The topographical microenvironment of healthy and diseased skin sites in AD.
- The diversity and composition of microbiota in skin, in gut, and of other organ systems such as the lung in AD patients compared to healthy individuals.
- Microbiota research extended to the metabolome and its impact on microbe–microbe interactions on barrier function and skin redox state.
- Effects of macro- or micro-environmental factors on the composition and diversity of the microbiota, including hormones and human or microbial antimicrobial peptides (microenvironment), or pollutants, food, temperature, and water (macro-environment).
- Impact of topical (topical steroids and calcineurin inhibitors) or systemic therapies with antibiotics or immune-modifying/suppressive drugs and the biologicals. The impact of microbiota on potentiation or inhibition of treatments (e.g., via metabolism of active substances or indirect regulation of target cells).
- The impact of stress on microbiota and thus on skin homeostasis.

Psychoneurological aspects

Psychological stress can elicit flares of AD as well as asthma and other allergic diseases (29). Conditions like attention deficit hyperactivity syndrome (ADHS) have been observed in connection with AD. Itch as a subjective sensation is difficult to be measured objectively, although there are imaging studies having visualized central nervous itch perception and processing (30). There is little specific and effective antipruritic treatment for eczema itch (31).

Key questions to be addressed as follows:

- Neurogenic inflammation including neuropeptide–neurotrophic axis (including influence of the brain) and pruritus as an important pathophysiologic aspect of AD.
- Studies on psychiatric comorbidities in comparison with coping behavior in AD.
- Quality of life and psychosocial burden of diseases.
- The influence of culture and ethnicity in the clinical course and psychosocial aspects of AD.

- Better and objective measurements for quantitative assessment and for differentiating qualitative aspects of various kinds of itch sensation.
- The role of different histamine receptors (histamine H1, H2, H3, and H4 receptors) and respective agonists as well as antagonists.
- Understanding the impact of newly developed molecules and mediators (anticytokine, antireceptors, specific inhibitors, etc.) on itch.
- The role of psychosomatic interactions in management by the physician. Need for confident and empathic doctors.
- Mother/parent and child interactions as a 'complex unit' requiring also the 'treatment of the parent or relatives' in parallel to treatment of the affected child. Give self-assurance to the mother and take away any feelings of guilt for exacerbations or worsening of clinical course of eczema.
- Psychosomatic interventions in the management of severe and chronic atopic dermatitis. Controlled trials for various psychosomatic interventions. Reimbursement issues.
- The basis for the high suggestibility (placebo and nocebo response) in AD patient.
- Addition of education in basic psychosomatic competence for dermatology/allergists.

Education

Atopic dermatitis/eczema represents a kind of paradigmatic disorder where, despite its substantial prevalence, there are obviously substantial gaps in the communication between the patients and the different stakeholders involved in the management. Indeed, the kind of information exchanged between, for example, scientists, specialist physicians, general practicioners (GP) and pediatricians, allied healthcare professionals, pharmacists, payers, and policymakers must be adapted and by essence diverges significantly (32). For most effective patient outcomes (33), AD management requires interprofessional care (34); it seems obvious that it also requires interprofessional education (IPE) (35, 36).

Key questions to be addressed as follows:

- Providing key knowledge to GP and other specialists taking care of AD patients and families.
- Understanding and appreciating the needs of the different physician groups handling patients with atopic dermatitis.
- Build education programs for different physician groups based on their gaps of knowledge, skills and attitude (i.e., their competency gaps between best practice and their current performance).
- Enabling interprofessional learning within the continuum of medical education.
- Establish 'guidelines' for affected patients and families.
- Educate physician for missing skills in the management of AD.
- Improve collaboration between different disciplines (e.g., dermatologists and pediatricians).
- Implementation of educational programs ('eczema school') and availability to as many patients as possible.
- Allied health personal and other health professionals as target groups for eczema education namely nurses, nursery nurses, or pharmacists.
- Use of electronic media such as Web-based learning resources, games, and social media to increase acceptance.

Conclusion

Among allergic diseases, AD is a paradigmatic disorder due to its genetic, immunological and phenotypical complexity. Thus, the so far classical unifying approach usually mirrored in most of the recent guidelines needs to be thoroughly revisited, and, beside some interesting animal models, the focus should be concentrated on human translational research involving large prospective cohorts. The output of the working groups of the GAF 2015 outlines a number of challenges and opportunities to be addressed in the future in order to have a comprehensive picture of AD with all its multiple facets as the background for precision medicine. Thus, building high-quality dynamic registries fed with detailed phenotypical data linked to biobanks with a variety of tissue samples will provide the basis for the discovery and validation of biomarkers with the aim to stratify AD into more homogeneous subgroups. This strategy has the potential to better select the responding populations in the development of forthcoming biologicals (37) and specific immunotherapy regimen (38). Hence, more tailored preventative and therapeutic approaches including interprofessional educational activities will be developed to significantly improve the management of AD.

Conflicts of interest

The authors declare that they have no conflicts of interest.

T. Bieber[1,2], C. Akdis[1,3], R. Lauener[1,4,5], C. Traidl-Hoffmann[1,6], P. Schmid-Grendelmeier[1,7], G. Schäppi[1], J.-P. Allam[1,2], C. Apfelbacher[8], M. Augustin[9], L. Beck[10], T. Biedermann[11], C. Braun-Fahrländer[12], F. T. Chew[13], T. Clavel[14], R. Crameri[1,3], U. Darsow[11], M. Deleuran[15], D. Dittlein[6], H.-W. Duchna[16], L. Eichenfeld[17], K. Eyerich[11], R. Frei[1,3], C. Gelmetti[18], U. Gieler[19], S. Gilles[1,6], M. Glatz[7], K. Grando[7], J. Green[20], J. Gutermuth[21], E. Guttman-Yassky[22], J. Hanifin[23], D. Hijnen[24], W. Hoetzenecker[1,7], A. Irvine[25], A. Kalweit[16], N. Katoh[26], E. Knol[27], H. Koren[28], M. Möhrenschlager[16], D. Münch[1], N. Novak[1,2], L. O'Mahony[1,3], A. S. Paller[29], C. Rhyner[1,3], C. Roduit[1,4,5], K. Schiesser[7], J. Schröder[30], D. Simon[31], H.-U. Simon[32], M. Sokolowska[1,3], P. Spuls[33], J.-F. Stalder[34], D. Straub[1], Z. Szalai[35], A. Taieb[36], R. Takaoka[37], G. Todd[38], A. Todorova[1,5], C. Vestergaard[15], T. Werfel[39], A. Wollenberg[40] and J. Ring[1,16]

[1]*Christine Kühne – Center for Allergy Research and Education (CK-CARE) Davos-Augsburg-Bonn-St. Gallen-Zürich, Davos, Switzerland and Germany;*

[2]*Department of Dermatology and Allergy, University Bonn, Bonn, Germany;*

[3]Swiss Institute of Allergy and Asthma Research (SIAF), Davos;
[4]Children's Hospital of Eastern Switzerland, St. Gallen;
[5]University of Zurich, Zurich, Switzerland;
[6]Institute of environmental medicine, UNIKA-T, Technical University and HelmholtzCenter, Munich, Germany;
[7]Allergy Unit, Department of Dermatology, University Hospital, Zurich, Switzerland;
[8]Medical Sociology, Institute of Epidemiology and Preventive Medicine, University of Regensburg, Regensburg;
[9]Institute for Health Services Research in Dermatology and Nursing, University of Hamburg, Hamburg, Germany;
[10]Department of Dermatology, University of Rochester Medical Center, Rochester, NY, USA;
[11]Department of Dermatology and Allergy Biederstein, Technical University, Munich, Germany;
[12]Swiss Tropical and Public Health Institute, EPH, Basel, Switzerland;
[13]Department of Biological Sciences, National University of Singapore, Singapore, Singapore;
[14]ZIEL, Technische Universität München, Freising-Weihenstephan, Germany;
[15]Department of Dermatology, Aarhus University Hospital, Aarhus, Denmark;
[16]Hochgebirgsklinik, Davos, Switzerland;
[17]Rady Children's Hospital, San Diego School of Medicine, San Diego University of California, San Diego, IL, USA;
[18]Unit of Dermatology and Pediatric Dermatology, Department of Pathophysiology and Transplantation, Fondazione IRCCS Cà Granda 'Ospedale Maggiore Policlinico', University of Milan, Milan, Italy;
[19]Department of Dermatology, University Medical Center, Giessen, Germany;
[20]Private Educational Consultant, Professional, Resource Network, Inc., Chapel Hill, NC, USA;
[21]Department of Dermatology, University of Brussels, Brussels, Belgium;
[22]Dermatology Department, Icahn School of Medicine at Mount Sinai, New York, NY;
[23]Oregon Health and Science University, Portland, OR, USA;
[24]Department of Dermatology, University Medical Center, Utrecht, The Netherlands;
[25]Department of Dermatology, Our Lady's Children's Hospital Crumlin, Dublin, Ireland;
[26]Department of Dermatology, Kyoto Prefectural University of Medicine, Kyoto, Japan;
[27]Department of Immunology and Department of Dermatology/Allergology, University Medical Center Utrecht, Utrecht, The Netherlands;
[28]Environmental Health, LLC, Durham, NC;
[29]Departments of Dermatology and Pediatrics, Northwestern University Feinberg School of Medicine, Chicago, IL, USA;
[30]Department of Dermatology, University Hospital Schleswig-Holstein, Kiel, Germany;
[31]Department of Dermatology, Inselspital, University Hospital;
[32]Institute of Pharmacology, University of Bern, Bern, Switzerland;
[33]Academic Medical Centre, University of Amsterdam, Amsterdam, The Netherlands;
[34]Department of Dermatology, University of Nantes, Nantes, France;
[35]Department of Dermatology, Heim Pal Children's Hospital Budapest, Budapest;
[36]Department of Dermatology, University of Bordeaux, Bordeaux, France;
[37]Department of Dermatology, University of Sao Paulo School of Medicine, SaoPaulo, Brazil;
[38]Department of Medicine, Faculty of Health Sciences, University of Cape Town, Cape Town, South Africa;
[39]Department of Dermatology, Hannover Medical School, Hannover;
[40]Department of Dermatology, University of Ludwigs-Maximilians, Munich, Germany

References

1. Flohr C, Mann J. New insights into the epidemiology of childhood atopic dermatitis. *Allergy* 2014;**69**:3–16.
2. Mortz CG, Andersen KE, Dellgren C, Barington T, Bindslev-Jensen C. Atopic dermatitis from adolescence to adulthood in the TOACS cohort: prevalence, persistence and comorbidities. *Allergy* 2015;**70**: 836–845.
3. Zuberbier T, Lotvall J, Simoens S, Subramanian SV, Church MK. Economic burden of inadequate management of allergic diseases in the European Union: a GA(2) LEN review. *Allergy* 2014;**69**: 1275–1279.
4. Weidinger S, Novak N. Atopic dermatitis. *Lancet* 2015; doi:10.1016/S0140-6736(15) 00149-X.
5. Dharmage SC, Lowe AJ, Matheson MC, Burgess JA, Allen KJ, Abramson MJ. Atopic dermatitis and the atopic march revisited. *Allergy* 2013;**69**:17–27.
6. Saunders SP, Moran T, Floudas A, Wurlod F, Kaszlikowska A, Salimi M, et al. Spontaneous atopic dermatitis is mediated by innate immunity, with the secondary lung inflammation of the atopic march requiring adaptive immunity. *J Allergy Clin Immunol* 2016;**137**: 482–491.
7. Garcia-Aymerich J, Benet M, Saeys Y, Pinart M, Basagana X, Smit HA, et al. Phenotyping asthma, rhinitis and eczema in MeDALL population-based birth cohorts: an allergic comorbidity cluster. *Allergy* 2015;**70**:973–984.
8. Deckert S, Kopkow C, Schmitt J. Nonallergic comorbidities of atopic eczema: an overview of systematic reviews. *Allergy* 2014;**69**:37–45.
9. Bieber T. Personalized management of atopic dermatitis: Beyond emollients and topical steroids. In: Bieber T, Nestlé F, editors. *Personalized Treatment Options in Dermatology*. London: Springer, 2015: 61–76.
10. Ring J, Akdis C, Behrendt H, Lauener RP, Schappi G, Akdis M, et al. Davos declaration: allergy as a global problem. *Allergy* 2012;**67**:141–143.
11. Ring J, Akdis C, Lauener R, Schappi G, Traidl-Hoffmann C, Akdis M, et al. Global Allergy Forum and Second Davos Declaration 2013 Allergy: barriers to cure–challenges and actions to be taken. *Allergy* 2014;**69**:978–982.
12. Garg N, Silverberg JI. Epidemiology of childhood atopic dermatitis. *Clin Dermatol* 2015;**33**:281–288.
13. Hay RJ, Johns NE, Williams HC, Bolliger IW, Dellavalle RP, Margolis DJ, et al. The

global burden of skin disease in 2010: an analysis of the prevalence and impact of skin conditions. *J Invest Dermatol* 2014;**134**:1527–1534.
14. de Korte-de BD, Mommers M, Gielkens-Sijstermans CM, Creemers HM, Mujakovic S, Feron FJ, et al. Stabilizing prevalence trends of eczema, asthma and rhinoconjunctivitis in Dutch schoolchildren (2001–2010). *Allergy* 2015;**70**:1669–1673.
15. Hjuler KF, Bottcher M, Vestergaard C, Deleuran M, Raaby L, Botker HE, et al. Increased prevalence of coronary artery disease in severe psoriasis and severe atopic dermatitis. *Am J Med* 2015;**128**:1325–1334.
16. Bousquet J, Anto JM, Wickman M, Keil T, Valenta R, Haahtela T, et al. Are allergic multimorbidities and IgE polysensitization associated with the persistence or re-occurrence of foetal type 2 signalling? The MeDALL hypothesis *Allergy* 2015;**70**:1062–1078.
17. Deckers IA, McLean S, Linssen S, Mommers M, van Schayck CP, Sheikh A. Investigating international time trends in the incidence and prevalence of atopic eczema 1990–2010: a systematic review of epidemiological studies. *PLoS One* 2012;**7**:e39803.
18. Thyssen JP, Tang L, Husemoen LL, Stender S, Szecsi PB, Menne T, et al. Filaggrin gene mutations are not associated with food and aeroallergen sensitization without concomitant atopic dermatitis in adults. *J Allergy Clin Immunol* 2015;**135**:1375–1378.
19. van Ginkel CD, Flokstra-de Blok BM, Kollen BJ, Kukler J, Koppelman GH, Dubois AE. Loss-of-function variants of the filaggrin gene are associated with clinical reactivity to foods. *Allergy* 2015;**70**:461–464.
20. Eyerich K, Eyerich S, Biedermann T. The multi-modal immune pathogenesis of atopic eczema. *Trends Immunol* 2015;**36**:788–801.
21. McAleer MA, Pohler E, Smith FJ, Wilson NJ, Cole C, MacGowan S, et al. Severe dermatitis, multiple allergies, and metabolic wasting syndrome caused by a novel mutation in the N-terminal plakin domain of desmoplakin. *J Allergy Clin Immunol* 2015;**136**:1268–1276.
22. Malajian D, Guttman-Yassky E. New pathogenic and therapeutic paradigms in atopic dermatitis. *Cytokine* 2015;**73**:311–318.
23. Eyerich K, Novak N. Immunology of atopic eczema: overcoming the Th1/Th2 paradigm. *Allergy* 2013;**68**:974–982.
24. Suarez-Farinas M, Ungar B, Correa da Rosa J, Ewald DA, Rozenblit M, Gonzalez J, et al. RNA sequencing atopic dermatitis transcriptome profiling provides insights into novel disease mechanisms with potential therapeutic implications. *J Allergy Clin Immunol* 2015;**135**:1218–1227.
25. Gilles S, Behrendt H, Ring J, Traidl-Hoffmann C. The pollen enigma: modulation of the allergic immune response by non-allergenic, pollen-derived compounds. *Curr Pharm Des* 2012;**18**:2314–2319.
26. Oh J, Byrd AL, Deming C, Conlan S, Kong HH, Segre JA. Biogeography and individuality shape function in the human skin metagenome. *Nature* 2014;**514**:59–64.
27. Kong HH, Oh J, Deming C, Conlan S, Grice EA, Beatson MA, et al. Temporal shifts in the skin microbiome associated with disease flares and treatment in children with atopic dermatitis. *Genome Res* 2012;**22**:850–859.
28. Seite S, Bieber T. Barrier function and microbiotic dysbiosis in atopic dermatitis. *Clin Cosmet Investig Dermatol* 2015;**8**:479–483.
29. Peters EM, Michenko A, Kupfer J, Kummer W, Wiegand S, Niemeier V, et al. Mental stress in atopic dermatitis–neuronal plasticity and the cholinergic system are affected in atopic dermatitis and in response to acute experimental mental stress in a randomized controlled pilot study. *PLoS One* 2014;**9**:e113552.
30. Napadow V, Li A, Loggia ML, Kim J, Mawla I, Desbordes G, et al. The imagined itch: brain circuitry supporting nocebo-induced itch in atopic dermatitis patients. *Allergy* 2015;**70**:1485–1492.
31. Mollanazar NK, Smith PK, Yosipovitch G. Mediators of chronic pruritus in atopic dermatitis: getting the itch out? *Clin Rev Allergy Immunol* 2015; [Epub ahead of print].
32. Barbarot S, Bernier C, Deleuran M, De Raeve L, Eichenfield L, El Hachem M, et al. Therapeutic patient education in children with atopic dermatitis: position paper on objectives and recommendations. *Pediatr Dermatol* 2013;**30**:199–206.
33. Stalder JF, Bernier C, Ball A, De Raeve L, Gieler U, Deleuran M, et al. Therapeutic patient education in atopic dermatitis: worldwide experiences. *Pediatr Dermatol* 2013;**30**:329–334.
34. Chalmers JR, Schmitt J, Apfelbacher C, Dohil M, Eichenfield LF, Simpson EL, et al. Report from the third international consensus meeting to harmonise core outcome measures for atopic eczema/dermatitis clinical trials (HOME). *Br J Dermatol* 2014;**171**:1318–1325.
35. Moore DE Jr, Green JS, Gallis HA. Achieving desired results and improved outcomes: integrating planning and assessment throughout learning activities. *J Contin Educ Health Prof* 2009;**29**:1–15.
36. WHO. Framework for Action on Interprofessional Education and Collaborative Practice. 2010 [cited; Available from: http://whqlibdoc.who.int/hq/2010/WHO_HRH_HPN_10.3_eng.pdf?ua = 1
37. Beck LA, Thaçi D, Hamilton JD, Graham NM, Bieber T, Rocklin R, et al. Dupilumab treatment of adults with moderate-to-severe atopic dermatitis. *N Engl J Med* 2014;**371**:130–139.
38. Jutel M, Agache I, Bonini S, Burks AW, Calderon M, Canonica W, et al. International consensus on allergy immunotherapy. *J Allergy Clin Immunol* 2015;**136**:556–568.