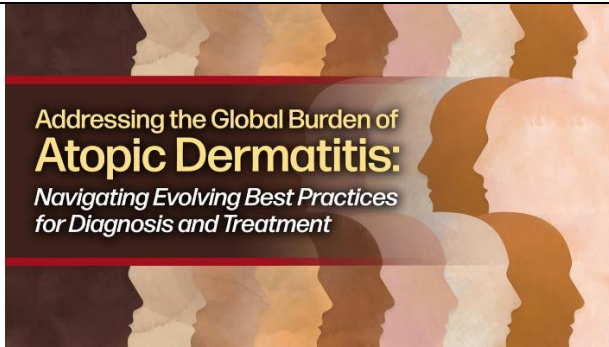
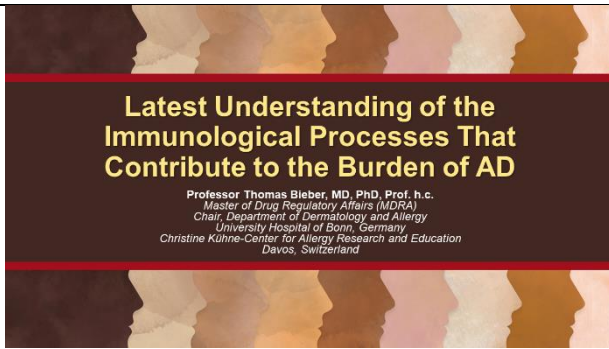



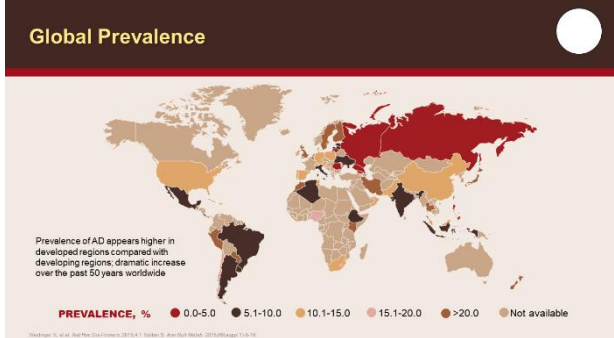
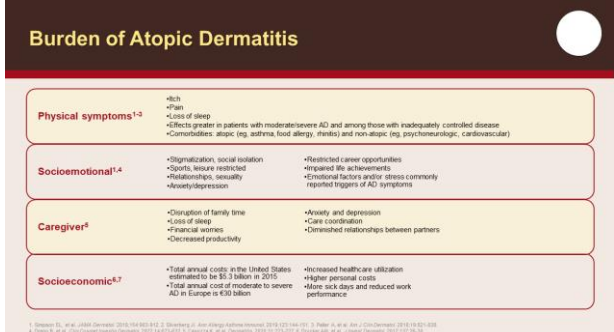
Addressing the Global Burden of Atopic Dermatitis: Navigating Evolving Best Practices for Diagnosis and Treatment

Latest Understanding of the Immunological Processes That Contribute to the Burden of AD

1	 <p>Addressing the Global Burden of Atopic Dermatitis: <i>Navigating Evolving Best Practices for Diagnosis and Treatment</i></p>	<p>Hello, my name is Thomas Bieber, I'm a dermatologist and allergist at the University of Bonn in Germany, and I welcome you to this series of presentations, Addressing the Global Burden of Atopic Dermatitis.</p>
2	 <p>Latest Understanding of the Immunological Processes That Contribute to the Burden of AD</p> <p><small>Professor Thomas Bieber, MD, PhD, Prof. h.c. Master of Drug Regulatory Affairs (MDRA) Chair, Department of Dermatology and Allergy University Hospital of Bonn, Germany Christine Kühne-Center for Allergy Research and Education Davos, Switzerland</small></p>	<p>In this presentation, I will go through the different aspects of atopic dermatitis with relationship to the immunological processes that are contributing to the disorder.</p>
3	 <p>Epidemiology</p> <ul style="list-style-type: none"> Atopic dermatitis (AD), also known as eczema or atopic eczema 15%-20% of children and 3%-10% of adults in high-income countries Characterized by pruritus, recurrent lesions, and heterogeneous clinical phenotype Can occur at any age, but usually onset in early childhood (3-6 months) <p><small>Langan SM, et al. N Engl J Med. 2020;382:1459-1470. Images obtained with permission from Christel Bonn-Zentgraf/bonnzentralfoto.com</small></p>	<p>So as you certainly know, this disorder is the most common chronic inflammatory skin disorder in dermatology, of course, besides psoriasis. And it's also known as eczema or atopic eczema. It's the most frequent one that affects, I would say, a quarter of the children or the newborns and drops to 3% to 10% of the adult population, and this is due, mainly, because there is this very strange phenomenon of spontaneous remission that occurs in childhood between the ages of, let's say, 5 and 10 years. The disease itself is characterized by quite substantial pruritus with recurrent lesions, flares, and, most importantly I think for the practice, is that we have to understand that this disorder is really a highly heterogeneous</p>

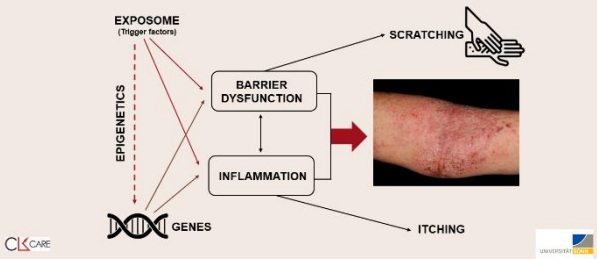
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		<p>clinical phenotype. So, most of the age of onset typically is localized in the early childhood between 3 months and 6 months of age, but it could also be appearing afterwards, between 2 years and 6 years. We also have some patients starting the disorder during adolescence and, overall, 20% of the patients start the disease in adulthood.</p>
<p>4</p>	 <p>Global Prevalence</p> <p>Prevalence of AD appears higher in developed regions compared with developing regions; dramatic increase over the past 50 years worldwide</p> <p>PREVALENCE, % ● 0.0-5.0 ● 5.1-10.0 ● 10.1-15.0 ● 15.1-20.0 ● >20.0 ● Not available</p> <p><small>Sheehan N, et al. J Am Acad Dermatol. 2018;79(1):1-7. Scales S, et al. JAMA. 2019;321(18):1767-1774.</small></p>	<p>With regard to the global prevalence, we have a number of data and studies available. For example, the ISAAC study has nicely analyzed the incidence and the prevalence of the disease among different countries. And you see here that the prevalence seems to be low, in particular, in Russia, while it is quite substantial in other countries, particularly in Western countries. And that's the situation that currently has been analyzed, and we see definitely a dramatic increase over the last, I would say, 40 to 50 years.</p>
<p>5</p>	 <p>Burden of Atopic Dermatitis</p> <p>Physical symptoms^{1,2}</p> <ul style="list-style-type: none"> Itch Wash Loss of sleep Effects greater in patients with moderate/severe AD and among those with inadequately controlled disease Comorbidities: atopic (eg, asthma, food allergy, rhinitis) and non-atopic (eg, psychoneurologic, cardiovascular) <p>Socioemotional^{3,4}</p> <ul style="list-style-type: none"> Stigmatization, social isolation Optic issues restricted Relationships, sexuality Anxiety/depression Restricted career opportunities Impaired life achievements Emotional factors and/or stress commonly reported triggers of AD symptoms <p>Caregivers⁵</p> <ul style="list-style-type: none"> Disruption of family time Loss of sleep Financial worries Decreased productivity Anxiety and depression Care coordination Disturbed relationships between partners <p>Socioeconomic^{6,7}</p> <ul style="list-style-type: none"> Total annual costs in the United States estimated to be \$5.3 billion in 2015 Total annual cost of moderate to severe AD in Europe is €50 billion Increased healthcare utilization Higher personal costs More sick days and reduced work performance <p><small>1 Sheehan N, et al. JAMA Dermatol. 2018;54(8):812-21. Sheehan N, et al. JAMA Dermatol. 2018;54(8):812-21. 2 Sheehan N, et al. JAMA Dermatol. 2018;54(8):812-21. 3 Sheehan N, et al. JAMA Dermatol. 2018;54(8):812-21. 4 Sheehan N, et al. JAMA Dermatol. 2018;54(8):812-21. 5 Sheehan N, et al. JAMA Dermatol. 2018;54(8):812-21. 6 Sheehan N, et al. JAMA Dermatol. 2018;54(8):812-21. 7 Sheehan N, et al. JAMA Dermatol. 2018;54(8):812-21.</small></p>	<p>So, the disease itself is well known to induce quite a substantial burden on these patients, particularly due to the itch sensation, which induces loss of sleep, and has quite a number of comorbidities, so all the atopic, all other atopic</p>

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		<p>disorders, like asthma, food allergy, and rhinitis, as well as non-atopic comorbidities, like psychoneurological and cardiovascular disorder, can appear in the course of the atopic dermatitis. We have a number of socio-emotional aspects, particularly the stigmatization of these patients, particularly when some areas like the face and the hands are particularly involved. For the caregivers, atopic dermatitis is sometimes a huge issue, for the kids in the family. And this leads not seldomly to a disruption of the family time and to main issues related to the financial worries that the patients or the caregivers have in the context of the management of this disorder, and this is reflected by the socioeconomic aspects. So just to give you some numbers, the total annual cost of moderate-to-severe atopic dermatitis in Europe is estimated to be 30 billion Euros.</p>
6	<p>Putting Complex Gene-Gene and Gene-Environment Interactions in a Nutshell</p> 	<p>So, in a nutshell, when I'm explaining the disorder to my patients, that's the typical picture that I'm showing. I'm trying to educate the patients in a very simple way, showing them where the issues are. And the issues are definitely first in the genes that are encoding, on one hand, the barrier dysfunction, on the</p>

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		<p>other hand, are responsible also for a number of immunologically relevant structures that are involved in the induction of the inflammation. On the other hand, we have the exposome or the environmental trigger factors that may play a role and that also are able to interact with the immune systems through the barrier dysfunction, but also in terms of epigenetic regulation, we think that there is something here that could be of interest in research for the next decades of work. In terms of symptoms, the scratching is very important, and this is the main symptom of most of these patients and this scratching, of course, is the result of this intense itching sensation that most of these patients have and that is triggered by the inflammatory reaction.</p>														
7	<p>Environmental Factors/Exposome</p> <table border="1"> <tr> <td>In utero</td> <td>Maternal stress, cigarette smoke, antibiotic exposure, alcohol consumption, omega-3 long-chain polyunsaturated fatty acids, and probiotics</td> </tr> <tr> <td>Skin exposures</td> <td>Irritants and pruritogens</td> </tr> <tr> <td>Early life exposure to dirt and pathogens</td> <td>Farm and rural living, manure or microbial exposure in home, bacterial endotoxins, helminths, Herpesviridae, farm animals, dogs, unpasteurized milk, early day care, chickenpox infection, and respiratory syncytial virus</td> </tr> <tr> <td>Skin flora</td> <td><i>S. aureus</i> and microbial diversity and <i>Malassezia</i></td> </tr> <tr> <td>Climate</td> <td>Temperature, humidity, ultraviolet radiation, and precipitation</td> </tr> <tr> <td>Air pollutants</td> <td>Outdoor and indoor pollutants</td> </tr> <tr> <td>Other</td> <td>Cigarette smoking, water hardness, urban living, diet and adiposity, breastfeeding, probiotics, and prebiotics</td> </tr> </table> <p><small>© Springer. Dermatitis/Atopic Dermatitis. Bieber T, von Steigender H. 2015. Chapter 11.8-16. Barber R, Scharfetter C. Atopic Dermatitis. 2017. 11.10-20.</small></p>	In utero	Maternal stress, cigarette smoke, antibiotic exposure, alcohol consumption, omega-3 long-chain polyunsaturated fatty acids, and probiotics	Skin exposures	Irritants and pruritogens	Early life exposure to dirt and pathogens	Farm and rural living, manure or microbial exposure in home, bacterial endotoxins, helminths, Herpesviridae, farm animals, dogs, unpasteurized milk, early day care, chickenpox infection, and respiratory syncytial virus	Skin flora	<i>S. aureus</i> and microbial diversity and <i>Malassezia</i>	Climate	Temperature, humidity, ultraviolet radiation, and precipitation	Air pollutants	Outdoor and indoor pollutants	Other	Cigarette smoking, water hardness, urban living, diet and adiposity, breastfeeding, probiotics, and prebiotics	<p>So in terms of environmental factors or exposome, we know that there are a number of different kinds of factors playing a role, particularly the skin exposure with irritants and pruritogens in the very early phase of the disorder. The microbiome issue, which is heavily debated currently — which is very hyped, I would say — so the skin flora and the composition, the real role of</p>
In utero	Maternal stress, cigarette smoke, antibiotic exposure, alcohol consumption, omega-3 long-chain polyunsaturated fatty acids, and probiotics															
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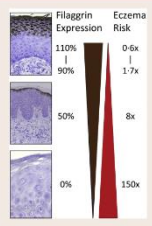
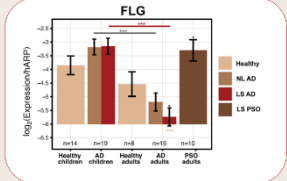
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		<p><i>Staphylococcus aureus</i> seems to be prominent, I think prominently more in the pediatric population than in adults. Of course, air pollutants may play a role as provocation factors. And last but not least, cigarette smoking is well known as a provocation factor and an important environmental factor in the context of many epidemiological studies.</p>
<p>8</p>	<p>Genetic Factors</p> <ul style="list-style-type: none"> More than 30 genetic loci have been linked to AD across different populations Loss of function mutations in the <i>FLG</i> gene are a major predisposing factor <p><small>CD1, interleukin 2, interleukin 3, interleukin 4, interleukin 5, interleukin 6, interleukin 7, interleukin 8, interleukin 9, interleukin 10, interleukin 11, interleukin 12, interleukin 13, interleukin 14, interleukin 15, interleukin 16, interleukin 17, interleukin 18, interleukin 19, interleukin 20, interleukin 21, interleukin 22, interleukin 23, interleukin 24, interleukin 25, interleukin 26, interleukin 27, interleukin 28, interleukin 29, interleukin 30, interleukin 31, interleukin 32, interleukin 33, interleukin 34, interleukin 35, interleukin 36, interleukin 37, interleukin 38, interleukin 39, interleukin 40, interleukin 41, interleukin 42, interleukin 43, interleukin 44, interleukin 45, interleukin 46, interleukin 47, interleukin 48, interleukin 49, interleukin 50, interleukin 51, interleukin 52, interleukin 53, interleukin 54, interleukin 55, interleukin 56, interleukin 57, interleukin 58, interleukin 59, interleukin 60, interleukin 61, interleukin 62, interleukin 63, interleukin 64, interleukin 65, interleukin 66, interleukin 67, interleukin 68, interleukin 69, interleukin 70, interleukin 71, interleukin 72, interleukin 73, interleukin 74, interleukin 75, interleukin 76, interleukin 77, interleukin 78, interleukin 79, interleukin 80, interleukin 81, interleukin 82, interleukin 83, interleukin 84, interleukin 85, interleukin 86, interleukin 87, interleukin 88, interleukin 89, interleukin 90, interleukin 91, interleukin 92, interleukin 93, interleukin 94, interleukin 95, interleukin 96, interleukin 97, interleukin 98, interleukin 99, interleukin 100</small></p>	<p>So, with regard to the genetic factors, I think as I mentioned before, we have two classes of genes that are relevant here. The first class is those genes relevant for the issue of the barrier function, and this is shown on the left side of the slide. Particularly filaggrin, which is the most prominent one which is detected, I would say in something like 50% of the patients overall worldwide. On the other hand, we also know candidate genes related to a number of structures, including the Toll-like receptors, but also the cytokines, proinflammatory cytokines, and other chemokines that are relevant for our understanding of the immunology of this disorder.</p>

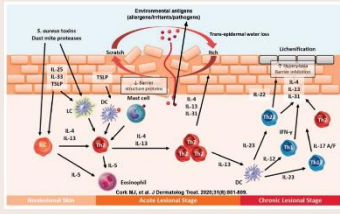
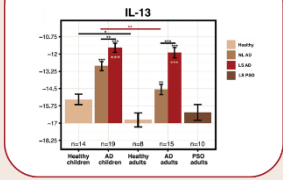
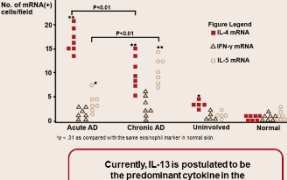
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<p>9</p>	<p>FLG Loss of Function Mutations and AD</p> <ul style="list-style-type: none"> Occur in up to 40% of patients with AD,¹ with distinct mutations observed in different populations^{2,3} Associated with increased risk of severe AD with earlier onset, longer persistence, and skin infections, particularly homozygous mutations⁴ FLG expression correlates with eczema risk⁵  <p><small>1. Irvine AD, et al. N Engl J Med. 2014;371:1464-74. 2. Palmer CE, et al. Nat Genet. 2007;39:1147-51. 3. Hahnel B, et al. J Invest Dermatol. 2014;124:1073-77. 4. Palmer CE, et al. J Allergy Clin Immunol. 2014;134:1042-51. 5. Palmer CE, et al. J Allergy Clin Immunol. 2014;134:1042-51.</small></p>	<p>And when it comes to the filaggrin mutation, we know that this is extremely important because, as I mentioned, it occurs in the substantial part of the patients, it's associated with an increased risk for severe AD. But not only that, it also is highly associated with the persistence of the disorder, skin infections, and also I think it's well known that these patients have a high risk to develop food allergy and some other comorbidities.</p>
<p>10</p>	<p>FLG Loss of Function Mutations and AD</p> <ul style="list-style-type: none"> However, the pathophysiology of AD goes beyond FLG mutations...^{1,2} <ul style="list-style-type: none"> Japanese and Korean patients have lower frequency of FLG mutations than Western patients^{3,4} Approximately 40% of individuals with FLG-null alleles do not show characteristics of AD⁵ FLG expression is reduced in patients with AD even with no FLG mutation <ul style="list-style-type: none"> Upregulation of IL-4 and IL-13 lowers FLG expression, which leads to skin barrier defects^{6,7}  <p><small>1. Palmer CE, et al. J Allergy Clin Immunol. 2014;134:1042-51. 2. Palmer CE, et al. J Allergy Clin Immunol. 2014;134:1042-51. 3. Palmer CE, et al. J Allergy Clin Immunol. 2014;134:1042-51. 4. Palmer CE, et al. J Allergy Clin Immunol. 2014;134:1042-51. 5. Palmer CE, et al. J Allergy Clin Immunol. 2014;134:1042-51. 6. Palmer CE, et al. J Allergy Clin Immunol. 2014;134:1042-51. 7. Palmer CE, et al. J Allergy Clin Immunol. 2014;134:1042-51.</small></p> <p>FLG expression similar in children with AD vs healthy children, challenging the notion of FLG as central for disease initiation⁸</p>	<p>So, the filaggrin mutation is one thing, but we know that the pathophysiology of AD goes beyond that filaggrin mutation. We have a number of different kinds of gene variants and mutations that are known to be quite different depending on the different kinds of populations that we consider and whether we consider also patients in adulthood or in childhood. So, the filaggrin expression is similar in children with AD with healthy children, but challenging the notion of the filaggrin mutation as a central part of the disease initiation.</p>

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<p>11</p>	<h3 style="background-color: #800000; color: white; padding: 5px;">Skin Barrier Dysfunction</h3> <ul style="list-style-type: none"> ▪ Considered to be the first step in AD development ▪ Penetration of environmental antigens results in interaction with local immune cells and release of AD-related pro-inflammatory cytokines ▪ Immune dysregulation and increase in type 2 responses contribute to amplify skin barrier defects and AD phenotype  <p style="font-size: small;">CC-BY-NC-SA. Source: Langan et al. N Engl J Med. 2014;371(12):1216-1223. Copyright 2014. All rights reserved. Reproduced with permission from the publisher.</p>	<p>So, there are a number of other genes that may be responsible for this, and this is a little bit depicted here. The skin barrier dysfunction, of course, is of importance because it allows the penetration of a number of environmental allergens and irritants. And all the kinds of pathogens that then are able to go through the disrupted barrier function and to interact directly with the local immune system.</p>
<p>12</p>	<h3 style="background-color: #800000; color: white; padding: 5px;">Question</h3> <p>Which cytokine(s) is known to play a key role in the inflammation associated with AD?</p> <ul style="list-style-type: none"> A. IL-2 B. IL-13 C. IL-6 D. IL-10 	<p>So one of the first questions is: Which cytokine is known to play a key role in the inflammation associated with atopic dermatitis? So, you have the choice between four here: IL-2, IL-13, IL-6, and IL-10. And, of course, the answer is IL-13.</p>
<p>13</p>	<h3 style="background-color: #800000; color: white; padding: 5px;">AD Has a Strong Th2 Component Associated With IL-4 and IL-13 Overproduction¹</h3> <div style="display: flex; justify-content: space-around;"> <div style="width: 45%;"> <p style="text-align: center; color: red; font-weight: bold;">TH2 CYTOKINES ARE GREATLY INCREASED IN CHILDREN WITH AD^{2†}</p>  <p style="font-size: x-small;"> * IL-4 and IL-13 levels correlate with AD disease activity¹ † CCL26, CCL18, IL-6, and IL-31 also reduced </p> </div> <div style="width: 45%;"> <p style="text-align: center; color: red; font-weight: bold;">INCREASED LEVELS OF IL-4, IL-5, AND IFN-γ OBSERVED IN LESIONS FROM ADULTS WITH AD³</p>  <p style="text-align: center; border: 1px solid red; padding: 2px; font-weight: bold; color: red;">Currently, IL-13 is postulated to be the predominant cytokine in the pathophysiology of AD</p> </div> </div> <p style="font-size: x-small;"> ¹ Langan et al. N Engl J Med. 2014;371(12):1216-1223. Copyright 2014. All rights reserved. Reproduced with permission from the publisher. ² Langan et al. N Engl J Med. 2014;371(12):1216-1223. Copyright 2014. All rights reserved. Reproduced with permission from the publisher. ³ Langan et al. N Engl J Med. 2014;371(12):1216-1223. Copyright 2014. All rights reserved. Reproduced with permission from the publisher. </p>	<p>You will ask why is IL-13 so important and not IL-4? First, I think we have good evidence currently that IL-13 is probably the major driving force of inflammation in atopic dermatitis, because you can measure these cytokines in high levels, not only in the skin, but also in the circulation of the patients suffering from this particular disorder. But, of course, you can measure a number of other cytokines in the skin, as well as a biomarker in the periphery.</p>

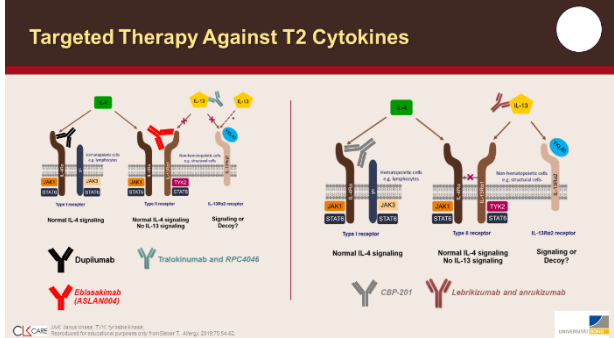
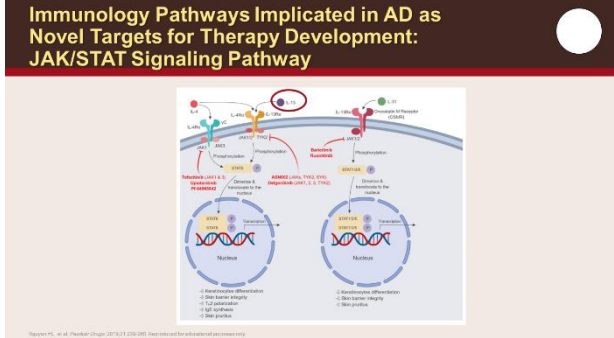
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<p>14</p>	<p>Postulated Primary Roles of IL-4 and IL-13</p> <p>While IL-4 seems to exert a more central activity (overlapping with the preferential expression of the type I receptor), IL-13 may be the more dominant T2 cytokine in the periphery, where the type II receptor is preferentially expressed by tissue cells</p> <p><small>Ortiz et al. J Allergy Clin Immunol. 2015;135:105-112. doi:10.1016/j.jaci.2014.10.012. Copyright © 2015 Elsevier Inc. All rights reserved.</small></p>	<p>However, most probably IL-4 is not playing that same role in the periphery. In contrast, IL-4 is known to be a cytokine that is mainly expressed in the central part of the immune system and most probably related particularly to other mechanisms, like the humoral immunity, and IL-4 is well known to be one of the most important cytokines in the regulation of the IgE synthesis, and you know that IgE is a typical hallmark in the vast majority of patients suffering from atopic dermatitis.</p>
<p>15</p>	<p>Sources and Impact of IL-13 in Skin</p> <p>In contrast to IL-4 and in line with the concept that IL-13 is the dominant T2 cytokine in the periphery, IL-13 is overexpressed by different cell types in the skin of AD. There, this T2 cytokine has a wide impact, including the decrease of the barrier function, inducing itch and affecting the microbiome.</p> <p><small>Tsai et al. J Allergy Clin Immunol. 2015;135:105-112. doi:10.1016/j.jaci.2014.10.012. Copyright © 2015 Elsevier Inc. All rights reserved.</small></p>	<p>On the other hand, as I mentioned, IL-13 is the most important driving force in terms of cytokines in the skin itself. You can measure a huge amount of this cytokine in the tissue, particularly in the lesional skin, but also in the nonlesional skin and the biological activity of those cytokines is just depicted here. You see here clearly that IL-13 is not only inducing inflammation, but has a deep impact on the barrier function, it has an impact on the microbiome, it is also able to directly induce itching sensation, and indirectly, by inducing the collagen synthesis, it somehow also contributes to the dermal fibrosis that is seen in most of the patients. So now the question is: How</p>

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		<p>can we, by kind of strategic pharmacological approach, try to have an impact, particularly on IL-13?</p>
<p>16</p>	 <p>Targeted Therapy Against T2 Cytokines</p> <p>The diagram illustrates the signaling pathways for Type I, II, and III receptors. Type I receptor (IL-4) signaling involves JAK1 and STAT3. Type II receptor (IL-13) signaling involves JAK1, JAK3, and STAT3. Type III receptor (IL-13/IL-4 heterodimer) signaling involves JAK1, JAK3, and STAT3. The diagram also shows the signaling of or decay for these pathways. Targeted therapies are shown: Dupilumab (anti-IL-4/IL-13), Tralokinumab and RPC4046 (anti-IL-13), Eblasakimab (ASLAN004) (anti-IL-4), CBP-201 (anti-IL-13/IL-4 heterodimer), and Lebrikizumab and anrilokizumab (anti-IL-13).</p>	<p>And now currently, we are very happy to have at least two biologics which are targeting IL-4 and IL-13 either by binding at the receptor like dupilumab or binding at the free cytokine like tralokinumab. And this picture also shows you clearly that we have a number of other molecules currently in the pipeline, particularly lebrikizumab, which is now in the final phases of the approval, and some others like cendakimab or RPC4046, which are also in the pipeline, as well as eblasakimab. So, you see here currently the number of molecules or biologics that are in the pipeline are interesting and I think we are all keen to see all these products be available in the next time for our patients.</p>
<p>17</p>	 <p>Immunology Pathways Implicated in AD as Novel Targets for Therapy Development: JAK/STAT Signaling Pathway</p> <p>The diagram shows the JAK/STAT signaling pathway. It starts with the binding of cytokines (IL-4, IL-13) to their receptors (Type I, II, III). This activates JAK1 and JAK3, which then phosphorylate STAT3. The phosphorylated STAT3 dimerizes and translocates into the nucleus to bind to DNA, leading to the transcription of target genes. The diagram also shows the inhibition of this pathway by JAK inhibitors (JAKi) and the role of various molecules in the pathway.</p>	<p>Beside these biologics that have to be applied by injection, of course, we have now the new generation of the so-called JAK kinase inhibitors. These inhibitors, in fact, are acting directly on the signal transduction machinery, which is involved in the biological activity, particularly of IL-4 and IL-13, but also of other cytokines, like IL-31, which is mainly</p>

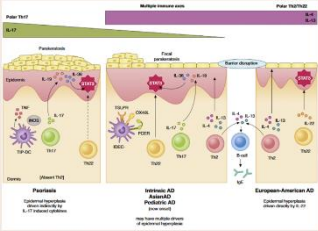
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		<p>responsible for the itching sensation. And these pictures just show you the different kinds of kinases involved here: JAK1, JAK2, JAK3, and TYK2. For all these different kinds of JAK kinases, we now have different kinds of products available, the so-called JAK kinase inhibitors, for example, baricitinib, which is blocking JAK1 and JAK2, or upadacitinib and abrocitinib that are binding mainly or selectively to JAK1. And of course, a number of other molecules which are less selective, so-called pan-JAK kinase inhibitors, like delgocitinib that are also acting efficiently in this disorder.</p>
<p>18</p>	<p>Vicious Cycle Between Barrier Impairment and Allergic Disorder in AD</p> <p>FLG deficiency is a typical cause of barrier impairment (as seen in ichthyosis vulgaris), which allows protein antigens to penetrate through stratum corneum, leading to LC-mediated Th2 allergic responses. The resultant upregulation of IL-4/IL-13 production reduces FLG expression, resulting in further reduction in barrier and promotion of allergic reaction.</p>	<p>So, one of the biggest issues in that particular disorder is this vicious cycle between the barrier impairment and the allergic disorder in atopic dermatitis, because as I already mentioned, we know that the barrier impairment allows the penetration of quite substantial number of substances in the skin, and then by this they have direct contact to the local antigen-presenting cells, particularly the Langerhans cells in the epidermis and other cells, like dermal dendritic cells. And in combination to, particularly the filaggrin mutation and the local inflammatory reaction, this</p>


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		<p>leads in fact, at the end, to the activation of or to the emergence of hygiene-mediated sensitization that particularly emerges from that interaction in the skin of the allergens to the antigen-presenting cells, and then the antigen presentation leading, finally, to a specific adaptive immune response, including the generation of allergen-specific IgE.</p>
<p>19</p>	<p>Beyond the T2 Immune Response: Evidence for Widening of the Immune Response in AD</p> <ul style="list-style-type: none"> AD skin in Asian patients has higher Th17 and lower Th1 gene expression¹ Pediatric AD skin has more Th17-related cytokines and antimicrobial peptides than adult AD skin² Intrinsic AD shows a correlation between Th17 molecules and SCORAD scores, whereas extrinsic AD shows a correlation between SCORAD scores and Th2 cytokine levels²  <p><small>EMC: A European Association of Dermatology and Allergy (EAD) initiative. © 2014. All rights reserved. This document is for personal use only. It is not to be distributed, reproduced, or stored in a retrieval system. For more information, please contact the EAD office at ead@ead-dermatology.com.</small></p>	<p>And this, as already mentioned, this highlights the role of the so-called T2 immune response in the context of atopic dermatitis. But as mentioned here, we now know that this T2 response is not the only one that is effective. We know that there are a number of other immune responses like Th22, Th17, and Th1 that are also relevant, particularly in the Asian population where Th17-related cytokines have been measured in high amounts in lesional skin of atopic dermatitis. In the so-called atopic dermatitis of the intrinsic form, there may also be some correlation with the Th17 pathway, but this is still unclear and needs further confirmation. I hope I was able to summarize here, somehow, the current knowledge in the immunology of atopic dermatitis and to highlight a little bit the issue of the core</p>

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		<p>T2 immune response that is followed by the widening of the immune response in this atopic dermatitis issue. This, in fact, somehow resembles to a kind of immunological march, and that immunological march is in fact offering a number of targets for pharmacological interventions and for the development of new drugs.</p>
20		<p>Thank you very much for your attention.</p>