



Current pharmaceutical developments in atopic dermatitis

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Atopic dermatitis (AD) is an inflammatory, pruritic, chronic or chronically relapsing skin disease that typically begins in early childhood and is occurring frequently in families with other atopic diseases (bronchial asthma and/or allergic rhinoconjunctivitis). Thanks to immunological and neurobiological research, the era of new treatments is coming as well as it occurred with psoriasis 15 years ago. Many treatments targeting cytokines (IL-4, IL-13, IL-31, TSLP) or neurotransmitters (substance P, opioids) or their respective receptors as well as phosphodiesterase-4 or the Jak/Stat pathways are under development. Antagonists of cytokines and anti-jak have promising effects on pruritus while it is more difficult to discriminate the effects of other drugs from the placebo effect on itch, which is known to be high.

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Atopic dermatitis (AD) is an inflammatory, pruritic, chronic or chronically relapsing skin disease that typically begins in early childhood and is occurring frequently in families with other atopic diseases (bronchial asthma and/or allergic rhinoconjunctivitis) [1]. AD is one of the most common skin diseases which affects up to 20% of children and 1–3% of adults in most countries of the world [2]. AD is often associated with other atopic diseases such as rhinitis, conjunctivitis and/or asthma. Diagnostic criteria of AD are based on clinical findings [3,4], and at the

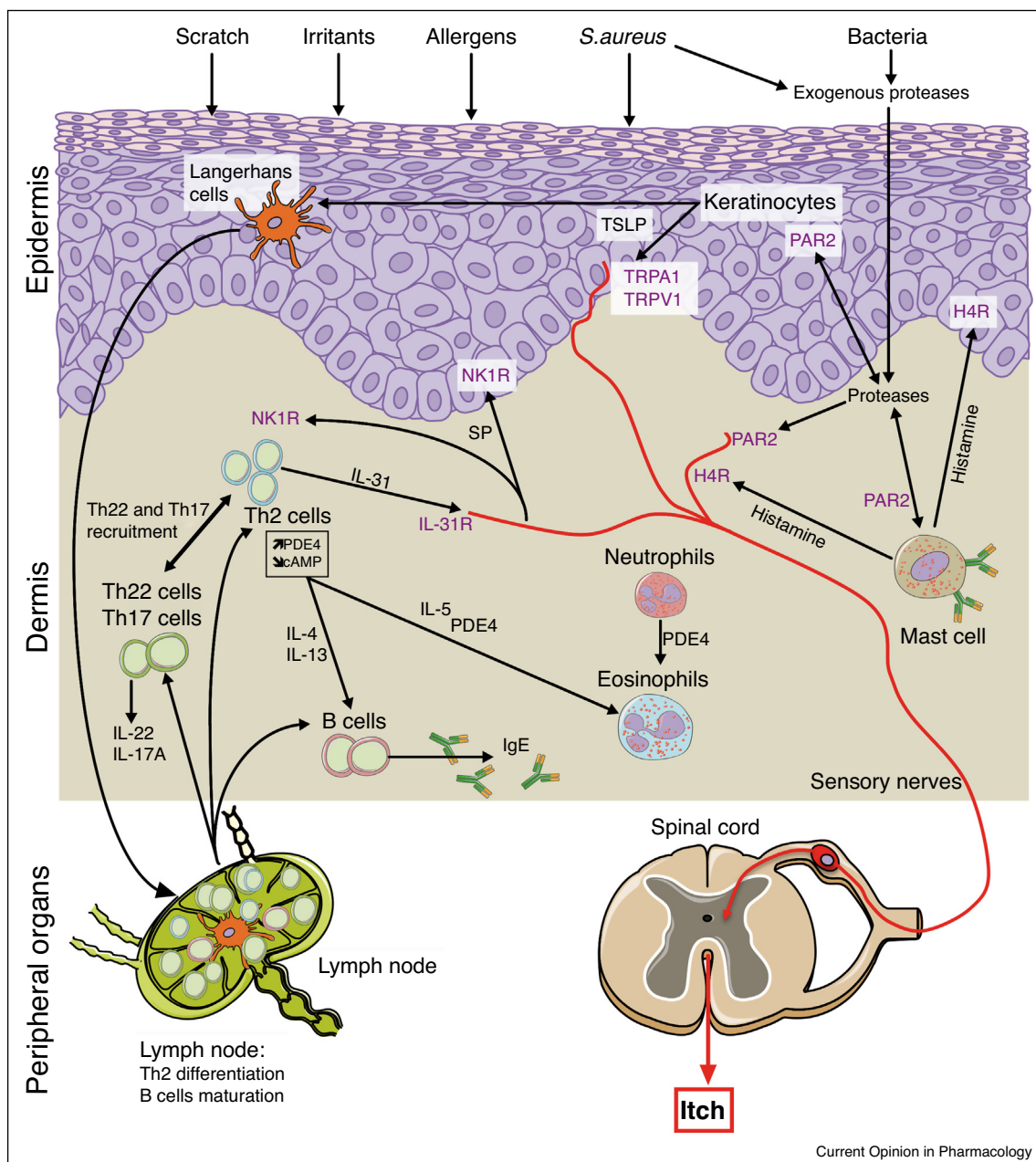
moment, there is no pathognomonic laboratory biomarker for the diagnosis of AD. Elevation of total or allergen-specific IgE levels in serum or detection of IgE-mediated sensitization in the skin test is not present in all individuals suffering from AD, and the subgroup of patients with a non-IgE-associated AD is called ‘intrinsic AD’ to distinguish it from ‘extrinsic’ (IgE-associated) forms of AD [5,6]. This controversy in terminology may have practical implications with regard to specific avoidance strategies in the management of this disease and the choice of treatment. In any case, AD is characterized by erythematous and itchy skin lesions which can involve the entire body and cause a strong impact on the quality of life of patients, with a high burden, especially in severe forms [7,8,9]. Consequently, there is an urge to better understand AD and treat patients because they have numerous unmet needs.

AD pathophysiology

AD is a multifactorial disease with a strong genetic influence (72% concordance in monozygous twins, 23% in heterozygous twins) [10] — but not an inherited disease — and the main pathophysiological mechanisms can be summarized as follows [1]: (1) an immune deviation toward Th2 in the initiation phase with consequent increased IgE production, (2) a deficient skin barrier function due to abnormal lipid metabolism and/or epidermal structural protein formation, (3) an abnormal microbial colonization with pathogenic organisms such as *Staphylococcus aureus* or *Malassezia furfur*, (4) a neurogenic inflammation. The pathophysiology of AD is summarized in Figure 1.

Nowadays, there is a very dynamic research on pathophysiology and treatment of AD, especially regarding itch [11]. Among the proteins involved in the maintenance of the epidermal barrier, filaggrin is the most studied and genetic variations, and loss of function variants within the FLG gene have been evidenced as a major risk factor in AD [12,13]. Proteins are not the only components of the barrier since lipids, mainly ceramides (with ester linked v-hydroxyl ceramide (EO ceramide), free fatty acids (FFA) and cholesterol, constitute the lipid matrix that is organized in lamellar bodies and located between corneocytes [14]. In AD, this lipid matrix is disorganized, and an alteration of the epidermal barrier is induced. AD patients show a reduction of long chains, an increase of unsaturated FFAs and a decrease of very long chains of ceramides in the skin [15].

Figure 1



Pathophysiology of AD.

With regard to inflammation, AD is characterized by an overexpression of pro-inflammatory molecules such as Th2 cytokines (IL-4, IL-5 and IL-13), IL-22 and thymic stromal lymphopoietin (TSLP) [11,16]. The non-lesional skin of AD patients also shows signs of low-grade inflammation with presence of Th2 and Th22 cell infiltration [17]. IL-31 and IL-33 are also related to the pathogenesis of AD [18–20]. In the acute phase of AD, skin barrier defects allow the penetration of antigens and lead to the

production of TSLP by keratinocytes. In the chronic phase, the continuous activation of Th2 and Th22 increase in the affected epidermal barrier accelerating also local inflammation leading to a vicious cycle [21]. TSLP secretion by keratinocytes [22**] is induced by sensitizing antigens, Th2 cytokines or the activation of toll-like receptor (TLR) pathways [23,24]. TSLP plays a role in immune processes at the epithelial interface with the external environment by acting on dendritic cells,

mast cells and Th-lymphocytes. Activation of dendritic cells by TSLP promotes the transformation of Th-naïve lymphocytes to the Th2 phenotype and the secretion of Th2 cytokines [25]. TSLP directly activates cutaneous sensory nerve endings via its specific receptor and then specifically promotes itching [22^{••}].

Because of the close associations among skin, immune system, and nervous system, nerve endings are very important in the pathophysiology of inflammatory dermatoses, especially in AD. Many neurotransmitters, especially substance P, and nerve growth factors released from nerve endings in the blood or skin are involved in neurogenic inflammation, thereby enhancing and maintaining the inflammation induced by immune cells. During times of stress, their release is highly enhanced [26,27]. Neurogenic inflammation, as well as chronic activation of transient receptor proteins such as TRPV1 and TRPA1, is highly involved in the vicious inflammatory cycle in AD [28].

Itch is the main complaint of patients with AD. Fortunately, there is a growing knowledge of its mechanisms [29]. Briefly, the role of histamine is probably restrained in humans, whereas TSLP and IL-31 are highly involved in the triggering of atopic itch, under the control of IL-4, IL-13, and maybe IL-33.

The Janus kinase/signal transducer and activator of transcription (JAK/STAT) signaling axis have been shown to play a critical role in the dysregulation of immune responses in AD, involving amplification of Th2 cell response, instigation of eosinophils, and suppression of regulatory T cells [16,30]. In addition, the JAK/STAT pathway, when activated by IL-4, IL-13, and TSLP, plays an important role in the pathogenesis of AD by upregulating the expression of epidermally derived chemokines and a cascade of pro-inflammatory cytokines as well as downregulating structural epidermal proteins, for example filaggrin, involucrin, or loricrin, ultimately diminishing the skin barrier function [16].

Anti-IL-4/13

Dupilumab

Dupilumab is the first marketed monoclonal antibody (mAb) in the treatment of AD. Dupilumab binds to the α -subunit of the IL-4 receptor, which is part of both the IL-4 and IL-13 receptor complex. The safety and efficacy of dupilumab were primarily established in three placebo-controlled studies in moderate to severe AD [16]. Dupilumab showed significant clinical effects across three distinct severity assessment tools: Eczema Area and Severity Index (EASI), Investigator's Global Assessment (IGA), and SCORing Atopic Dermatitis (SCORAD) [31^{••},32,33]. Moreover, dupilumab treatment significantly reduced pruritus. More recent trials have evaluated long-term management of AD with dupilumab and

concomitant topical steroids [34]. An important observation was the positive effect of dupilumab on both intrinsic and extrinsic AD. Several ongoing studies involving both children and adolescents will show whether these subgroups of the AD population may experience equally positive effects, expanding the treatment indication for dupilumab further.

Dupilumab treatment was in general well tolerated with few serious adverse events. The main side effects are ocular, such as non-infectious conjunctivitis and inflammation of the cornea were observed more commonly in the dupilumab group compared to placebo-treated subjects [31^{••},32].

Tralokinumab

Tralokinumab is an IL-13 neutralizing human IgG4 monoclonal antibody targeting IL-13. In a double-blind placebo controlled phase IIb study including 204 adults suffering from moderate to severe AD, tralokinumab demonstrated some efficacy in the primary and key secondary end points and had an adverse event profile comparable to placebo [35]. The most frequent adverse events in all groups (tralokinumab and placebo) were nasopharyngitis (17%), upper respiratory tract infection (9%), and headache (6%) [16]. Several new phase III trials are ongoing.

Lebrikizumab

Lebrikizumab is a humanized mAb that specifically targets IL-13. The drug was originally subjected to clinical evaluation in an asthmatic adult population and five trials were included in a meta-analysis [36]. There was no significant difference in the incidence of adverse events in patients with lebrikizumab compared to placebo. In a randomized, placebo-controlled, double-blind, phase 2 study, adults with moderate to severe AD were required to use topical corticosteroids twice daily and then randomized. At week 12, significantly more patients achieved EASI-50 with lebrikizumab 125 mg every 4 weeks than placebo, with similar adverse events in both groups [37].

Anti-IL31

Nemolizumab (previously CIM331) is a humanized IL-31 receptor A (IL-31RA) monoclonal antibody, which was specifically developed for the treatment of AD-related pruritus and inhibits the IL31 signalling. In an animal model, IL-31-induced scratching was suppressed after a single injection of nemolizumab [38]. In 2016, results of the first trial were published. A single nemolizumab subcutaneous injection reduced pruritus visual analogue scale (VAS) score to about -50% at week 4 compared with -20% with placebo in patients with AD [39]. The study did not assess the relief of the eczema, however, use of hydrocortisone decreased. In a subsequent phase 2, randomised, double-blind, placebo-controlled, 12-week

trial, nemolizumab at monthly doses significantly improved pruritus. A total of 216 adult patients with moderate-to-severe atopic dermatitis received subcutaneous nemolizumab (0.1 mg, 0.5 mg, or 2.0 mg per kilogram of body weight) or placebo every 4 weeks or an exploratory dose of 2.0 mg of nemolizumab per kilogram every 8 weeks [40**]. At week 12, pruritus VAS was reduced by 43.7% (0.1-mg group), 59.8% (0.5-mg group), and 63.1% (2.0-mg group), and 20.9% (placebo group; $p < 0.01$ for all comparisons). Eczema EASI scores improved to up to 40% compared to 27% in the placebo group [40**]. In a 52-week, double-blind extension of the previous described study, pruritus was reduced up to 90% and eczema scores up to 80% [41]. These studies demonstrated that nemolizumab is efficacious and well tolerated in patients with moderate-to-severe atopic dermatitis inadequately controlled by topical therapy. Some patients in the nemolizumab developed peripheral edema [41].

Targeting JAK/STAT pathways

Inhibitors of the JAK/STAT signalling axis are categorized as small molecules blocking intracellular targets. Several compounds targeting TYK2, JAK1, JAK2 and JAK3 are being evaluated for oral treatment of moderate to severe AD.

Baricitinib

Baricitinib is a small molecule inhibiting both JAK1 and JAK2. It is an oral treatment taken once daily. The first phase II study to investigate safety and efficacy of the drug has recently been completed (NCT02576938) and published. A total of 124 adults with moderate to severe AD were enrolled. Patients were randomised to once daily placebo, baricitinib 2 mg, or baricitinib 4 mg for 16 weeks. Use of TCS was permitted during the study. The patients treated with baricitinib showed significant reduction in the activity of eczema compared to the placebo group and baricitinib also improved pruritus (45% change in itch NRS at week 1) and sleep loss. Treatment-emergent adverse events were mainly infections and a few patients in the active treatment group were discontinued due to low white cell counts [42]. The drug has also been thoroughly tested in rheumatoid arthritis (RA), psoriasis, alopecia areata, and other inflammatory or auto-immune conditions, with promising results and only few side-effects. A slightly increased rate of infection, risk of low neutrophils and reduced haemoglobin levels have been observed.

Tofacitinib

Tofacitinib inhibits JAK1 and JAK3 and in theory interfere to a larger extent with lymphocyte activation and Th2-skewing than the inhibitors also targeting JAK2 which is more involved in Th1 signalling [43]. It has been studied in a minor case series involving six patients revealing a significant reduction in SCORAD [44]. The

oral formulation of the drug is not subject to any clinical trials involving AD, but it is approved for RA.

Upadacitinib

Upadacitinib is a small molecule targeting only JAK1. It has been investigated in a phase IIb placebo-controlled multicentre study to evaluate the safety and efficacy in adult participants with moderate to severe AD (NCT02925117). The results are so far not published but has been presented at an international meeting (Guttman-Yasky, E *et al.* Primary Results from a Phase 2b, Randomised, Placebo-Controlled Trial of Upadacitinib for Patients with Atopic Dermatitis. American Academy of Dermatology. February 2018). The study included three dosing groups, 30/15/7.5 mg once-daily, and one placebo group for 16 weeks. Upadacitinib showed a significant reduction in itch as early as Week 1 and improvement in the extent and severity of skin lesions at Week 2 for all doses compared to placebo. An investigator global assessment (IGA) of 0/1 was observed in 50% of cases in the 30 mg/day treated group versus 2% in the placebo group at 16 weeks. Additionally, a 74% reduction in EASI score was observed in the 30 mg treated group compared to 23% reduction of EASI in the placebo group. The most common adverse events were upper respiratory tract infection, atopic dermatitis worsening, and acne.

PF-04965842

PF-04965842 targets JAK1 only. Its safety and efficacy have been evaluated in a phase II trial of adults with moderate to severe AD (NCT02780167). The results are so far unpublished but have been presented at an international meeting (Gooderham M *et al.* PF-04965842, a JAK1 inhibitor, for treatment of atopic dermatitis: a 12-week, randomised, double-blind, placebo-controlled trial. Presented at EADV 2017, Geneva, Switzerland). Treatment with 200 mg PF-04965842 daily resulted in a disease activity of 0/1 in 44.5% of patients, judged by investigator global assessment (IGA), at 12 weeks compared to 6.3% of patients in the placebo group. An 82% reduction in EASI score was also observed in the 200 mg treatment group versus 35% in the placebo group.

Anti-TSLP

Thymic Stromal Lymphopoietin (TSLP) plays a crucial role in AD and the atopic march. TSLP is released by keratinocytes after stimulation by not only Th2 cytokines but also *S. aureus* [45]. In turn, TSLP polarizes toward Th2 responses and is involved in pruritus pathways [22**]. Thus, TSLP is a very interesting target in AD. Because data on the role of TSLP are very new, therapeutic research is only emerging.

Tezepelumab is an mAB-targeting circulating TSLP. The drug previously revealed its efficacy and safety in asthma [46]. Tezepelumab has completed phase 1 (AMG-157; NCT00757042) and phase 2a (MEDI9929,

NCT02525094) randomized, double-blinded, placebo-controlled studies to evaluate the efficacy and safety in subjects with moderate to severe AD. Results have just been listed in clinicaltrials.gov but are not published yet. The percentage of patients achieving EASI 50 in the tezepelumab group at week 12 was 64.7% versus 48.2% in the placebo group (Odds ratio 1.97, IC95 0.90–4.33). Another study with an anti-TSLP drug (MK-8226), was tested in a phase Ib (NCT01732510) but was prematurely stopped and no data was posted.

Anti-phosphodiesterase-4 (anti-PDE4)

PDE4 is an enzyme involved in regulation of pro-inflammatory cytokines via degradation of cyclic adenosine monophosphate (cAMP). Inhibition of PDE4 leads to increase intracellular cAMP which leads to decrease the levels of pro-inflammatory cytokines such as TNF- α , IL-4 and 31 [47]. Increased PDE4 levels has been described in cells from AD patients [48], thus PDE4 seems to be an interesting target in AD [49]. Currently, several trials investigate various topical and systematically administered PDE4 inhibitors.

Topical PDE4 inhibitor

Crisaborole 2% ointment is the first drug and the only one approved (FDA, 2016) so far in this class for the treatment of patients aged of 2 years and greater with mild to moderate AD. In two phase II studies, some more crisaborole-treated than vehicle-treated patients achieved ISGA score success with a greater percentage with clear/almost clear. Crisaborole-treated patients achieved success in ISGA score and improvement in pruritus earlier than those treated with vehicle. Treatment-related adverse events were infrequent and mild to moderate in severity [50].

Oral PDE4 inhibitor

Apremilast is an oral PDE4 inhibitor approved for psoriasis and arthritis psoriasis. Two open-label phase II studies, revealed modest efficacy (EASI and IGA score) with dose-dependent mild side effects (nausea, vomiting and headache) [51,52]. Results from phase II trial (apremilast 30 or 40 mg daily) for patients with moderate to severe AD have been listed in clinicaltrials.gov (NCT02087943) but have yet to be published. Results revealed statistically significant reduction in EASI score in the 40 mg study group (–31.57%) versus placebo (–10.98%) ($p = 0.03$). In each treatment group compared to placebo, the percentage of participants who achieved a score of 0 (clear) or 1 (almost clear) and at least a 2-point reduction from baseline in a Static Physician's Global Assessment of Acute Signs at week 12 did not reach statistically significant levels.

Neurokinin-1 (NK1) antagonists

Several inflammatory neuropeptides are involved in the pathophysiology of pruritus in AD. Among them,

substance P (SP) and its main receptor, NK1-receptor, are particularly implicated. Thus, the levels of SP are associated with disease activity of AD and increased pruritus [53]. Tradipitant (VLY-688) is an oral NK1-receptor antagonist. Two phase II study has been completed but results have yet to be published (NCT02651714 and NCT02975206) and a phase III study is currently trialed (NCT03568331). Serlopitant (VPD-737) is another NK1-receptor currently in phase II trials for AD.

Kappa-opioid receptor agonists

Kappa-opioids are inhibitors of pruritus. Their receptors located in the peripheral and central nervous system are downregulated in the epidermis of AD patients' [54]. Asimadoline is an orally active, selective kappa-opioid receptor agonist and has demonstrated efficacy in several preclinical pruritus models [55]. A Phase II study to evaluate the safety, tolerability and clinical efficacy of asimadoline in patients with pruritus associated with atopic dermatitis has been completed but results have yet to be published (NCT02475447).

Antihistamines

There is currently no high-level evidence to support (or refute) the efficacy or safety of oral H1 antihistamines used as monotherapy for eczema, especially regarding anti-pruritic effects [56**]. The potential role of histamine via H4 (in contrast to H1) could be discussed. A study on ZPL-3893787 (a selective H₄ receptor antagonist) has been performed in moderate/severe AD [57]. This randomized, double-blind, placebo-controlled, parallel-group study was conducted with 30 mg once daily oral therapy in adult patients. Treatment showed a placebo-adjusted reduction in EASI score at Week 8 was 5.1. There was a 3-point reduction (scale 1–10) in pruritus with ZPL-389, but there was a similar reduction with placebo, resulting in a non-significant difference. ZPL-3893787 was well tolerated. This study confirms that the effects of H4-antagonists are rather anti-inflammatory than anti-pruritic.

Conclusion

It is very encouraging to observe that there is a dynamic research field at the moment to get new treatments for AD and also pruritus. Most of them will be developed for systemic use and some of them for topical use. Dupilumab (systemic) and crisaborole (topical) are the first available treatments coming from this new research but we believe that many others will come in the next future. There are a very high number of clinical trials on atopic dermatitis (according clinicaltrials.gov, 648 on November 27th, 2018).

Conflict of interest statement

Laurent Misery: Abbvie, Bayer, Beiersdorf, Bioderma, Celgene, Expanscience, Galderma, GSK, Johnson &

Johnson, Leo, Lilly, Menlo, Novartis, Pfizer, Pierre Fabre, Roche-Posay, Sanofi, Trevi, UCB, Uriage.

Olivier Gouin: Uriage.

Flavien Huet: Beiersdorf, Celgene, Novartis.

Mette Deleuran: Regeneron, Sanofi Genzyme, Eli Lilly, Leo Pharma, Pierre Fabre, Meda Pharma, AbbVie, CK-Care, La Roche-Posay Foundation, Galapagos, NeRRe Therapeutics.

Sonja Ständer: Bayer, Beiersdorf, Celgene, Dermasence, Leo, Galdema, Kiniksa, Menlo, Nerre, Novartis, Pfizer, Pierre Fabre, Sanofi, Sienna, Trevi.

References and recommended reading

Papers of particular interest, published within the period of review, have been highlighted as:

- of special interest
- of outstanding interest

1. Ring J, Alomar A, Bieber T, Deleuran M, Fink-Wagner A, Gelmetti C, Gieler U, Liposencic J, Luger T, Oranje AJ *et al.*: **Guidelines for treatment of atopic eczema (atopic dermatitis) (part II).** *J Eur Acad Dermatol Venereol* 2012, **26**:1176-1193.
 2. Williams HC (Ed): *Atopic Dermatitis. The Epidemiology, Causes and Prevention of Atopic Eczema*. Cambridge University Press; 2000.
 3. Hanifin JM, Rajka G: **Diagnostic features of atopic dermatitis.** *Acta Derm Venereol* 1980, **92**:44-47.
 4. Williams HC, Burney PG, Hay RJ *et al.*: **The U.K. Working Party's Diagnostic Criteria for Atopic Dermatitis. I. Derivation of a minimum set of discriminators for atopic dermatitis.** *Br J Dermatol* 1994, **131**:383-396.
 5. Wüthrich B, Schmid-Grendelmeier P: **The atopic eczema/dermatitis syndrome. Epidemiology, natural course, and immunology of the IgE-associated ('extrinsic') and the nonallergic ('intrinsic') AEDS.** *J Invest Allergol Clin Immunol* 2003, **13**:1-5.
 6. Roguedas-Contios AM, Misery L: **What is intrinsic atopic dermatitis?** *Clin Rev Allergy Immunol* 2011, **41**:233-236.
 7. Dalgard FJ, Gieler U, Tomas-Aragones L, Lien L, Poot F, Jemec GBE, Misery L, Szabo C, Linder D, Sampogna F *et al.*: **The psychological burden of skin diseases: a cross-sectional multicenter study among dermatological out-patients in 13 European countries.** *J Invest Dermatol* 2015, **135**:984-991.
- This international study clearly demonstrates the psychological burden of skin diseases, including AD.
8. Misery L, Sénéchal J, Reguiat Z, Merhand S, Héas S, Huet F, Taieb C, Ezzedine K: **Patient burden is associated with alterations in quality of life in adult patients with atopic dermatitis.** *Acta Derm Venereol* 2018, **98**:713-714.
 9. Misery L, Sénéchal J, Reguiat Z, Merhand S, Héas S, Huet F, Taieb C, Ezzedine K: **The impact of atopic dermatitis on sexual health.** *J Eur Acad Dermatol Venereol* (in press).
 10. Schult-Larsen F: **Atopic dermatitis: a genetic-epidemiologic study in a population-based twin sample.** *J Am Acad Dermatol* 1993, **28**:719-723.
 11. Huet F, Severino-Freire M, Chéret J, Gouin O, Praneuf J, Pierre O, Misery L, Le Gall-Ianotto C: **Reconstructed human epidermis for in vitro studies on atopic dermatitis: a review.** *J Dermatol Sci* 2018, **89**:213-218.
 12. Brown SJ, Kroboth K, Sandilands A, Campbell LE, Pohler E, Kezic S, Cordell HJ, McLean WHI, Irvine AD: **Intragenic copy number variation within filaggrin contributes to the risk of atopic dermatitis with a dose-dependent effect.** *J Invest Dermatol* 2012, **132**:98-104.
 13. Brown SJ, McLean WHI: **One remarkable molecule: filaggrin.** *J Invest Dermatol* 2012, **132**:751-762.
 14. Elias PM: **Structure and function of the stratum corneum extracellular matrix.** *J Invest Dermatol* 2012, **132**:2131-2133.
 15. Janssens M, van Smeden J, Gooris GS, Bras W, Portale G, Caspers PJ, Vreeken RJ, Hankemeier T, Kezic S, Wolterbeek R *et al.*: **Increase in short-chain ceramides correlates with an altered lipid organization and decreased barrier function in atopic eczema patients.** *J Lipid Res* 2012, **53**:2755-2766.
 16. Nygaard U, Vestergaard C, Deleuran M: **Emerging therapeutic options in atopic dermatitis: systemic therapies.** *Dermatology* 2017, **233**:344-357.
 17. Weidinger S, Novak N: **Atopic dermatitis.** *Lancet* 2016, **387**:1109-1122.
 18. Paller AS, Kabashima K, Bieber T: **Therapeutic pipeline for atopic dermatitis: end of the drought?** *J Allergy Clin Immunol* 2017, **140**:633-643.
 19. Cornelissen C, Marquardt Y, Czaja K, Wenzel J, Frank J, Lüscher-Firzlaff J, Lüscher B, Baron JM: **IL-31 regulates differentiation and filaggrin expression in human organotypic skin models.** *J Allergy Clin Immunol* 2012, **129**:426-433.
 20. Seltsmann J, Roesner LM, von Hesler FW, Wittmann M, Werfel T: **IL-33 impacts on the skin barrier by downregulating the expression of filaggrin.** *J Allergy Clin Immunol* 2015, **135**:1659-1661.
 21. Noda S, Krueger JG, Guttman-Yassky G: **The translational revolution and use of biologics in patients with inflammatory skin diseases.** *J Allergy Clin Immunol* 2015, **135**:324-336.
 22. Wilson SR, Thé L, Batia LM, Beattie K, Katibah GE, McClain SP, Pellegrino M, Estandian DM, Bautista DM: **The epithelial cell-derived atopic dermatitis cytokine TSLP activates neurons to induce itch.** *Cell* 2013, **155**:285-295.
- This wonderful work clearly demonstrates that TSLP can induce itch.
23. Takai T, Chen X, Xie Y, Vu AT, Le TA, Kinoshita H, Kawasaki J, Kamijo S, Hara M, Ushio H *et al.*: **TSLP expression induced via toll-like receptor pathways in human keratinocytes.** *Methods Enzymol* 2014, **535**:371-387.
 24. Tatsuno K, Fujiyama T, Yamaguchi H, Waki M, Tokura Y: **TSLP directly interacts with skin-homing Th2 cells highly expressing its receptor to enhance IL-4 production in atopic dermatitis.** *J Invest Dermatol* 2015, **135**:3017-3024.
 25. Soumelis V, Reche PA, Kanzler H, Yuan W, Edward G, Homey B, Gilliet M, Ho S, Antonenko S, Lauerma A *et al.*: **Human epithelial cells trigger dendritic cell mediated allergic inflammation by producing TSLP.** *Nat Immunol* 2002, **3**:673-680.
 26. Misery L: **Atopic dermatitis and the nervous system.** *Clin Rev Allergy Immunol* 2011, **41**:259-266.
 27. Gouin O, Lebonvallet N, L'Herondelle K, Le Gall-Ianotto C, Buhé V, Plée-Gautier E, Carré JL, Lefeuvre L, Misery L: **Self-maintenance of neurogenic inflammation contributes to a vicious cycle in skin.** *Exp Dermatol* 2015, **24**:723-726.
 28. Gouin O, L'Hérondelle K, Buscaglia P, Le Gall-Ianotto C, Philippe R, Legoux N, Mignen O, Buhé V, Leschiera R, Sakka M *et al.*: **Major role for TRPV1 and InsP3R in PAR-2-elicited inflammatory mediator production in differentiated human keratinocytes.** *J Invest Dermatol* 2018, **138**:1564-1572.
 29. Trier AM, Kim BS: **Cytokine modulation of atopic itch.** *Curr Opin Immunol* 2018, **54**:7-12.
 30. Bao L, Zhang H, Chan LS: **The involvement of the JAK-STAT signaling pathway in chronic inflammatory skin disease atopic dermatitis.** *JAKSTAT* 2013, **2**:e24137.
 31. Thaci D, Simpson EL, Beck LA, Bieber T, Blauvelt A, Papp K *et al.*: **Efficacy and safety of dupilumab in adults with moderate-to-severe atopic dermatitis inadequately controlled by topical**

treatments: a randomised, placebo-controlled, dose-ranging phase 2b trial. *Lancet* 2016, **387**:40-52.

This is the first paper demonstrating the interest of anti-IL4/13 in AD.

32. Beck LA, Thaci D, Hamilton JD, Graham NM, Bieber T, Rocklin R et al.: **Dupilumab treatment in adults with moderate-to-severe atopic dermatitis.** *N Engl J Med* 2014, **371**:134-139.
33. Simpson EL, Bieber T, Guttman-Yassky E, Beck LA, Blauvelt A, Cork MJ et al.: **Two phase 3 trials of dupilumab versus placebo in atopic dermatitis.** *N Engl J Med* 2016, **375**:2335-2348.
34. Blauvelt A, de Bruin-Veller M, Gooderham M, Cather JC, Weisman J, Pariser D, Simpson EL, Papp KA, Hong HC, Rubel D et al.: **Long-term management of moderate-to-severe atopic dermatitis with dupilumab and concomitant topical corticosteroids (LIBERTY AD CHRONOS): a 1-year, randomised, double-blinded, placebo-controlled phase 3 trial.** *Lancet* 2017, **389**:2287-2303.
35. Wollenberg A, Howell MD, Guttman-Yassky E, Silverberg JI, Kell C, Ranade K, Moate R, van der Merwe R: **Treatment of atopic dermatitis with tralokimab, an anti-IL-13 mAb.** *J Allergy Clin Immunol* (in press).
36. Liu Y, Zhang S, Chen R, Wei J, Guan G, Zhou M, Dong N, Cao Y: **Meta-analysis of randomized controlled trials for the efficacy and safety of anti-interleukin-13 therapy with lebrikizumab in patients with uncontrolled asthma.** *Allergy Asthma Proc* 2018, **39**:332-337.
37. Simpson EL, Flohr C, Eichefield LF, Bieber T, Sofen H, Taieb A, Owen R, Putman W, Castro M, DeBusk K et al.: **Efficacy and safety of lebrikizumab (an anti-IL-13 monoclonal antibody) in adults with moderate-to-severe atopic dermatitis inadequately controlled by topical corticosteroids: a randomized, placebo-controlled phase II trial (TREBLE).** *J Am Acad Dermatol* 2018, **78**:863-871.
38. Oyama S, Kitamura H, Kuramochi T, Higuchi Y, Matsushita H, Suzuki T, Goto M, Adachi H, Kasutani K, Sakamoto A et al.: **Cynomolgus monkey model of interleukin-31-induced scratching depicts blockade of human interleukin-31 receptor A by a humanized monoclonal antibody.** *Exp Dermatol* 2018, **27**:14-21.
39. Nemoto O, Furue M, Nakagawa H, Shiramoto M, Hanada R, Matsuki S, Imayama S, Kato M, Hasebe I, Taira K 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.
40. Ruzicka T, Hanifin JM, Furue M, Pulka G, Mlynarczyk I, Wollenberg A, Galus R, Etoh T, Mihara R, Yoshida H et al.: **Anti-interleukin-31 receptor A antibody for atopic dermatitis.** *N Engl J Med* 2017, **376**:826-835.
41. Kabashima K, Furue M, Hanifin JM, Pulka G, Wollenberg A, Galus R, Etoh T, Mihara R, Nakano M, Ruzicka T: **Nemolizumab in patients with moderate-to-severe atopic dermatitis: randomized, phase II, long-term extension study.** *J Allergy Clin Immunol* 2018, **142**:1121-1130.
42. Guttman-Yassky E, Silverberg JI, Nemoto O, Forman SB, Wilke A, Prescilla R, de la Peña A, Nunes FP, Janes J, Gamalo M et al.: **Baricitinib in adult patients with moderate-to-severe atopic dermatitis: a phase 2 parallel, double-blinded, randomized placebo-controlled multiple-dose study.** *J Am Acad Dermatol* [Epub ahead of print].
43. O'Shea JJ, Plenge R: **JAK and STAT signaling molecules in immunoregulation and immune-mediated disease.** *Immunity* 2012, **36**:542-550.
44. Levy LL, Urban J, King BA: **Treatment of recalcitrant atopic dermatitis with the oral Janus kinase inhibitor tofacitinib citrate.** *J Am Acad Dermatol* 2015, **73**:395-399.
45. Vu AT, Baba T, Chen X, Le TA, Kinoshita H, Xie Y, Kamijo S, Hiramatsu K, Ikeda S, Ogawa H et al.: **Staphylococcus aureus membrane and diacylated lipopeptide induce thymic stromal lymphopoietin in keratinocytes through the Toll-like receptor 2-Toll-like receptor 6 pathway.** *J Allergy Clin Immunol* 2010, **126**:985-993 993.e1-3.
46. Corren J, Parnes JR, Wang L, Mo M, Roseti SL, Griffiths JM, van der Merwe R: **Tezepelumab in adults with uncontrolled asthma.** *N Engl J Med* 2017, **377**:936-946.
47. Grewe SR, Chan SC, Hanifin JM: **Elevated leukocyte cyclic AMP-phosphodiesterase in atopic disease: a possible mechanism for cyclic AMP-agonist hyporesponsiveness.** *J Allergy Clin Immunol* 1982, **70**:452-457.
48. Chan SC, Reifsnnyder D, Beavo JA, Hanifin JM: **Immunochemical characterization of the distinct monocyte cyclic AMP-phosphodiesterase from patients with atopic dermatitis.** *J Allergy Clin Immunol* 1993, **91**:1179-1188.
49. Zebda R, Paller AS: **Phosphodiesterase 4 inhibitors.** *J Am Acad Dermatol* 2018, **78**:S43-S52.
50. Paller AS, Tom WL, Lebwohl MG, Blumenthal RL, Boguniewicz M, Call RS, Eichenfield LF, Forsha DW, Rees WC, Simpson EL et al.: **Efficacy and safety of crisaborole ointment, a novel, nonsteroidal phosphodiesterase 4 (PDE4) inhibitor for the topical treatment of atopic dermatitis (AD) in children and adults.** *J Am Acad Dermatol* 2016, **75**:494-503.
51. Volf EM, Au S-C, Dumont N, Scheinman P, Gottlieb AB: **A phase 2, open-label, investigator-initiated study to evaluate the safety and efficacy of apremilast in subjects with recalcitrant allergic contact or atopic dermatitis.** *J Drugs Dermatol* 2012, **11**:341-346.
52. Samrao A, Berry TM, Goreski R, Simpson EL: **A pilot study of an oral phosphodiesterase inhibitor (apremilast) for atopic dermatitis in adults.** *Arch Dermatol* 2012, **148**:890-897.
53. Toyoda M, Nakamura M, Makino T, Hino T, Kagoura M, Morohashi M: **Nerve growth factor and substance P are useful plasma markers of disease activity in atopic dermatitis.** *Br J Dermatol* 2002, **147**:71-79.
54. Tominaga M, Ogawa H, Takamori K: **Possible roles of epidermal opioid systems in pruritus of atopic dermatitis.** *J Invest Dermatol* 2007, **127**:2228-2235.
55. Machelska H, Pflüger M, Weber W, Piranvisseh-Völk M, Daubert JD, Dehaven R, Stein C: **Peripheral effects of the kappa-opioid agonist EMD 61753 on pain and inflammation in rats and humans.** *J Pharmacol Exp Ther* 1999, **290**:354-361.
56. van Zuuren EJ, Apfelbacher CJ, Fedorowicz Z, Jupiter A, Mattered U, Weishaar E: **No high level evidence to support the use of oral H1 antihistamines as monotherapy for eczema: a summary of a Cochrane systematic review.** *Syst Rev* 2014, **3**:25.

This systematic review does not show evidences for anti-pruritic effects of H1 antihistamines in AD.