International e-Symposium on Atopy

REPORT

Complex paediatric atopic dermatitis: focus on systemic therapies

According to the communication of Prof Carsten Flohr, London, United Kingdom
Report written by Dr Rémi Maghia, Brest, France

Some new targeted therapies are emerging for atopic dermatitis (AD): lebrikizumab, tralokinumab, dupilumab, nemolizumab, omalizumab, and selective JAK inhibitors.
However, for part of our practice, conventional systemic treatments will continue to be used as first-line therapies for severe cases of AD in adults and children: azathioprine, cyclosporin (approved for more than 16 years), methotrexate, and mycophenolate mofetil.
The studies carried out in paediatrics have been few in number and mainly included case series and case-control studies. In the studies available, the data of paediatric patients are not frequently reported separately.
Severe AD is a complex disease. Several factors come into play that include skin infections, food allergies, asthma, hay fever, sleep disturbances, anxiety and depression. There is a vicious circle of itching-scratching-skin inflammation.
Treating severe AD often requires a multidisciplinary approach and teamwork, with the involvement of a paediatric dermatologist, paediatric allergist, clinical psychologist, paediatric pulmonologist, clinical research team, and patient education programme.
Dupilumab is approved for the treatment of **moderate to severe** AD in adults and adolescents aged 12 and over who are candidates for systemic therapy. It is also approved children aged six to 11 with **severe** AD who are candidates for systemic therapy.

Dupilumab-associated conjunctivitis

It occurs in over 30% of cases in real-life cohorts. It takes the forms of foreign body sensations, burning and itching. There is limbal hyperaemia. This side effect is not observed in trials on asthma and nasal polyps.
Its pathophysiology is not yet clear. Simultaneous blockage of the IL-4 and IL-13 signalling pathways may increase the activity of the ligands involved in atopic keratoconjunctivitis. Another hypothesis: Demodex may proliferate in an environment of reduced ocular cytokines.
This side effect is also observed in trials with lebrikizumab, but not with tralokinumab, which tends to show that it is not related to specific IL-13 blockage.

We are lacking head-to-head trials for severe paediatric AD:

Such as: conventional vs conventional treatment, conventional vs new treatment, new treatments compared with one another.
The TREAT trial, undertaken in the United Kingdom with a focus on children aged two to 16, compares methotrexate with cyclosporin A. The study is now complete and will be published in 2022.
The speaker is leading a network meta-analysis (NMA) currently being published in the BMJ (1). It provides a systematic review of systemic immunomodulatory treatments for AD. It combines the data of children and adults, since in the majority of studies, paediatric data are not reported separately. The results of this NMA have not yet been published, so without going into detail, we can say that for the difference in terms of EASI vs dupilumab, the following perform better: abrocitinib 200 mg once/day, and upadacitinib 15 and 30 mg once/day. These two medications are approved for patients aged 12 and over.
With regard to abrocitinib, the speaker participated in a study in adolescents (aged 12-17) in combination with topical treatment for moderate to severe AD. It was published in JAMA Dermatology in 2021. Two hundred and eighty-seven adolescents were randomly treated with abrocitinib 200 mg, abrocitinib 100 mg or a placebo. All received topical corticosteroids. In the two abrocitinib groups, around 70% of patients achieved an EASI 75 response, versus 40% in the placebo group. These were similar to the results in adults.
Carsten Flohr is also running the UK-Irish Atopic Eczema Systemic Therapy Register (A-STAR), whose goal is to obtain long-term real-life data concerning the efficacy and safety of new and conventional systemic AD treatments.

Key messages

- Methotrexate (0.4 mg/kg/week): often the first-line systemic treatment used by the speaker (off-label use).
- Cyclosporin (4-5 mg/kg/day) for faster action (the only conventional treatment with MA).
- JAK inhibitors (abrocitinib and upadacitinib) are promising, even for patients not responding to dupilumab.
- The main potential side effects: nausea, headaches, acne and herpes simplex and herpes zoster infections.
- Alert concerning tofacitinib (for rheumatoid arthritis): serious infections, thromboembolic events and myocardial infarction (NEJM 2022).
- Usefulness of treatment registers to assess long-term efficacy and safety.
- Need for more head-to-head trials.

(1) Network meta-analysis by Drucker A, et al. Flohr C. *JAMA Dermatology 2022* in press – www.eczematherapies.com

Atopic dermatitis (AD) behind pruritus

According to the communication of Prof Laurent Misery, Brest, France
Report written by Dr Rémi Maghia, Brest, France

The human burden of chronic pruritus in inflammatory dermatoses is high. This was shown in a European study (JAAD 2018) that included 1552 patients with various pruritic dermatoses (psoriasis 32%, AD 29%). Pruritus can be experienced very frequently as stressful, horrible, terrible and refractory, making patients aggressive.

Pruritus is a challenge

It is the main symptom of AD, on and away from lesions. It is chronic and has a major impact on sleep, cognition, appearance, psychological well-being, quality of life, and sex life.
Pruritus has been poorly understood up to now and treatments are disappointing.

There are many **factors that aggravate** pruritus: heat, clothing (wool), insomnia, anxiety, depression, the vicious cycle of scratching, perspiration, inflammation, dry skin, and night time.

Pruriceptors

These are specific receptors of itching sensations in the skin's nerve endings (epidermal and sub-epidermal). Numerous receptors are expressed. It should be noted that the histamine H1 receptor is one of them, even though it is not very involved in pruritus in AD. Through mediators such as cytokines, enzymes (proteases) and neuromediators, these receptors interact with many cells (macrophages, keratinocytes, mast cells, T cells).

There are several pruritogenic mediators in AD, including kallikrein, tryptase, bradykinin, serotonin, endothelin-1, IL-3, TSLP, substance P, PAF, artemin, IL-2, GRP, and CGRP.

The role of TSLP

TSLP is a cytokine produced by keratinocytes in the epidermis; through dendritic cells, it increases the production of pro-inflammatory cytokines (Th2 pathway) such as IL-4 by T cells. TSLP does not act on the Th1 and Th17 pathways.
In response to various stimuli (nettle, parasites, mast cells), proteases lead to the production of PAR2 within keratinocytes, causing Ca2+ to be released. This results in the release of TSLP which activates TSLP-R receptors in the afferent C fibre endings with membrane depolarisation. Nerve impulses reach the spinal cord and then the brain, thereby triggering pruritus.

The role of IL-31

Th2 cells produce IL-31, which alters the skin barrier with action on dermal eosinophils, macrophages, basophils and mast cells. This results in dermal inflammation, nerve elongation (increased neuronal growth and nerve ending density) and pruritus.

The role of IL-4 and IL-13

IL-4 and IL-13 directly activate sensory neurons. IL-4 increases the neuronal response to various pruritogens. JAK1 is involved.

Sensitisation for pruritus

In cases of chronic pruritus, epidermal peripheral stimulation via pruriceptors activates the central nervous system. Chronic stimulation of the peripheral and central nervous systems ends up leading to sensitisation for pruritus, with phenomena such as allokinesis (where normal sensations are perceived as itchy) and hyperkinesis (exacerbated sensations of itching in an area adjacent to that scratched).

Skin barrier impairment and pruritus

Skin barrier impairment causes nerve endings to be in closer contact with the external environment.
Barrier impairment or inflammation causes skin and immune cells to release mediators that can activate pruriceptors on the nerve endings of C fibres.

There are many targets for improving pruritus

- NGF: pegcantranib
- TRPV1: capsaicin
- TRPM8: menthol, menthoxypropanediol
- IL-4, IL-13: dupilumab, lebrikizumab
- IL-31: nemolizumab
- IL-33
- NK1: aprepitant, serlopitant, tradipitant
- PDE4: apremilast, crisaborole, difamilast, lotamilast
- CB1/CB2: cannabinoids
- KOR: difelikefalin, nalbuphine, nalfurafine
- MOR: naloxone, naltrexone
- JAK: baricitinib, delgocitinib, tofacitinib, upadacitinib

A statement on the management of pruritus and pain in AD was published in JEADV 2021

- 1st step (often sufficient): treatment of AD, emollients, patient education, psychological support.
- If pruritus persists: cyclosporin, dupilumab, nemolizumab, gabapentinoids, antidepressants, JAK inhibitors, PDE4 inhibitors, k-opioids, NK1 inhibitors.
- If pain persists: common analgesics, gabapentinoids, antidepressants, JAK inhibitors, PDE4 inhibitors, μ-opioids.

Key messages

- Pruritus is the main concern of patients with AD and their families.
- Research into pruritus (in particular in AD) is providing several therapeutic targets.
- Emollients are useful both to combat dryness and to relieve itching.

Role of skincare products in the management of atopy and impact on the skin barrier

According to the communication of Dr Sandy Skotnicki, University of Toronto, Canada
Report written by Dr Rémi Maghia, Brest, France

The skin barrier

It limits transepidermal water loss (TEWL), prevents dryness and protects against harsh external factors.
It is made of a dense network of intracellular keratin filament aggregates, hydrolipidic film, intercellular lipidic cement and tight junctions.
In atopic dermatitis (AD), there is a lack of barrier proteins, a lack of lipids, an altered surface pH, cutaneous bacterial dysbiosis, and an altered immune response.
As a result, allergens can penetrate more easily, NMF decreases and TEWL increases, causing skin inflammation.

Therapeutic importance of emollients

Emollients are included in the European recommendations: they should be used in appropriate quantities, at a good frequency, and should contain higher levels of lipids in winter. In moderate to severe AD, this reduces the need for steroids, but it is first necessary to achieve remission through topical corticosteroids or calcineurin inhibitors. In the European recommendations, this is valid for adults and children. It is also part of the US recommendations, which also indicate that these emollients should be applied shortly after taking a bath.
Emollients should be used on a daily basis. The quantities should be appropriate and they are high:

TABLE 1 Suggested weekly quantity of topical therapies

Moisturizer	Basic management (grams per week)
Child	150-200
Adolescent or Adult	500
Ointment	**Twice daily acute therapy (grams per week)**
Child	125-250
Adolescent or Adult	260-330
Cream	**Twice daily acute therapy (grams per week)**
Child	140-275
Adolescent or Adult	290-330

According to *Fleischer et al. Atopic dermatitis: skin care and topical therapies. Semin Cutan Med Surg. 36: 104-110.*

Compliance is frequently lacking in AD: two out of three patients do not comply with their topical treatment, and one in two patients uses a quantity of emollients lower than the recommended quantity.

What ingredients do these emollients contain?

Some useful ingredients include ceramides, cholesterol, phytosphingosine (a natural component of ceramides), essential fatty acids, and colloidal oatmeal.

Which ones should we choose?

We should combine: efficacy, safety, absence of burning and tingling sensations, and convenience of use, to ensure long-term compliance and results.

The example of Atoderm Intensive Baume* by Bioderma*

The Lipigenium complex* contains pure phytosphingosine and biomimetic lipids that help restore the lipid barrier.
Enoxolone has anti-inflammatory and anti-pruritic action and reduces the expression of TSLP in the atopic epidermis.
Topical palmitoylethanolamide (PEA) has anti-pruritic action.

A randomised, placebo-controlled double-blind study with 130 patients between the ages of six months and 15 years with moderate AD compared treatment with topical corticosteroids or tacrolimus combined with either Atoderm Intensive Baume* or an emollient acting as a placebo for six months.
Without going into the details of the study, the differences were constantly significant in favour of Atoderm Intensive Baume* vs the placebo, both for the decrease in the SCORAD observed by the doctors and patients and in terms of improved quality of life. Seventy-six percent of the patients treated with the balm had not experienced any relapse after six months and had 20 more relapse-free days than those treated with the placebo. Ninety-four percent of the patients had less of an urge to scratch and 88% had a sustained break from pruritus.

Key messages

- Skincare products are useful for protecting and strengthening the skin barrier in AD.
- Topical therapy should be tailored to each patient's specific needs.
- These products should be well tolerated and pleasant to use with the goal of promoting patient compliance.