

Medical news in the world of Atopic Dermatitis

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The role of intestinal dysbiosis is becoming clearer

Song H, Yoo Y, Hwang J, Na YC, Kim HS.

Faecalibacterium prausnitzii subspecies-level dysbiosis in the human gut microbiome underlying atopic dermatitis.

J Allergy Clin Immunol 2016;137:852-860.

The link between the digestive tract and atopic dermatitis has been studied for many years, and new ground has been broken thanks to studies on the intestinal flora made possible with bacterial metagenomic techniques. Through the detailed analysis of the fecal microbiome of atopic and non atopic subjects, Korean researchers have found no major difference in the diversity patterns of the species present. However, they have identified an abnormality, a dysbiosis, in the subspecies *Faecalibacterium prausnitzii*, primary bacterium in the digestive microbiota. From early childhood, L2-6 species are more preponderant in atopic subjects than A2-165 species. This dysbiosis leads to a decrease in the production of butyrate and propionate, short chain fatty acids with anti-inflammatory properties. The resulting inflammation increases intestinal permeability and the absorption of poorly digested foods, toxins and bacteria, leading to a TH2 immune system imbalance resulting in atopic manifestations. The next step will consist in investigating if modifications in intestinal flora, and in particular the proportion of *Faecalibacterium prausnitzii* subspecies, are likely to prevent or improve atopy. In 1921, Otto Prausnitz, after whom the bacterium was named, observed circulating antibodies as a result of the immediate allergy caused by the sub-cutaneous injection of serum from his colleague Küstner, who was allergic to fish. Prausnitz then ate some fish and developed an urticarial plaque around the injection site.

Atopic dermatitis and cardiovascular risk

Andersen YM, Egeberg A, Gislason GH, Hansen PR, Skov L, Thyssen JP.

Risk of myocardial infarction, ischemic stroke, and cardiovascular death in patients with atopic dermatitis.

J Allergy Clin Immunol 2016, publié en ligne le 10 Mars.

Recently, several studies have shown a link between atopic dermatitis and an increase in cardiovascular risk. This study confirmed the link in an adult population in Denmark. Two groups were



studied: 2527 patients with severe atopic dermatitis who had received a general immunosuppressant treatment, and 26 898 patients with "minor" atopic dermatitis for which no treatment was given. They were compared with 145 372 non-atopic adults. The cardiovascular risk only increased moderately with severe AD (incidence rate 1.17) and tended to decrease with minor AD (incidence rate 0.80). The analysis of the risk factors and comorbidities suggests that lifestyle issues explain the increase in risk and not the AD itself or the associated chronic inflammation. Patients suffering from severe AD consume more alcohol and tobacco than the general population; they are more often sedentary, as well as more prone to depression, and present several cardiovascular risk factors (pre-diabetes, excess weight, hypertension). It is therefore recommended that special attention be paid to comorbidities in atopic adults in order to reduce the cardiovascular risk.

The parents are trustworthy

Assessment of atopic dermatitis using self-report and caregiver report: a multicentre validation study.

Silverberg JI, Patel N, Immaneni S, et al.

Br J Dermatol 2015;173:1400-1404.

In major epidemiological surveys using national health records available in several countries, including the USA, the diagnosis of atopic dermatitis, or eczema, is not based on a clinical examination but on the answer to a single question: "Has a doctor already told you that you (or your child) have eczema?" Patients over 18 years answer the question themselves, but for patients under 18 years it is the caregiver, often the mother. So, how reliable are the answers? To find out, the authors questioned 782 patients waiting to consult a dermatologist. The investigation did not therefore concern the general population, but a very select group. First, they asked the above question, which concerned the last twelve months and their entire life. They were then examined by a dermatologist who diagnosed atopic dermatitis, or not, according to the very detailed criteria of Hanifin and Rajka. Regarding the response for children, the specificity was very good (96%). The sensitivity was good, but was only 70%, indicating that the prevalence of atopic dermatitis is a little under-estimated. For adults, the specificity and the predictive value of the interview were also very good, but the sensitivity was low (only 43%). In other words, numerous adults had atopic dermatitis without knowing the exact diagnosis. However, the authors conclude that the validity of the data from interviews in epidemiological studies is satisfactory.

The benefits of written action plans

Gilliam AE, Madden N, Sendowski M, Mioduszewski M, Duderstadt KG.

Use of Eczema Action Plans (EAPs) to improve parental understanding of treatment regimens in pediatric atopic dermatitis (AD): A randomized controlled trial.

J Am Acad Dermatol 2016;74:375-377.

The therapeutic workshops and the atopy schools have proven beneficial, but they are not accessible to all patients or parents due to issues with access and availability. Written "action plans" are easy ways to improve the efficacy of the consultations. Similarly to what is done with asthma, these action plans are based on detailed information about the disease and its treatments, and provide instructions regarding the steps to be taken in different circumstances, including eczema flare-ups that occur outside consultations. Through the comparison of two groups of atopic children aged 4 years on average, this study shows that the written action plans improve understanding of the treatment, parents' confidence in their ability to cope with new situations, and overall quality of life.

Difficulties with clinical evaluation

Futamura M, Leshem YA, Thomas KS, Nankervis H, Williams HC, Simpson EL.

A systematic review of Investigator Global Assessment (IGA) in atopic dermatitis (AD) trials: Many options, no standards.

J Am Acad Dermatol 2016;74:288-294.

Researchers in the field of atopic dermatitis, as well as the physicians who treat the patients, find it very hard to assess the intensity of the disease, which is why it is essential to understand the evolution of each patient and to assess treatment efficacy. Is it mild? Moderate? Severe? Very severe? Did the treatment improve the situation? Stabilize it? Make it worse?

Severity scores have been proposed to answer these questions. The most well-known are SCORAD, used predominantly in Europe, and EASI, used predominantly in North America. Other scores exist, but the fact that there are so many makes it even more difficult to compare studies. These detailed scores are complicated and overall scores, called "Investigator (or Physician) Global Assessment", are therefore preferred. In this case, the physician globally assesses the patient's condition according to a 4, 5 or 7-point scale ranging from "healed" to "very severely affected" with varying degrees in-between (almost healed, minor, moderate, severe). These global scales may seem less accurate than scores measuring several parameters, but they are particularly recommended by the highly influential FDA as the main parameter in the assessment of atopic dermatitis treatments, as well as psoriasis. The problem that this article clearly highlights is that nothing is standardized in this field. The authors only

examined randomized controlled studies in the literature, which are probably the most rigorous. A third of the 317 trials published since 2000 include a global scale, but under various names and with extremely variable methods. The authors conclude that the variability is unacceptable and the content inadequate, and would like to see the standardization of methods of assessment of clinical trials at international level.

An anti-IL-31 against pruritus

Nemoto O, Furue M, Nakagawa H, et al.

The first trial of CIM331, a humanized antihuman interleukin-31 receptor A antibody, in healthy volunteers and patients with atopic dermatitis to evaluate safety, tolerability and pharmacokinetics of a single dose in a randomized, double-blind, placebo-controlled study.

Br J Dermatol 2016;174:296-304.

Clinical trials for which the results were published in 2014 and 2015 indicate that a monoclonal antibody directed against the IL-4 receptor could improve severe forms of atopic dermatitis in adults. This antibody, called dupilumab, blocks interleukin IL-4 and IL-13 signaling. These cytokines are involved in the most characteristic abnormality of the disease, which is a predominance of TH2 lymphocytes that cause the atopic inflammation. Dupilumab is probably the first biological drug proposed to atopic patients. At the start of 2016, the first article was published relating to the performance of a second monoclonal antibody for the treatment of atopic dermatitis called CIM331. It is directed against the IL-31 receptor, a cytokine produced mainly by activated TH2 lymphocytes, which has a specific biological function and can be considered as the pruritus cytokine. It acts on the receptors located in the nerve fibers and on keratinocytes, thus triggering pruritus. IL-31 inhibition could therefore decrease pruritus, and this is in fact what the preliminary study shows regarding adults with severe atopic dermatitis and in particular high pruritus scores. At the most effective doses, a single sub-cutaneous injection of CIM331 decreases pruritus by approximately 50% after one month, compared to approximately 20% with the injection of a placebo. Sleep is also improved, and the consumption of topical corticosteroids reduced. Tolerance appears to be good, but it is too early to have any real insight regarding the tolerance profile of CIM331. So, as we have seen over the past fifteen years for psoriasis, biological products will probably become a new therapeutic weapon against atopic dermatitis, as well as against other atopic symptoms, and undoubtedly some non-atopic pruritus.

The burden of atopic dermatitis in adults

Simpson EL, Bieber T, Eckert L, et al.

Patient burden of moderate to severe atopic dermatitis (AD): Insights from a phase 2b clinical trial of dupilumab in adults.

J Am Acad Dermatol 2016;74:491-498.

The patients considered in this study are probably the most severely affected atopic patients. Indeed, the condition of the adults recruited for the dupilumab anti-IL-4 monoclonal antibody clinical trial was not "moderate to severe" as the title indicates, but clearly severe, with an average SCORAD index of 64. Another indication of the severity is that half of these patients required systemic corticosteroids at least once, even though we know they are not recommended. Within the framework of the evaluation prior to inclusion in the clinical trial, 380 patients filled out several questionnaires to accurately assess the different aspects of the burden of the disease from which they had suffered most of their lives: frequency of atopic symptoms, pruritus, SCORAD severity index of eczema, anxiety and depression scales, and measure of quality of life. The results confirm the severity of atopic dermatitis in adults. Pruritus in particular considerably disrupts daily life, sleep is an issue every night or almost, and school or professional activities are affected. Overall quality of life is severely altered. Levels of anxiety and depression were clinically significant for 22% of patients. The need for progress in the treatment of these severe forms of atopic dermatitis is clear.