DOI: 10.1111/jdv.18345 JEADV

GUIDELINE

# European guideline (EuroGuiDerm) on atopic eczema: part I – systemic therapy

A. Wollenberg,[1,2,*] M. Kinberger,[3] B. Arents,[4] N. Aszodi,[1] G. Avila Valle,[3] S. Barbarot,[5] T. Bieber,[6] H.A. Brough,[7,8] P. Calzavara Pinton,[9] S. Christen-Zäch,[10] M. Deleuran,[11] M. Dittmann,[3] C. Dressler,[3] A.H. Fink-Wagner,[12] N. Fosse,[13] K. Gáspár,[14] L. Gerbens,[15] U. Gieler,[16] G. Girolomoni,[17] S. Gregoriou,[18] C.G. Mortz,[19] A. Nast,[3] U. Nygaard,[20] M. Redding,[21] E.M. Rehbinder,[22] J. Ring,[23] M. Rossi,[24] E. Serra-Baldrich,[25] D. Simon,[26] Z.Z. Szalai,[27] J.C. Szepietowski,[28] A. Torrelo,[29] T. Werfel,[30] C. Flohr[31,32,*]

[1]Department of Dermatology and Allergy, LMU Munich, Munich, Germany
[2]Department of Dermatology, Vrije Universiteit Brussel (VUB), Universitair Ziekenhuis Brussel (UZ Brussel), Brussels, Belgium
[3]Division of Evidence-Based Medicine (dEBM), Department of Dermatology, Venereology and Allergology, Charité – Universitätsmedizin Berlin, corporate member of Freie Universität Berlin and Humboldt-Universität zu Berlin, Berlin, Germany
[4]European Federation of Allergy and Airways Diseases Patients' Associations (EFA), Brussels, Belgium
[5]Department of Dermatology, CHU Nantes, UMR 1280 PhAN, INRAE, Nantes Université, Nantes, France
[6]Department of Dermatology and Allergy, University Hospital of Bonn, Bonn, Germany
[7]Children's Allergy Service, Evelina London Children's Hospital, Guy's and St. Thomas' NHS Foundation Trust, London, UK
[8]Paediatric Allergy Group, Department of Women and Children's Health, School of Life Course Sciences, King's College London, London, UK
[9]Dermatology Department, University of Brescia, Brescia, Italy
[10]University Hospital Lausanne, Lausanne, Switzerland
[11]Aarhus University Hospital, Aarhus, Denmark
[12]Global Allergy and Airways Diseases Patient Platform GAAPP, Vienna, Austria
[13]Department of Dermatology, University Hospital Basel, Basel, Switzerland
[14]Department of Dermatology of the University of Debrecen, Debrecen, Hungary
[15]Department of Dermatology, Amsterdam UMC (University Medical Centers), Amsterdam, The Netherlands
[16]Department of Dermatology, University of Giessen, Giessen, Germany
[17]Dermatology and Venereology Section, Department of Medicine, University of Verona, Verona, Italy
[18]Faculty of Medicine, National and Kapodistrian University of Athens, Athens, Greece
[19]Department of Dermatology and Allergy Centre, Odense University Hospital, University of Southern Denmark, Odense, Denmark
[20]Department of Dermato-Venerology, Aarhus University Hospital, Aarhus, Denmark
[21]Eczema Outreach Support (UK), Linlithgow, UK
[22]Dermatology Department, Oslo University Hospital, Oslo, Norway
[23]Department of Dermatology Allergology Biederstein, Technical University Munich, Munich, Germany
[24]Dermatology Unit, Spedali Civili Hospital Brescia, Brescia, Italy
[25]Dermatology, Hospital of Sant Pau, Barcelona, Spain
[26]Department of Dermatology, Inselspital, Bern University Hospital, University of Bern, Bern, Switzerland
[27]Pediatric Dermatology Unit, Heim Pál National Children's Institute Budapest, Budapest, Hungary
[28]Department of Dermatology, Venereology and Allergology, Wroclaw Medical University, Wroclaw, Poland
[29]Hospital Infantil Niño Jesús, Madrid, Spain
[30]Hannover Medical School, Hannover, Germany
[31]St John's Institute of Dermatology, King's College London, London, UK
[32]Guy's & St Thomas' NHS Foundation Trust, London, UK
*Correspondence: A. Wollenberg, E-mail: wollenberg@lrz.uni-muenchen.de and C. Flohr, E-mail: carsten.flohr@kcl.ac.uk

## Abstract

The evidence- and consensus-based guideline on atopic eczema was developed in accordance with the EuroGuiDerm Guideline and Consensus Statement Development Manual. Four consensus conferences were held between December 2020 and July 2021. Twenty-nine experts (including clinicians and patient representatives) from 12 European countries participated. This first part of the guideline includes general information on its scope and purpose, the health questions covered, target users and a methods section. It also provides guidance on which patients should be treated with systemic therapies, as well as recommendations and detailed information on each systemic drug. The systemic treatment

options discussed in the guideline comprise conventional immunosuppressive drugs (azathioprine, ciclosporin, glucocorticosteroids, methotrexate and mycophenolate mofetil), biologics (dupilumab, lebrikizumab, nemolizumab, omalizumab and tralokinumab) and janus kinase inhibitors (abrocitinib, baricitinib and upadacitinib). Part two of the guideline will address avoidance of provocation factors, dietary interventions, immunotherapy, complementary medicine, educational interventions, occupational and psychodermatological aspects, patient perspective and considerations for paediatric, adolescent, pregnant and breastfeeding patients.
Received: 17 February 2022; Accepted: 29 April 2022

## Conflicts of interest

This is a short version of the EuroGuiDerm Guideline on AE. For additional chapters, see part 2 (https://doi.org/10.1111/jdv.18429) or for long version, methods report (including COI disclosures) and evidence report see https://www.edf.one/home/Guidelines/Guidelines.html.

## Funding sources

The development of this EuroGuiDerm guideline was funded through the EuroGuiDerm Centre for Guideline Development. The European Dermatology Forum is responsible for fundraising and holds all raised funds in one account. The EuroGuiDerm Team is not involved in fundraising or in the decision-making on which guideline (GL) or consensus statement (CS) development is funded. The decisions on which GL/CS is funded are made by the EuroGuiDerm Board of Directors independently. The EDF or any other body supporting the EuroGuiDerm is never involved in the guideline development and had no say on the content or focus of the guideline.

## Scoping and defining the purpose of the guideline

The aim of this guideline is to provide guidance on the management and treatment of patients with atopic eczema (AE) of all severities and age groups. According to the scoping document, the objectives of the guideline are as follows:

- To generate recommendations and treatment algorithms on topical therapy, phototherapy as well as novel and established systemic treatments for AE, based on the latest evidence.
- Provide guidance in the management of AE patients during pregnancy and AE patients with allergic and other comorbidities.

## Population and health questions covered by the guideline

The target population are patients with AE of all ages. Major health questions (regardless of sex, ethnicity or gender) regarding AE are as follows:

- What is the optimal treatment with regard to patients' needs, taking efficacy, safety/tolerability of different treatment options and comorbidities into consideration?
- How should the selected treatment option best be managed and monitored?

Whenever possible and feasible, the recommendations are evidence-based, taking into account the results of systematic evidence synthesis based on rigorous methods and on the practical experience obtained by the expert group.

## Targeted users of this guideline

This guideline has been prepared for physicians, especially dermatologists, paediatricians, allergists, general practitioners and other specialists taking care of patients with AE. Patients and caregivers may also be able to get reliable information and advice with regard to evidence-based therapeutic modalities.

## Methods section

The EuroGuiDerm guideline on AE was developed in accordance with the EuroGuiDerm Methods Manual v1.3. For the detailed description of the guideline development process and an overview of the evidence referred to, please see the EuroGuiDerm guideline on AE Methods Report and the Evidence Report. Both are available alongside the guideline document on the EDF website: https://www.edf.one/de/home/Guidelines/EDF-EuroGuiDerm.html.

### Nomination of experts, management of conflict of interest

The guideline development group comprised 26 experts from 12 countries nominated by EuroGuiDerm national partner societies or the two guideline co-coordinators (AW and *CF*). All nominations were reviewed and confirmed by the EuroGuiDerm Board of Directors. In addition, three patient representatives participated in the guideline development.

Thirty-eight percent of the experts declared personal-financial interests (for details on classification see EuroGuiDerm Methods Manual v1.3.). *These members were neither eligible to take the lead in a respective working group nor for voting on recommendations pertaining to systemic treatment or on the stepped-care plan.*

### Development of the guideline and the consensus process

The chapters of the guideline and the recommendations had been developed by the group members, who formed a number of working groups. Each chapter and all recommendations were reviewed, discussed and amended where appropriate by the entire group. All texts and recommendations were voted on with a necessary minimal agreement of >50% during the consensus conferences. AN facilitated all four consensus conferences using a structured consensus technique. Both internal and external review were conducted. Dissemination and implementation plans were developed. For more details, see Methods Report.

The wording of the recommendations was standardized (as suggested by the GRADE Working Group[1]).

*Wording of recommendations*

The recommendations are presented throughout this guideline as displayed below: alongside the wording of the recommendations (see Tables 1 and 2) the arrow(s) and colours indicate the direction and the strength of each recommendation (see Table 3). The rate of agreement (consensus strength) is also displayed as the actual percentage and in form of a category-type pie chart. For all systemic drugs, we added the dosages (according to the European Medicines Agency). Additionally, the certainty of evidence was added (see Table 3) where applicable (bold – significant difference; associations are reported in line with Drucker *et al.*[2]).

**Table 1** Terminology used throughout the guideline

| Terminology | Definition |
|---|---|
| Acute flare | Clinically significant worsening of signs and symptoms of AE requiring therapeutic intervention |
| Acute intervention | Treatments that address acute flares and typically lead to treatment response within days (in contrast to 'maintenance treatment') |
| Short term | When used in the context of clinical trials, this refers to treatment up to 16 weeks |
| Reactive | Treatment initiations or adaptations in response to a visible change in disease severity, in particular disease flares (in contrast to 'proactive' treatment) |
| Long term | When used in the context of clinical trials, this refers to treatment longer than 16 weeks |
| Proactive | Intermittent (typically twice a week) application of anti-inflammatory therapy to previously affected skin, in addition to an ongoing emollient treatment of unaffected and affected skin (in contrast to 'reactive' treatment) |
| Maintenance treatment | Regular, usually daily application of topical or systemic therapy for several months (in contrast to 'acute intervention') |

**Table 2** Definitions of treatment goals

| Treatment goal | Definition |
|---|---|
| Remission/ Control | Satisfactory reduction in the signs and symptoms of AE whilst being on a safe long-term anti-inflammatory treatment |
| Complete remission | Disappearance of the signs and symptoms of AE without use of anti-inflammatory treatment |

### Evidence

The living systematic review by Drucker et al.[3] was used as the evidence base based on which we created an evidence-to-decision framework (see Evidence Report). Furthermore, challenges exist with comparing clinical trials in AE due to their differences in trial design, including study comparators, rules for rescue treatment, washout periods for topical and systemic treatments, inclusion criteria and the duration of the screening period.[4] Finally, this analysis does not take into consideration the overall management plan that targets long-term stabilization, flare prevention and avoidance of side-effects beyond 16 weeks.[5] We only summarize the results here. For limitations, please refer to the website.

For each recommendation that is evidence-based, we added the certainty of the evidence when compared with placebo.[2] The assessment of the certainty of evidence leads to four grades (Table 5.1. GRADE Handbook[6]).

## Overview of recommendations

Stepped-care plans for the treatment of AE in adults (Fig. 1) and in children and adolescents (Fig. 2) can be found below. Table 4 shows general recommendations for systemic drugs for adult AE patients, who are candidates for systemic treatment.

## Introduction to systemic treatment

The area of systemic therapy of AE has flourished during the last few years, as many new substances are marketed, licensed, or in the last step of clinical development. The licensing programmes of the various new biologics and small molecules are providing much better levels of evidence than what is available for the longer existing drugs.

By tradition, systemic therapy of AE is deemed necessary if the signs and symptoms of AE cannot be controlled sufficiently with appropriate topical treatments and UV-light therapy. Systemic therapy can also be useful to reduce the total amount of topical corticosteroids (TCS) in patients who need large amounts of potent TCS for large body areas over prolonged periods to control their AE.

**Table 3** Recommendation strengths – wording, symbols and interpretation and definition of certainty of evidence[6]

| Strength | Wording | Symbols | Implications |
|---|---|---|---|
| **Strong** recommendation **for** the use of an intervention | **'We recommend . . .'** | ↑↑ | We believe that all or almost all informed people would make this choice. |
| **Weak** recommendation **for** the use of an intervention | **'We suggest . . .'** | ↑ | We believe that most informed people would make this choice, but a substantial number would not. |
| **No recommendation** with respect to an intervention | **'We cannot make a recommendation with respect to . . .'** | **0** | At the moment, a recommendation in favour of or against an intervention cannot be made due to certain reasons (e.g. no reliable evidence available, conflicting outcomes) |
| **Weak** recommendation **against** the use of an intervention | **'We suggest against . . .'** | ↓ | We believe that most informed people would make a choice against this intervention, but a substantial number would not. |
| **Strong** recommendation **against** the use of an intervention | **'We recommend against . . .'** | ↓↓ | We believe that all or almost all informed people would make a choice against this intervention. |

| |
|---|
| **High** ⊗⊗⊗⊗: we are **very confident** that the true effect lies close to that of the estimate of the effect. |
| **Medium** ⊗⊗⊗○: we are **moderately confident** in the effect estimate: The true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different. |
| **Low** ⊗⊗○○: our **confidence in the effect estimate is limited: The true effect may be substantially different** from the estimate of the effect. |
| **Very low** ⊗○○○: we have **very little confidence** in the effect estimate: The true effect is likely to be substantially different from the estimate of effect. |

Candidates for systemic treatment may be either patients with a high composite score such as a SCORAD above 50 (scale definition), or to patients clinically failing to respond to an appropriately conducted topical therapy (functional definition), or patients unable to participate in normal daily life activities whilst following an adequate treatment regimen (social definition).

Local regulations may necessitate the use of other scores such as physician-based scores (e.g. EASI) in combination with patient-reported outcomes (e.g. DLQI). Many other scores exist summarized and assessed by the HOME initiative that may also serve as a base to classify disease severity.[7]

It must be highlighted that the indication to systemic treatment is a patient individual decision, and that a signs-only score, such as EASI, is not an adequate tool to discriminate for providing or declining systemic therapy to an individual patient.

100% agreement.

Before starting systemic treatment, it is important to rule out relevant differential diagnoses such as cutaneous T-cell lymphoma and in selected cases primary immunodeficiency syndromes,[8] and to ascertain that potential trigger factors such as allergic contact dermatitis, and behavioural as well as educational reasons for poor responses.

Until recently, rather broad acting immunosuppressants, such as systemic corticosteroids (SCS), ciclosporin (CyA), azathioprine (AZA), mycophenolate mofetil (MMF), enteric-coated mycophenolate sodium (EC-MPS) and methotrexate (MTX) were the only systemic treatment options available for difficult-to-treat AE. Most were not licensed for this indication (see Table 4). These drugs may roughly be divided in two groups: SCS and CyA have a rapid onset of action and can be used to treat flares of AE or to bridge the time until onset of action of slow acting systemic immunosuppressants such as MTX, AZA and MMF/EC-MPS. The kinetics of the novel januskinase inhibitors baricitinib (Bari), abrocitinib (Abro) and upadacitinib (Upa) place these agents in the fast-acting group, whereas the Th2-blocking agents dupilumab (Dupi), tralokinumab and lebrikizumab, as well as the IL31-receptor blocking agent nemolizumab (Nemo) need some weeks to reach full efficacy.

Special considerations should be taken during the ongoing COVID-19 pandemic, as indicated by recommendations from the European Taskforce for Atopic Dermatitis.[9,10] Particular caution is required where patients receive combined systemic therapy.

The following recommendations for systemic drugs are based on expert opinions, the living systematic review by Drucker *et al.*,[3] other published literature and medical considerations, and may differ from the legal licensing status and access routes, which are not uniform in European countries.

## Conventional systemic drugs

### Azathioprine (AZA)

| | | |
|---|---|---|
| We **suggest** using azathioprine in AE patients who are candidates for systemic treatment. | ↑ | >75%<br>  <br>(15/16)<br>Evidence and consensus based, see Evidence Report |
| azathioprine: off licence; commonly used dosage<br>adults: 1-3 mg/kg per day<br>children: 1-3 mg/kg per day | | |
| Certainty of evidence[2,3]:<br>Short term (8-16 weeks) vs placebo (NMA main analysis)<br>⊗⊗○○ LOW for mean difference / standardized mean difference **change in signs**, DLQI, Itch VAS; OR undesirable effects<br>Short term (8-16 weeks) vs placebo (NMA currently used drugs)<br>⊗⊗○○LOW for standardized mean difference **change in signs**, QoL<br>⊗○○○ VERY LOW for standardized mean difference change in itch<br>*For azathioprine versus other drugs, see Evidence Report* | | |

*Mechanisms of action and efficacy* AZA is a prodrug which is rapidly converted *in vivo* to the antimetabolite 6-mercaptopurine (6-MP), following cleavage of its imidazole side chain. It is believed to exert its primary immunosuppressant effect *via* metabolites of 6-MP, thioguanine nucleotides, which are subsequently incorporated into DNA, inhibiting its synthesis.[11]

The efficacy of AZA is comparable to that of MTX but lower compared to dupilumab and ciclosporin in clearing clinical signs of AE.[2]

Randomized clinical trials report a significant superiority of AZA *vs* placebo, with a decrease in clinical scores such as Six Area, Six Sign Atopic Dermatitis and Scoring Atopic Dermatitis (SASSAD) by 26% to 39% after 12 weeks.[12] However, results from retrospective studies are less favourable with a percentage of AZA treatment failure varying from 30% to 57% due to adverse effects or lack of effectiveness.[13–15] An observational follow-up study of 36 adult patients with severe AE treated with MTX or AZA over a 24-week period demonstrated less improvement in subjects with filaggrin mutations (36%, 13/36) compared with those without filaggrin mutations.[12]

Long-term studies on adult patients treated with either AZA or MTX showed a relative reduction in SCORAD of 53% ($P < 0.01$) and 63% ($P < 0.01$) after 2 years, and 54% and 53% after 5 years, respectively.[12,16] Patients with a Filaggrin mutation seemed to have slower but prolonged effects of therapy compared with patients without a mutation.[12,16]

*Dosage: acute flare, short term, long term*

- off licence
- commonly used dosage
  - adults and children: 1–3 mg/kg bodyweight per day
  - If no improvement of AE occurs within 3 months, withdrawing azathioprine should be considered.

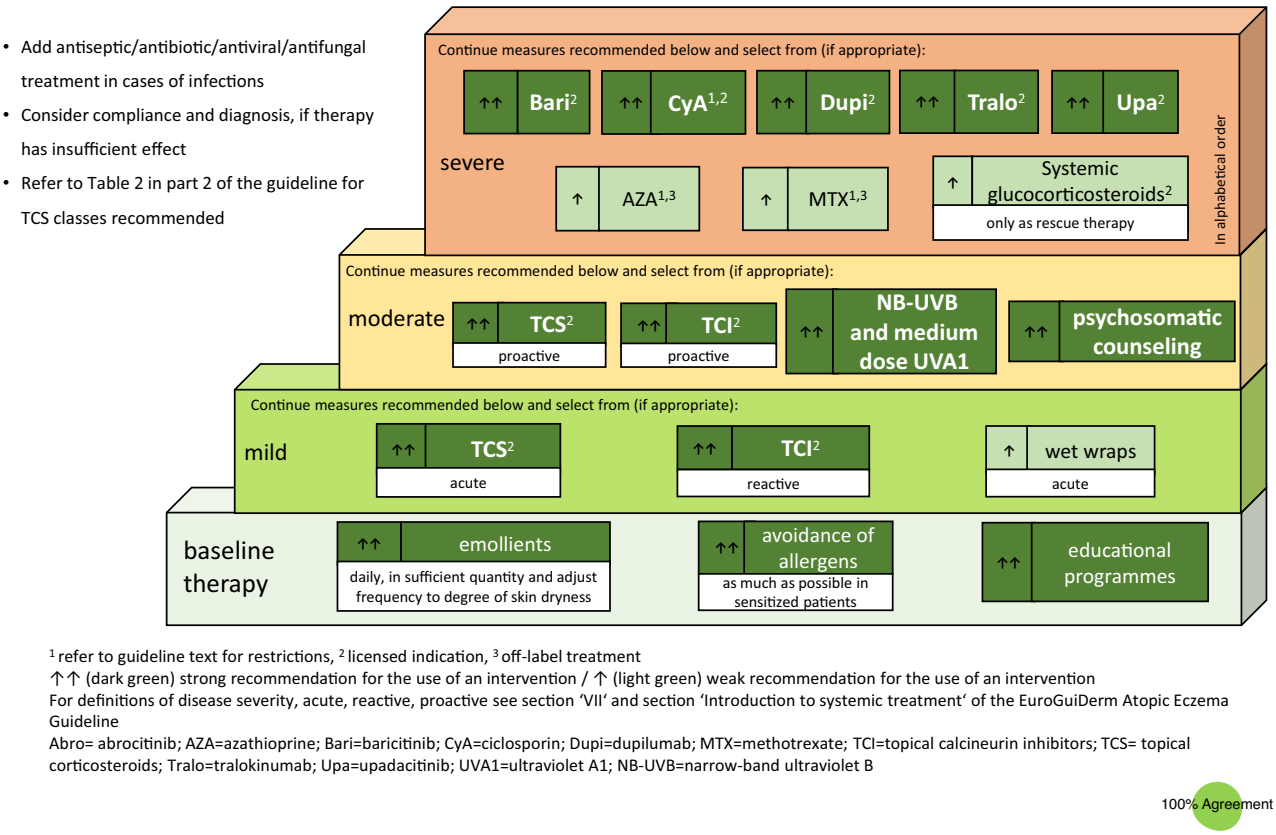
- We recommend combining AZA, as any systemic treatment with emollients and, whenever needed, topical anti-inflammatory treatment in AE patients.
- If timely thiopurine S-methyltransferase (TPMT) activity measurement is available, the following dosing of AZA has been suggested:
  - very low activity (<2.5 per mL red blood cells [RBC]), treatment should not be started
  - intermediate activity (2.5–7.5 nmol/h/mL RBC): 0.5 mg/kg bodyweight per day for the first 4 weeks and then increase to 1.0 mg/kg bodyweight per day
  - normal activity (>7.5 nmol/h/mL RBC): 2.0 mg/kg bodyweight per day for the first 4 weeks and then increase to 2.5–3.0 mg/kg bodyweight per day

Low azathioprine doses (0.5–1.0 mg/kg bodyweight per day) for the first 4 weeks were shown to reduce gastrointestinal side-effects.[17]

If TPMT results are not available prior to starting AZA therapy, then half the standard treatment should be given for about 4–6 weeks under close monitoring of full blood count and liver profile, prior to going up the full treatment dose.

*Safety* In the short and medium term, the most commonly reported serious dose-dependent effects are hepatotoxicity and myelotoxicity, together with gastrointestinal disturbances. Furthermore, idiosyncratic hypersensitivity reactions (e.g. fever, rigours, myalgia, arthralgia and occasionally pancreatitis) may occur.[18]

Concerns have been raised about the potential carcinogenecity induced by long-term treatment with azathioprine (predominantly squamous cell skin cancer and non-Hodgkin's




[1] refer to guideline text for restrictions, [2] licensed indication, [3] off-label treatment
↑↑ (dark green) strong recommendation for the use of an intervention / ↑ (light green) weak recommendation for the use of an intervention
For definitions of disease severity, acute, reactive, proactive see section 'VII' and section 'Introduction to systemic treatment' of the EuroGuiDerm Atopic Eczema Guideline
Abro= abrocitinib; AZA=azathioprine; Bari=baricitinib; CyA=ciclosporin; Dupi=dupilumab; MTX=methotrexate; TCI=topical calcineurin inhibitors; TCS= topical corticosteroids; Tralo=tralokinumab; Upa=upadacitinib; UVA1=ultraviolet A1; NB-UVB=narrow-band ultraviolet B

100% Agreement

| Symbols | Implications (adapted from GRADE [1]) |
|---|---|
| ↑↑ | We believe that all or almost all informed people would make that choice. |
| ↑ | We believe that most informed people would make that choice, but a substantial number would not. |
| 0 | We cannot make a recommendation. |
| ↓ | We believe that most informed people would make a choice against that intervention, but a substantial number would not. |
| ↓↓ | We believe that all or almost all informed people would make a choice against that choice. |
| | No recommendation. |

**Figure 1** Stepped-care plan for adults with AE.

lymphoma), especially if AZA is combined with other immunosuppressant regimens.[19]

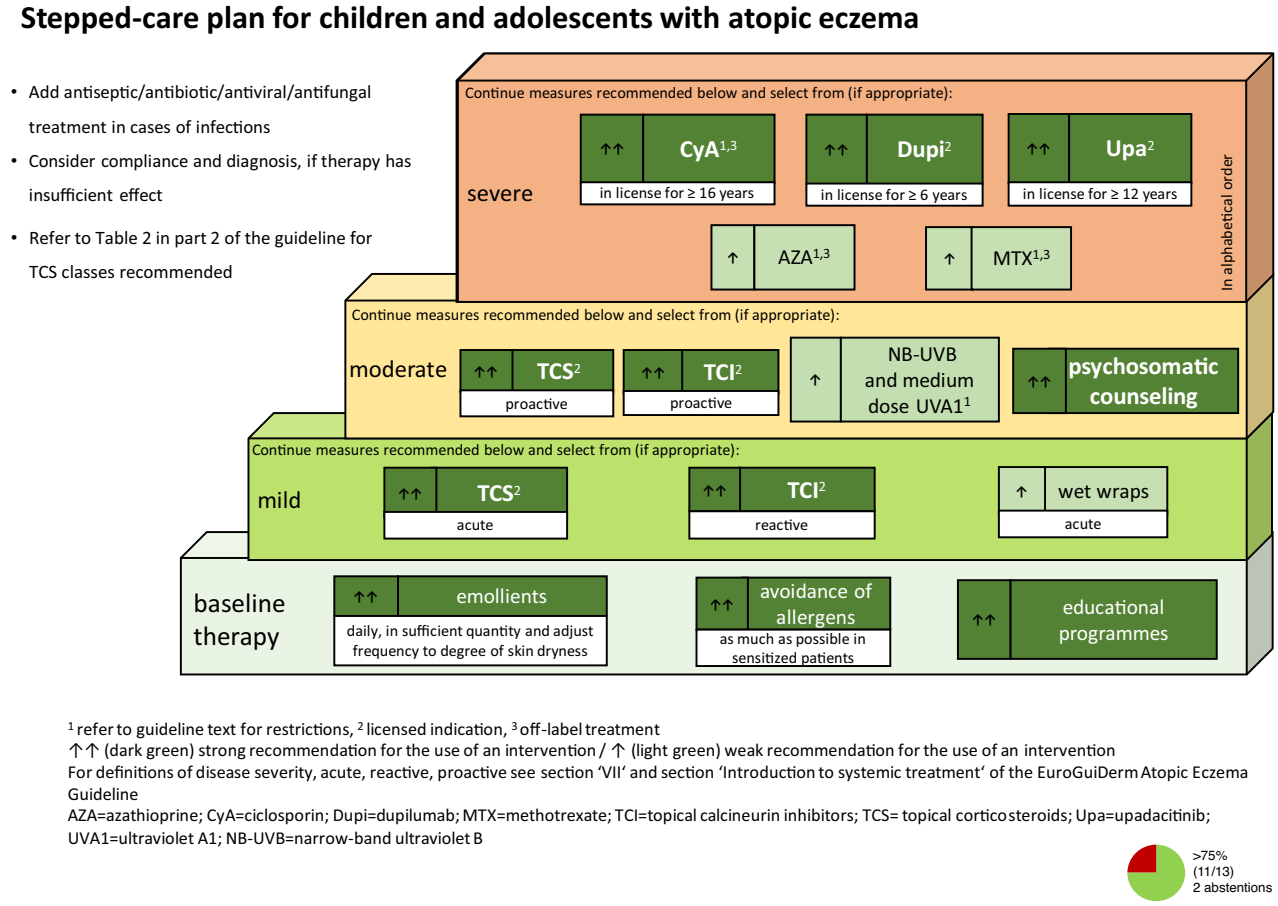
*Monitoring*

- Baseline: Complete blood count, renal and liver profile.
- TPMT activity if available.
- Screening for chronic infections (e.g. hepatitis B/C, HIV) before therapy should be considered.
- Follow-up: Complete blood count, renal and liver profile twice monthly for 2 months, monthly for 4 months, then every other month and with dose increases.
- Pregnancy testing before and during AZA therapy where indicated.

*Combination with other treatments* Concomitantly to AZA, topical therapy with corticosteroids and or calcineurin inhibitors can be applied.

Because of a potentially increased risk to develop skin cancer, AZA should not be combined with UV light (UVA, UVB and PUVA).

*Special considerations* There is a theoretical risk of teratogenesis with AZA. This is based on studies in animals in which very high doses of AZA were used. However, in practice, AZA has been used for over 30 years in sexually active men and women and no definite association between the drug and the incidence of fetal abnormalities has been observed. There also seems to be no effect on fertility.




| Symbols | Implications (adapted from GRADE [1]) |
|---|---|
| ↑↑ | We believe that all or almost all informed people would make that choice. |
| ↑ | We believe that most informed people would make that choice, but a substantial number would not. |
| 0 | We cannot make a recommendation. |
| ↓ | We believe that most informed people would make a choice against that intervention, but a substantial number would not. |
| ↓↓ | We believe that all or almost all informed people would make a choice against that choice. |
| | No recommendation. |

**Figure 2** Stepped-care plan for children and adolescents with AE.

According to a recent position paper by ETFAD,[20] AZA use during pregnancy should be avoided as there are better options, but may be used off-label in the absence of other alternatives as continuation of treatment in women already receiving this treatment at the time of conception. According to experts' opinion of the ETFAD, the dosage of azathioprine should be reduced by 50% if it is continued during pregnancy. Initiation of azathioprine after conception is not recommend.

The use of AZA during lactation is debated. The WHO has recommended that the potential side-effects of AZA outweigh the effects and benefits of the treatment,[21] and studies suggest that AZA intake during breastfeeding could increase the long-term risk of immunosuppression and carcinogenesis in the child.[22]

AZA is not licensed for the treatment of AE in children but it has proven beneficial in several retrospective paediatric case series. The main disadvantage of AZA is that it reaches its maximum treatment effect only after 3–4 months.[23]

**Table 4** General recommendations for systemic drugs in adult AE patients who are candidates for systemic treatment (for details see corresponding chapter)

| | Conventional systemic treatments | | | Biologics | | JAK-inhibitors | | Rescue therapy |
|---|---|---|---|---|---|---|---|---|
| | Ciclosporin | Methotrexate | Azathioprine | Dupilumab | Tralokinumab | Baricitinib | Upadacitinib | Systemic corticosteroids |
| **Recommendation** | ↑↑ | ↑ | ↑ | ↑↑ | ↑↑ | ↑↑ | ↑↑ | ↑ |
| Dose for adults[1] | licensed ≥ 16 years standard dosage adults: 2.5-5 mg/ kg per day in two single doses | off-label; commonly used dosage adults: initial dose: 5-15 mg/ per week; maximum dose: 25 mg/ week | off-label; commonly used dosage adults: 1-3 mg/kg per day | licensed ≥ 6 years; adults: initially 600 mg s.c. day 1 followed by 300 mg Q2W | licensed for adults; initially 600 mg s.c. day 1 followed by 300 mg Q2W; consider Q4W dosing at week 16 in those achieving clear or almost clear skin | licensed for adults; dosage adults: 4 mg per day, reduction to 2 mg per day possible, depending on treatment response | licensed ≥ 12 years; dosage adults: 15 or 30 mg per day based on individual patient presentation; age ≥ 65: 15 mg per day; the lowest effective dose for maintenance should be considered | general licence for adults and children; dosage maximum: 1 mg/kg per day |
| Time to response (weeks)[2] | 1-2 | 8-12 | 8-12 | 4-6 | 4-8 | 1-2 | 1-2 | 1-2 |
| Time to relapse (weeks, based on expert experience)[2] | <2 | >12 | >12 | >8 | >8 | <2 | <2 | <2 |
| Monitoring | complete blood count, renal and liver profile, blood pressure, | complete blood count, renal and liver profile, PIIINP if available, screen for chronic infections | complete blood count, renal and liver profile, TPMT activity if available, screen for chronic infections | not required | not required | complete blood count, lipid profile, liver profile | complete blood count, lipid profile, liver profile | not required for short-term treatment, consider blood glucose and testing for adrenal gland suppression with high doses/ longer-term treatment |
| Selection of most relevant adverse events | serum creatinine↑, blood pressure ↑ | nausea, fatigue, liver enzymes ↑, myelotoxicity | gastrointestinal disturbances, idiosyncratic hypersensitivity reactions, hepatotoxicity, myelotoxicity | Conjunctivitis, upper respiratory tract infections, arthralgia | upper respiratory tract infections; conjunctitivitis | upper respiratory tract infections, increase in LDL cholesterol; thrombocytosis, nausea and abdominal pain herpes virus infections, acne | upper respiratory tract infections, acne; headache, anaemia and neutropenia, CK elevation, increase in LDL cholesterol, nausea and abdominal pain herpes virus infections | skin atrophy, weight gain, sleep disturbance, mood changes, hyperglycaemia or new onset diabetes, peptic ulcers/ gastritis, osteoporosis |

| Symbols | Implications (adapted from GRADE [1]) |
|---|---|
| ↑↑ | We believe that all or almost all informed people would make that choice. |
| ↑ | We believe that most informed people would make that choice, but a substantial number would not. |
| 0 | We cannot make a recommendation. |
| ↓ | We believe that most informed people would make a choice against that intervention, but a substantial number would not. |
| ↓↓ | We believe that all or almost all informed people would make a choice against that choice. |
| | No recommendation. |

[1]SmPC, [2]expert experience, ↑ rise, AE- atopic eczema; GL – guideline, LDL – low density lipoprotein, PIIINP - Procollagen III N-Terminal Propeptide, TPMT – Thiopurine-S-Methyltransferase

### Ciclosporin

| | | |
|---|---|---|
| We **recommend** using ciclosporin to achieve disease control in AE patients who are candidates for systemic treatment. | ↑↑ | >75%<br>  <br>(19/20)[1]<br>Evidence and consensus based, see Evidence Report |
| Ciclosporin: in licence for ≥ 16 years<br>standard dosage adults: 2.5-5 mg/kg per day in two single doses<br>commonly used dosage children: 2.5-5 mg/kg per day in two single doses | | |
| Certainty of evidence[2,3]:<br>Short term (8-16 weeks) vs placebo (NMA main analysis)<br>⊗⊗○○ LOW for mean difference / standardized mean difference **change in signs**, Itch VAS<br>Short term (8-16 weeks) vs placebo (NMA commonly used drugs)<br>⊗⊗○○LOW for standardized mean difference **change in signs**, **QoL**<br>⊗○○○ VERY LOW for standardized mean difference change in itch<br>*For ciclosporin versus other drugs, see Evidence Report* | | |

[1]1 abstention

| | | |
|---|---|---|
| We **recommend** to start with higher ciclosporin dosages in order to achieve a more rapid response in AE patients who are candidates for systemic treatment. | ↑↑ | >75%<br>  <br>(16/17)<br>Expert Consensus |
| We **recommend** close follow-up for potential blood pressure elevation and signs of renal impairment in AE patients on ciclosporin. | ↑↑ | >75%<br>  <br>(15/17)[1]<br>Expert Consensus |

[1]2 abstentions

*Mechanisms of action and efficacy* Ciclosporin inhibits T-cell activation and proliferation by blocking nuclear factor of activated T-cell (NFAT)-dependent cytokine production.

Ciclosporin has been approved for treatment of AE in adults in many European countries and is considered a first-line option for patients with severe disease if other, novel therapies are not available or indicated. Ciclosporin is very effective for AE in both children and adults with a better tolerability in children.[24,25] Although similarly effective in the above NMA meta-analysis evaluating trials up to 16 weeks, real-life data reveal a longer drug survival of dupilumab compared with CyA after 16 months.[2,26] In head-to-head trials ciclosporin was superior to MTX, prednisolone, IVIG, UVA and UVB, and similarly efficacious as EC-MPS.[12,27] In the short-term treatment of AE, higher ciclosporin dosages (5 mg/kg per day) lead to a more rapid response and are more efficacious than lower dosages (2.5–3 mg/kg per day).[12] Long-term use of ciclosporin up to 1 year can be recommended based on several trials; however, their evidence is limited because of the open-label design and high drop-out rates.[12]

*Dosage: acute flare, short term, long term*

- in licence for ≥16 years
- standard dosage adults: 2.5–5 mg/kg per day in two single doses
  - Acute flare, short-term: 4–5 mg/kg body weight per day
  - Long-term: 2.5–3 mg/kg body weight per day
- commonly used dosage children: 2.5–5 mg/kg per day in two single doses
  - We recommend combining CyA, as is the case with any systemic treatment, with emollients and, whenever needed, topical anti-inflammatory treatment in AE patients.

*Safety* Ciclosporin has a narrow therapeutic index and requires a close follow-up for blood pressure and signs of renal impairment. Of note, clinically relevant increase of creatinine seems less common than expected.[15,25]

*Monitoring*

- Blood pressure, full blood count, renal and liver profile (including GGT) according to national guidelines (e.g. at baseline, 4 weeks and then 3-monthly).

- Screening for hepatitis B/C and HIV before therapy should be considered.

*Combination with other treatments* Concomitantly to ciclosporin, topical therapy with corticosteroids and/or calcineurin inhibitors can be applied.

Because of a potentially increased risk to develop skin cancer, ciclosporin should not be combined with UV light (UVA, UVB and PUVA).

*Special considerations* Ciclosporin has been shown to be effective, safe and well tolerated in children and adolescents.[24,28]

Ciclosporin can be considered in pregnant woman with severe AE. So far, no increased risk of congenital malformations or fetal death compared to the background populations have been reported. An increased risk of low birthweight cannot be ruled out.[20] Where systemic therapy is likely to be needed throughout pregnancy, ciclosporin is first-choice therapy.[20]

- Short-term and long-term: not recommended.
- We recommend combining systemic glucocorticosteroids, as is the case with any systemic treatment, with emollients and, whenever needed, topical anti-inflammatory treatment in AE patients.

*Safety* Systemic glucocorticosteroids have a wide therapeutic index. Toxicity is related to the mean dose, cumulative dose and duration of use. At high doses and with long-term use (typically >0.5 mg/kg/day) important side-effects include skin atrophy, weight gain, sleep disturbance, mood changes, hyperglycaemia or new onset diabetes, peptic ulcers/gastritis, osteoporosis, and increased susceptibility to infections.[31] In particular with long-term use, patients can also develop adrenal suppression and together with a high risk of rebound flares when tapering the treatment dose, cessation can be challenging. Systemic glucocorticosteroids must therefore be avoided as a long-term treatment in adults and children. Even a fairly high dose can simply be stopped without tapering when used for no longer than 3 weeks.[32]

**Systemic glucocorticosteroids**

| | | |
|---|---|---|
| We **suggest** using systemic glucocorticosteroids *only* as rescue therapy for acute flares in AE patients. | ↑ | >75%<br>  <br>(13/17)[1]<br>Expert Consensus |
| Systemic glucocorticosteroids: general unspecific licence for steroid responsive skin disease adults and children; starting dose 0.5mg/kg per day; dosage maximum: 1 mg/kg per day | | |
| [1]1 abstention | | |
| We **recommend against** the long-term use of systemic glucocorticosteroids in AE patients. | ↓↓ | 100% agreement<br>  <br>(18/18)<br>Expert Consensus |

*Mechanisms of action and efficacy* Glucocorticoids are a class of steroid hormones that bind to the glucocorticoid receptor. The activated glucocorticoid receptor complex upregulates the expression of anti-inflammatory proteins and suppresses the expression of pro-inflammatory proteins, leading to broad anti-inflammatory property.[29]

There are only few studies in adult and paediatric AE patients, despite the regular use of systemic glucocorticosteroids in clinical practice. In studies conducted in children and adults, systemic glucocorticosteroids do not induce long-term remission and swift rebound is common. Systemic glucocorticosteroids have significantly inferior efficacy than ciclosporin.[24,30]

*Dosage: acute flare, short term, long term*

- Acute flare: Starting dose is usually 0.5 mg/kg bodyweight per day. Treatment should be discountinued or tapered as soon as possible.

*Monitoring* For acute rescue therapy, there is no standard set of laboratory parameters. Monitoring should there be based on individual patient needs.

*Combination with other treatments* None of the other treatments in AE are contraindicated when using systemic glucocorticosteroids.

*Special considerations* Treatment of acute flares of AE with oral glucocorticosteroids is moderately effective.[24,30]

Systemic glucocorticosteroids have an unfavourable risk/benefit ratio for the long-term treatment of adult and paediatric AE.

### Methotrexate

| | | |
|---|---|---|
| We **suggest** using methotrexate in AE patients who are candidates for systemic treatment. | ↑ | 100% agreement<br>(17/17)<br>Evidence and consensus based, see Evidence Report |
| Methotrexate: off licence; commonly used dosage<br>adults: initial dose: 5-15 mg per week; maximum dose: 25 mg per week<br>children: 0.3–0.4 mg/kg per week; maxium dose: 25mg per week | | |
| Certainty of evidence[2,3]:<br>Short term (8-16 weeks) vs placebo (NMA main analysis)<br>⊗⊗○○ LOW for standardized mean difference **change in signs**<br>Short term (8-16 weeks) vs placebo (NMA currently used drugs)<br>⊗⊗○○ LOW for standardized mean difference **change in signs**, QoI<br>⊗○○○ VERY LOW for standardized mean difference change in itch<br>*For methotrexate versus other drugs, see Evidence Report* | | |

*Mechanisms of action and efficacy* MTX is a folic acid antagonist that impedes cell division, DNA/RNA synthesis and repair and protein synthesis, altogether suppressing the activity of the immune system. Although its exact action in AE is not fully understood, inhibition of the janus kinase (JAK)/STAT pathway has been proposed.[33]

MTX has been used in the treatment of moderate and severe AE for years, but only a limited number of non-randomized controlled trials have examined the effect and treatment regimens. Consequently, recommendations have been primarily based on case series and expert consensus,[34–36] one controlled study comparing MTX with AZA in adults[37] and an open-label randomized multi-centre study in children.[38] Altogether these studies support that MTX can be considered a moderately effective, relatively safe and well-tolerated treatment for severe AE both in children and adults – findings also in keeping with recent retrospective studies.[39–41] The efficacy of MTX was comparable to AZA and lower than dupilumab and ciclosporin in clearing clinical signs of AE at week 16. However, there are no long-term follow-up head-to-head studies available for further comparison.[2] The onset of action takes several weeks and peak efficacy is seen after months, but speed of treatment effect onset depends on the dosing regimen.[34–36] One adult study suggests that patients who do not benefit from a moderate weekly dose (10–15 mg) of MTX over a 3-month treatment period will probably not benefit from an increased dosage. However, slow gradual up-dosing of MTX might underestimate the therapeutic potential of the drug in AE. In children 0.4 mg/kg/week is recommended, which is significantly higher than dosing in adults.[34] 25 mg per week is the widely used maximum treatment dose for adult and paediatric AE patients.

*Dosage: acute flare, short term, long term*

- off licence
- commonly used dosage
  - adults: initial dose: 5–15 mg/ per week; maximum dose: 25 mg/week
  - children: 0.3–0.4 mg/kg per week Acute flare and short-term: no relevant dosing
- Oral and subcutaneous delivery are considered equivalent options of administration. For patients in whom MTX 15 to 25 mg orally once weekly is ineffective or poorly tolerated, a trial of subcutaneous MTX administration is an alternative.
- We recommend combining MTX, as is the case with any systemic treatment, with emollients and, whenever needed, topical anti-inflammatory treatment in AE patients.
- Concomitant use of folic acid should be considered to reduce gastrointestinal and other side-effects related to the folic acid antagonistic effect of the drug.[42]

*Safety* As MTX is a commonly used drug in dermatology, the safety profile is well recognized, with nausea, fatigue and raised liver enzymes as main side-effects, while pancytopenia and idiopathic pulmonary fibrosis are of key concern but only very rarely seen.

MTX is generally well tolerated and is considered safe for long-term treatment, based on experience and multiple studies including both adults and children suffering from psoriasis and rheumatologic disease.[43,44]

*Monitoring* Complete blood count, renal and liver profile before and every 4 weeks for the first 3 months or, after increasing the dose, then every 8–12 weeks.

Type III procollagen peptide (PIIINP) should be monitored according to national and local guidelines when available. Fibroscan or liver biopsy when necessary in selected cases.

Screening for chronic infections (e.g. hepatitis B-/C, HIV, tuberculosis) before therapy should be considered.

Any noteworthy impact on liver or bone marrow function should give cause to dose reduction or transient or total discontinuation of treatment.

*Combination with other treatments* Combination with TCS, TCI or narrow band UV phototherapy are established treatment combinations and considered safe. Concomitant us of ciclosporin is a relative contraindication. There is experience from rheumatoid arthritis for combining with the JAK inhibitor baricitinib.

*Special considerations* MTX may be used for treatment of AE in both adults and children.

Subcutaneous administration increases bioavailability and tolerability, as well as adherence, compared to oral treatment.

MTX affects fertility and is teratogenic. Fertile women should use effective contraception. The same is recommended for men treated with MTX living with a woman of childbearing potential.

### Mycophenolate mofetil

| | | |
|---|---|---|
| We **cannot make a recommendation** with respect to mycophenolate mofetil/ mycophenolic acid for the treatment of AE. | 0 | >75%<br>(16/17)[1]<br>Expert Consensus |
| Mycophenolate mofetil: off licence; commonly used dosage<br>adults: 1-3 g per day<br>children: 30-50 mg/kg per day | | |

[1]1 abstention

*Mechanisms of action and efficacy* Mycophenolate mofetil is a prodrug of mycophenolic acid (MPA), an inhibitor of inosine-5′-monophosphate dehydrogenase. MPA depletes guanosine nucleotides preferentially in T and B lymphocytes and inhibits their proliferation. MPA also inhibits the glycosylation and expression of adhesion molecules, and the recruitment of lymphocytes and monocytes into sites of inflammation.[45]

A recent systematic review and meta-analysis[46] including 18 studies with a total of 140 adult and paediatric patients evaluated the efficacy of off-label use of MMF in patients with AE refractory or not tolerating other first-line systemic agents. There was a significant reduction in pre- to post-SCORAD scores by 18 points ($P = 0.0002$) with 77.6% of patients reporting partial or full remission. Relapses occurred in 8.2% of cases. The average time for initial effects was 6.8 ± 7 weeks.

*Dosage: acute flare, short term, long term*

- off licence
- commonly used dosage
  - adults: 1–3 g per day
  - children: 30–50 mg/kg bodyweight per day
  - typically given in two divided doses
- We recommend combining MMF, as is the case with any systemic treatment, with emollients and, whenever needed, topical anti-inflammatory treatment in AE patients.

*Safety* The most common side-effects include headaches and gastrointestinal symptoms, followed by infections, especially during long-term therapy.

Haematological adverse effects include anaemia, leukopenia, neutropenia and thrombocytopenia, albeit rarely.

*Monitoring*

- Complete blood count, renal and liver profile before therapy, then every 2 weeks for 1 month; monthly for 3 months; every 2–3 months thereafter.
- Screening for chronic infections (e.g. hepatitis B/C, HIV) according to national and local guidelines.
- Pregnancy testing before and during MMF therapy if indicated.

*Combination with other treatments* Concomitantly to MMF, topical therapy with corticosteroids and/or calcineurin inhibitors can be applied.

*Special considerations* In case series, the efficacy and safety of MMF in children have been investigated. The drug has shown a positive treatment response with minimal adverse effects and appears to be better tolerated than AZA.[47]

## Biologics

### Dupilumab

| | | |
|---|---|---|
| We **recommend** dupilumab in AE patients who are candidates for systemic treatment | ↑↑ | >75%<br>  <br>(16/17)[1]<br>Evidence and consensus based, see Evidence Report |
| Dupilumab: in licence for ≥ 6 years;<br>age 6-11: from 15kg <60kg, initially 300 mg s.c. day 1 and 15 followed by 300 mg Q4W, when ≥60 kg, initially 600 mg s.c. day 1 followed by 300 mg Q2W<br>age 12-17: <60 kg: initially 400 mg s.c. day 1 followed by 200 mg Q2W, when ≥60 kg: initially 600 mg s.c. day 1 followed by 300 mg Q2W<br>adults: initially 600 mg s.c. day 1 followed by 300 mg Q2W | | |
| Certainty of evidence[2,3]:<br>Short term (8-16 weeks) vs. placebo (NMA main analysis)<br>⊗⊗⊗⊗ HIGH for mean difference/ standardized mean difference **EASI, change in signs, POEM, DLQI**<br>⊗⊗⊗○ MODERATE for undesirable effects<br>Short term (8-16 weeks) vs. placebo (NMA currently used drugs)<br>⊗⊗⊗⊗ HIGH for standardized mean difference **change in signs**, **QoL**, **change in itch**<br>Long term (52 weeks) vs. placebo<br>RoB low for change in **EASI**, POEM, DLQI, undesirable effects<br>*For dupilumab versus other drugs, see Evidence Report* | | |

[1]1 abstention

*Mechanisms of action and efficacy* Dupilumab is the first marketed fully human IgG4 monoclonal antibody (mAb) in the treatment of AE and has been available for treatment of adults for more than 2 years in many countries. Recently, it has also been approved for adolescents and children from 6 years of age in some countries. Dupilumab binds to the α-subunit of the IL-4 receptor, which is part of both the IL-4 and the IL-13 receptor complex. The safety and efficacy of dupilumab was primarily established in placebo-controlled studies in moderate-to-severe AE.[48] Dupilumab showed significant clinical effects across 3 distinct severity assessment tools: Eczema Area and Severity Index (EASI), Investigator's Global Assessment (IGA) and SCORing Atopic Dermatitis (SCORAD). Moreover, dupilumab treatment significantly reduced pruritus. Dupilumab has shown efficacy in both intrinsic and extrinsic AE.[49] Dupilumab is also registered for treatment of moderate-to-severe asthma, eosinophilic esophagitis, and chronic rhinosinusitis with nasal polyps, thereby covering several type 2 inflammatory diseases.

*Dosage: acute flare, short term, long term* The approved dosing of dupilumab in adults consists of a 600 mg subcutaneous loading dose followed by maintenance doses of 300 mg every other week (Q2W). For children, the following dosing regimens are used: licensed for ≥6 years; age 6–11: from 15 kg <60 kg, initially 300 mg s.c. day 1 &15 followed by 300 mg Q4W, when ≥60 kg, initially 600 mg s.c. day 1 followed by 300 mg Q2W age 12–17: <60 kg: initially 400 mg s.c. day 1 followed by 200 mg Q2W, when ≥60 kg: initially 600 mg s.c. day 1 followed by 300 mg Q2W.

Dupilumab has been used in an open-label study for up to 3 years in adults with moderate-to-severe AE, but some former trial patients have continued open label on the medication much longer. Safety data were consistent with previously reported trials and the known dupilumab safety profile.[50]

*Safety* Dupilumab treatment is in generally well tolerated, and routine blood tests are not recommended, but a substantial number of patients develop conjunctivitis (over 30% in some 'real world' settings), of which most are mild-to-moderate.[51,52] Topical treatment with anti-inflammatory eyedrops is often sufficient, without need to discontinue treatment.[53]

*Monitoring* No biochemicals or instrumental exams are reported to be required for the monitoring of the therapy.

*Combination with other treatments* An additional phase III trial, evaluated dupilumab treatment and a concomitant topical corticosteroid (TCS) compared with placebo and a concomitant TCS over 52 weeks.[54] The co-primary end points included IGA score of 0 or 1 and EASI-75, were assessed at week 16: more patients who received dupilumab plus topical corticosteroids achieved the co-primary endpoints of IGA 0/1 and EASI 75. Results at 52 weeks were similar. Approximately 15% more subjects achieved a 75% reduction in the EASI score at week 16 in this trial compared with previous phase III studies where dupilumab was administered as monotherapy.[48]

Combination therapy with TCS, TCI, and UV light treatment is well established.

*Special considerations* AE patients with type 2 comorbidities such as asthma, allergic rhinoconjunctivitis with nasal polyps, or eosinophil esophagitis may also have benificial effects of dupilumab treatment on these diseases.

### Lebrikizumab

Lebrikizumab is currenty not licensed for any indication worldwide. Therefore, we do not give a specific recommendation for its use in AE.

*Mechanisms of action and efficacy* Lebrikizumab is a high-affinity humanized immunoglobulin G4 mAb that binds specifically to soluble interleukin 13 and selectively prevents formation of the IL-13Rα1/IL-4Rα heterodimer receptor signalling complex. In a randomized, placebo-controlled, double-blind, phase IIb study, adults with moderate-to-severe AE patients were randomized to placebo every 2 weeks or to subcutaneous injections of lebrikizumab at the following doses: 125 mg every 4 weeks (250 mg loading dose [LD]), 250 mg every 4 weeks (500-mg LD), or 250 mg every 2 weeks (500 mg LD at baseline and week 2).[55]

Compared with placebo, lebrikizumab groups showed dose-dependent, statistically significant improvement in EASI scores, pruritus NRS score, POEM and IGA.[55]

*Dosage: Acute flare, short term, long term* Although all the different dosages of lebrikizumab proved to be effective, optimal dosing regimens have yet to be determined. Phase 3 studies are currently underway testing lebrikizumab 250 mg Q2W the induction phase, and both 250 mg Q2W and Q4W in the maintenance phase.

*Safety* Treatment-emergent adverse events were reported in 24 of 52 placebo patients (46.2%) and in lebrikizumab patients as follows: 42 of 73 (57.5%) for 125 mg every 4 weeks, 39 of 80 (48.8%) for 250 mg every 4 weeks, and 46 of 75 (61.3%) for 250 mg every 2 weeks; most were mild-to-moderate and did not lead to discontinuation. In all lebrikizumab groups, herpes virus infections and conjunctivitis were reported at low rates.

Simpson *et al.* reported injection site reactions (1.3%), herpes infection (3.8%), eosinophilia (3.2%) with no associated clinical symptoms, and conjunctivitis (9.6%) as adverse events in patients treated with lebrikizumab.[56]

Notably, lebrikizumab appears to have lower rates of ocular complications than dupilumab.

*Monitoring* No biochemical or instrumental examinations are reported to be required for the monitoring of the therapy.

*Combination with other treatments* The use of topical corticosteroids during the flares of AE could be useful in combination with lebrikizumab, and is under investigation in the phase 3 program.

### Nemolizumab

Nemolizumab is currenty not licensed for any indication worldwide. Therefore, we do not give a specific recommendation for its use in AE.

*Mechanisms of action and efficacy* Nemolizumab is a humanized mAb targeting the IL-31 receptor alpha chain (IL-31RA), which was initially developed for the treatment of AE-related pruritus.

In a phase II, randomized, double-blind, placebo-controlled, 12-week trial, nemolizumab at monthly doses significantly improved pruritus.[57]

In a 2b study with nemolizumab 30 mg dosing and TCS, there were significant improvements in signs and symptoms of AE - EASI scores, PP-NRS, sleep and DLQI score, which was confirmed in a post-hoc sub-analysis of the EASI ≥16 cohort.[58,59]

In a recently published 16-week, double-blind, phase III trial, Japanese patients with AE and moderate-to-severe pruritus received subcutaneous nemolizumab (60 mg) or placebo every 4 weeks until week 16, with concomitant topical agents.[60] The primary end point was the mean per cent change in the visual-analogue scale (VAS) score for pruritus from baseline to week 16. Secondary end points included the time course of change in the VAS score for pruritus up to week 4, EASI score, DLQI, Insomnia Severity Index, and safety. At week 16, the mean per cent change in the VAS score was −42.8% in the nemolizumab group and −21.4% in the placebo group. The use of subcutaneous nemolizumab in addition to topical agents for atopic dermatitis resulted in a highly significant reduction in pruritus than placebo plus topical agents.

*Dosage: acute flare, short term, long term* The first phase II study investigating nemolizumab published in 2017 investigated 0.1, 0.5, 2 mg/kg dosages administered every 4 weeks and 2 mg/kg dosage administered every 8 weeks. Results at 12 weeks found a significant, dose-dependent improvement in the primary outcome of pruritus for all groups that received nemolizumab every 4 weeks, as compared with placebo.[57] In a two-part, phase II, randomized control trial published in 2018, Kabashima *et al.*[60] compared three different nemolizumab dosages: 0.1, 0.5, 2 mg/kg adminstered every 4 weeks and 2 mg/kg administered every 8 weeks. All the parameters considered in the study showed an improvement, and no evidence was found that the highest dosage was more effective than the lowest. Furthermore, the study showed that the positive outcomes obtained with nemolizumab were maintained for up to 64 weeks.

In another 24-week, randomized, double-blind, multicenter study published in 2019 by Silverberg *et al.*,[58] three different nemolizumab dosages, 10, 30 and 90 mg, were compared in an

ethnically more diverse population. The drug was administered once every 4 weeks and nemolizumab 30 mg showed maximum dosage efficacy in improving EASI, IGA, and pruritus.

In the latest published study conducted in Japanese patients,[60] the dosage tested was 60 mg, administered every 4 weeks. At the reported dosage, nemolizumab showed a greater efficacy in reducing pruritus, compared to placebo plus topicals.

*Safety* The most frequent adverse events related to the drug are reported to be injection-related reactions, musculoskeletal and connective tissue symptoms, upper respiratory tract infections, nasopharyngitis, peripheral oedema and increased creatine phosphokinase.[58]

The authors conclude that longer and larger trials are necessary to determine whether nemolizumab has a durable effect and is safe for AE patients.[58]

*Monitoring* No biochemical or instrumental exams are reported to be required for the monitoring of the therapy.

*Combination with other treatments* According to the available study trials, the use of topical treatments such as emollients, corticosteroids and calcineurin inhibitors as a rescue therapy, in addition to nemolizumab, could have a synergistic effect in the treatment of AE and AE-related pruritus.

## Omalizumab

| | | |
|---|---|---|
| We **cannot make a recommendation** with respect to the use of omalizumab for the treatment of AE**.** | **0** | 100% agreement<br>(17/17)<br>Expert Consensus |

Omalizumab: in label for allergic asthma (≥ 6 years), chronic rhinosinusitis with nasal polyps (CRSwNP) (≥ 18 years) and chronic spontaneous urticaria (≥ 12 years)
Commonly used dosage:
Dosage (allergic asthma and CRSwNP): depends on baseline IgE (IU/ml), measured before the start of treatment, and body weight. The maximum recommended dose is 600 mg omalizumab every two weeks. Please refer to the SmPC for further details. Dosage (chronic spontaneous urticaria): 300 mg every four weeks.

*Mechanisms of action and efficacy* Most AE patients have elevated serum IgE levels, but the pathogenic role of IgE in AE remains unknown. The anti-IgE antibody omalizumab has been used with great success for treatment of chronic spontaneous urticaria (CSU). A recent systematic review and meta-analysis has assessed the preclinical and trial data regarding omalizumab treatment of AE, which are conflicting.[61]

Omalizumab is licensed for treatment of asthma and CSU, but not for treatment for AE.

Omalizumab binds free IgE, which leads to immune complexes of IgE and omalizumab. IgE bound to omalizumab cannot bind to the alpha chain of the high-affinity receptor for IgE, thereby inhibiting its binding to mast cells, basophils and epidermal dendritic cells,[62,63] and subsequent immunological effects.

There are many case reports and case series,[61] but only few controlled trials studying omalizumab treatment of AE.[61,64] In summary, the data show a measurable, but moderate efficacy of omalizumab for improving signs and symptoms of AE.[61,65] There is no predictive marker linked to a better clinical response, and most of the published evidence is of low quality. The safety of omalizumab is very good,[61] but the unpredictable and statistically low efficacy prevents a general recommendation for omalizumab regarding treatment of AE.

*Dosage: acute flare, short term, long term* *Adult.* Different dosages have been tested in AE patients, ranging from 150 to 450 mg every 2 weeks or every 4 weeks. A recent systematic review and meta-analysis by Wollenberg *et al.* found that patients with lower baseline IgE showed a positive response to treatment with omalizumab compared with patients with very high-to-extremely high serum IgE.[61]

An older systematic review and meta-analysis by Wang *et al.* also found that IgE serum concentrations of less than 700 IU/mL were associated with a better clinical response, compared with with IgE concentrations of 700 to >5000 IU/mL. Age, sex, baseline clinical disease severity, a history of concomitant asthma, and the use of 600 mg/month or more of omalizumab showed no significant association with the clinical results associated with omalizumab use.[66]

*Children.* The ADAPT (Atopic Dermatitis Anti-IgE Paediatric Trial) trial evaluated the possible role of omalizumab in the management of severe paediatric AE with concomitant allergic disease (asthma, allergic rhinoconjuncitivitis or food allergies) for 24 weeks. The drug dose was determined by baseline total IgE (range: 30 to 1500 IU/mL), measured before the start of treatment, and body weight (kg) and calculated using the formula: 0.016 × weight (kg) × total IgE level (kU/L) in 2–4 weekly

injections. The study showed that omalizumab significantly reduced disease severity and improved QoL in paediatric patients with severe AE and highly elevated IgE levels (median baseline total IgE of 8373 IU/L) compared with placebo.[64] However, this improvement was below the minimal clinically important difference for the main outcome (objective SCORAD).

*Safety* There is a general consensus about the overall good safety profile of omalizumab, with some controlled studies reporting excellent tolerability up to 4 years. A 2009 revision of data from controlled trials concluded that incidence of anaphylaxis was 0.14% in omalizumab-treated patients and 0.07% in control subjects. Of note, no serum-sickness attributable to the drug and no anti-omalizumab antibodies have been reported to date.[67]

There are no reported interactions of omalizumab with other medications used for AE or other allergic diseases. If clinically needed, omalizumab may be considered during pregnancy. More attention has been put over the appearance of gut parasite infections in treated patients, as IgE is an important player in the host defence against parasitic helminths. A randomized placebo-controlled trial in 137 adult subjects with respiratory allergy at high risk of helminth infection showed a modest increase of the incidence of parasitism in the active group.[68]

*Monitoring* No biochemicals or instrumental examinations are reported to be required for the monitoring of the therapy. IgE levels increase following administration of omalizumab and may remain elevated for up to 1 year following discontinuation of the drug.

### Tralokinumab

*Mechanisms of action and efficacy* Tralokinumab is a fully human, high-affinity IgG4 mAb,which neutralizes IL-13, and has been approved by the EMA in summer 2021.[69] In two 52-week, double-blind, placebo-controlled phase III trials, adults with moderate-to-severe AE were randomized to subcutaneous tralokinumab 300 mg every 2 weeks or placebo.[70] Tralokinumab monotherapy was superior to placebo at 16 weeks of treatment. Coprimary end points were IGA score of 0 or 1 and EASI 75 at week 16. Patient achieving an IGA score of 0/1 and/or EASI 75 with tralokinumab at week 16 was rerandomized to tralokinumab Q2W or every 4 weeks or placebo for 36 weeks. The majority of week 16 tralokinumab-responders maintained response at week 52 with continued tralokinumab treatment without any rescue medication.

*Dosage: acute flare, short term, long term* The recommended dosage is 300 mg every 2 weeks after a loading dose of 600 mg at treatment onset. At prescriber's discretion, every fourth week dosing may be considered for patients who achieve clear or almost clear skin after 16 weeks of treatment.

Phase III trials have also investigated what happens when patients who do well for 16 weeks on tralokinumab continue treatment as labelled, reduce treatment frequency, or discontinue treatment.

After 16 weeks, patients who reached EASI 75 or IGA success were rerandomized to continue treatment every 2 weeks, titrate down to every 4 weeks, or use placebo. At 52 weeks, without TCS, more than 55% of patients who continued twice-monthly treatment maintained EASI 75, as did approximately 50% of patients treated monthly. More than 51% of patients who stayed on twice-monthly dosing maintained IGA 0 or 1, vs. 39% and 45% of patients who switched to monthly dosing.

*Safety* In the two studies, adverse events were reported in 76.4% and 61.5% of patients receiving tralokinumab and in 77.0% and 66.0% of patients receiving placebo in the 16-week initial period.

| | | |
|---|---|---|
| We **recommend** tralokinumab in AE patients who are candidates for systemic treatment. | ↑↑ | 100% agreement<br>(10/10)<br>Evidence and consensus based, see Evidence Report |
| Tralokinumab: in licence for adults;<br>Short term (8-16 weeks) vs. placebo (NMA main analysis)<br>dosage adults: initially 600 mg s.c. day 1 followed by 300 mg Q2W<br>At prescriber's discretion, every fourth week dosing may be considered for patients who achieve clear or almost clear skin after 16 weeks of treatment. | | |
| Certainty of evidence[2,3]:<br>⊗⊗⊗○MODERATE for mean difference/ standardized mean difference **EASI**, DLQI<br>⊗⊗○○ LOW for undesirable effects<br>*For tralokinumab versus other drugs, see Evidence Report* | | |

Notably, tralokinumab appears to have lower rates of ocular complications than dupilumab.[70]

The combination therapy with TCS, TCI and UV light treatment is possible.

*Monitoring* No biochemical or instrumental examinations are reported to be required for the monitoring of the therapy.

*Combination with other treatments* In an additional phase III double-blind, placebo study the efficacy and safety of tralokinumab in combination with TCS as needed in patients with moderate-to-severe AE were evaluated. At week 16, significantly more tralokinumab-treated patients than placebo achieved IGA 0/1 and EASI 75. Nine of ten EASI 75 responders at week 16 maintained response at week 32 with continued tralokinumab and TCS as needed.[71]

## JAK-Inhibitors

The JAK family, constituting JAK1, JAK2, JAK3 and tyrosine kinase 2 (TYK2), are a class of cytoplasmic tyrosine kinases.[72] JAKs dock to the intracellular part of cytokine receptor chains to generate functional signalling complexes and regulate the inflammatory process through activating the intracytoplasmic transcription factors termed as signal transducer and activator of transcription (STAT). When activated, STAT proteins produce dimers, which translocate into the nucleus and either positively or negatively regulate downstream target gene expression of inflammatory mediators, suggesting that inhibiting JAK activity may be more effective than targeting a single cytokine. Beyond the disruption of cutaneous inflammatory cytokine signalling, JAK inhibition has been reported to attenuate chronic itch and improve skin barrier function by regulating the expression of skin barrier protein filaggrin.[73,74]

### Abrocitinib

Abrocitinib is currently licensed for AE in those aged 12 and above in the United Kingdom. The EMA Committee for Medicinal Products for Human Use adopted a positive opinion on 14 October 2021, for adults only. As this approval came through after our consensus conferences, no consensus recommendation has been included in this iteration of the guideline.

*Mechanisms of action and efficacy* Abrocitinib is an oral JAK1 selective inhibitor and has shown efficacy in patients with moderate-to-severe AE when used as a monotherapy (MONO-1 and -2 studies) and in combination with topical therapies in achieving treatment response in comparison with placebo (COMPARE study), as measured using IGA and EASI-75 response. For instance, the proportion of patients with EASI-75 response at week 12 was significantly higher with abrocitinib 100 mg (~40–45%) and abrocitinib 200 mg (~61–63%) compared with placebo (~10–12%) in the MONO studies. In the COMPARE study, the proportion of patients with EASI-75 response was significantly higher with abrocitinib 100 mg (~59%) and abrocitinib 200 mg (~70%) compared with placebo (27%).[2] Similar efficacy has been demonstrated in the adolescent JADE TEEN trial for both the 100 mg and the 200 mg doses, in combination with topical therapies.[75] Importantly, in the COMPARE study (which had dupilumab as a comparator arm), higher responder rates were observed with abrocitinib 200 mg compared with dupilumab (*P*-values not calculated) after 16 weeks of treatment. The efficacy of abrocitinib 100 mg and dupilumab was similar in this subgroup. The results indicate that abrocitinib 200 mg may provide a higher probability of treatment response compared with dupilumab in patients with severe AE.[76]

*Dosage: acute flare, short term, long term* Abrocitinib is licensed at the 100 mg and the 200 mg daily doses, with the lower dose recommended for adolescents as a starting dose. One study assessed risk and probability of flares and recapture of treatment response following a flare. Of 1233 patients, 798 responders to induction with abrocitinib 200 mg (64.7%) were randomly assigned to dose maintenance, dose reduction or treatment withdrawal (placebo). The flare probability during maintenance was 18.9%, 42.6%, and 80.9% with abrocitinib 200 mg, abrocitinib 100 mg, and placebo, respectively, by week 52. Among patients with flare in the abrocitinib 200 mg, abrocitinib 100 mg, and placebo groups, 36.6%, 58.8%, and 81.6% regained IGA 0/1 response, respectively, and 55.0%, 74.5%, and 91.8% regained EASI index response, respectively, with rescue treatment of abrocitinib 200 mg plus medicated topical therapy.[77]

*Safety* Based on long-term follow-up of patients from the phase II and III trials as well as one long-term extension study, with a total *n* of 2856 [1614 patient-years (PY)]; total exposure in the all-abrocitinib cohort was ≥24 weeks in 1248 patients and ≥48 weeks in 606 (maximum 108 weeks). In the placebo-controlled cohort ($n = 1540$), dose-related adverse events (200 mg, 100 mg, placebo) were nausea (14.6%, 6.1%, 2.0%), headache (7.8%, 5.9%, 3.5%) and acne (4.7%, 1.6%, 0%). Platelet count was reduced transiently in a dose-dependent manner; two of 2718 patients (200-mg group) had confirmed platelet counts of $<50 \times 10^3/mm^3$ at week 4. Incidence rates (IRs) were 2.33/100PY and 2.65/100 PY for serious infection, 4.34/100PY and 2.04/100PY for herpes zoster, and 11.83/100PY and 8.73/100PY for herpes simplex in the 200-mg and 100-mg groups, respectively.[78]

*Monitoring* For baseline screening, the manufacturer's UK label laboratory monitoring recommendations are full blood count including platelet count, absolute lymphocyte count (ALC), absolute neutrophil count (ANC), and haemoglobin (Hb) as well as lipid parameters. A chest radiograph, creatinine phosphokinase level and an infection screening for HIV, hepatitis B and C as well as TB is advisable before initiation of therapy.

In practice, we recommend the same baseline screening and treatment monitoring investigations for all JAK

inhibitors. For baseline screening, this is a full blood count, renal, liver and lipid profile as well as creatinine phosphokinase levels and hepatitis and TB screen, including a chest radiograph.

For monitoring purposes, we recommend a full blood count, renal, liver and lipid profile as well as creatinine phosphokinase level at 4 weeks into treatment and then three-monthly while on therapy.

*Combination with other treatments* No studies assessing the use of abrocitinib with other systemic therapies have been published to date.

*Special considerations* Abrocitinib is a new JAK inhibitor and has not been formally tested in other inflammatory diseases.

### Baricitinib

*Safety* The most common side-effects with baricitinib in clinical trials include an increase in LDL cholesterol, upper respiratory tract infections and headache. Acne is less common than with other JAK inhibitors. Infections reported with baricitinib include herpes simplex. However, the rate of these events reported in a recent combined safety study including 2531 patients from eight RCTs who were given baricitinib for 2247 patient-years (median duration 310 days) was overall low: eczema herpeticum ($n$ = 11), cellulitis ($n$ = 6) and pneumonia ($n$ = 3). There were four opportunistic infections reported.[82] A transient increase in CPK may be seen, especially after extensive bodily exercise. No malignancies, gastrointestinal perforations, positively adjudicated cardiovascular events or tuberculosis were reported in the placebo-controlled period in baricitinib-treated patients. The frequency of herpes simplex was higher in the 4 mg group (6.1%) compared to the 2 mg (3.6%) and placebo groups (2.7%). Long-term safety data beyond 16 weeks are available from an integrated data base covering mostly rheumatoid arthritis patients for up to 9.3 years of treatment.[83]

| We **recommend** baricitinib in AE patients, who are candidates for systemic treatment. | ↑↑ | >75%<br>  <br>(15/16)[1]<br>Evidence and consensus based, see Evidence Report |
|---|---|---|
| Baricitinib: in licence for adults;<br>dosage adults: 4 mg per day, reduction to 2 mg per day possible, depending on treatment response | | |
| Certainty of evidence[2,3]:<br>Short term (8-16 weeks) vs. placebo (NMA main analysis)<br>⊗⊗⊗○MODERATE for mean difference/ standardized mean difference **EASI**, DLQI<br>⊗⊗⊗○MODERATE - ⊗⊗○○ LOW for undesirable effects<br>*For baricitinib versus other drugs, see Evidence Report* | | |

[1]1 abstention

*Mechanisms of action and efficacy* Baricitinib is an oral selective JAK1 and JAK2 inhibitor. The drug has been tested in one phase 2 and several phase 3 trials in adults with moderate-to-severe AE at 1, 2 and 4 mg once daily against placebo, showing significant improvement with regard to EASI from baseline to 16 weeks, in particular in the two higher doses {2 mg daily [mean difference, 5.6-point reduction; 95% CI, 0.4–10.9 (GRADE assessment: moderate certainty)] and 4 mg daily [mean difference, 5.2-point reduction; 95% CI, 0.1–10.4 (GRADE assessment: moderate certainty)]}.[2] Similar efficacy has been shown in these studies with regard to the IGA and itch scores. The concomitant use of topical corticosteroids was allowed in one trial.[79]

*Dosage: acute flare, short term, long term* At present, Baricitinib data are available up to 52 weeks of follow-up,[80] demonstrating sustained efficacy. There is no study that has looked at acute flare treatment and the paediatric study programme is still underway[81] and no clear dosing guidance for paediatric patients is currently available.

*Monitoring* For baseline screening, the manufacturer advises that patients with suspected hepatitis B consult a liver specialist for advice before initiation of treatment. Lipid and liver profiles need to be regularly monitored following treatment initiation. Screening for any haematological abnormalities is also advised.

In practice, we recommend the same baseline screening and treatment monitoring investigations for all JAK inhibitors. For baseline screening, this is a full blood count, renal, liver and lipid profile as well as creatinine phosphokinase levels and hepatitis and TB screen, including a chest radiograph.

For monitoring purposes, we recommend a full blood count, renal, liver and lipid profile as well as creatinine phosphokinase level at 4 weeks into treatment and then three-monthly while on therapy.

*Combination with other treatments* No studies assessing the use of baricitinib with other systemic therapies in AE patients have been published to date, but the combination therapy with MTX is an established combination regimen in the management of rheumatoid arthritis.[84]

*Special considerations* AE patients with concomitant inflammatory diseases, such as rheumatoid arthritis, ankylosing spondylitis and psoriatic arthritis are likely to experience beneficial effects. Baricitinib is already licensed for this indication.

## Upadacitinib

| | | |
|---|---|---|
| We **recommend** upadacitinib in AE patients who are candidates for systemic treatment. | ↑↑ | >50%<br>  <br>(8/15)<br>Evidence and consensus based, see Evidence Report |
| Upadacitinib: in licence for ≥ 12 years;<br>adults: 15 or 30 mg per day; age ≥ 65: 15 mg per day<br>age 12-17 (>= 30 kg bw): 15 mg per day | | |
| Certainty of evidence[2,3]:<br>Short term (8-16 weeks) vs. placebo (NMA main analysis)<br>⊗⊗○○ LOW for mean difference **POEM**<br>⊗○○○VERY LOW for undesirable effects<br>*For upadacitinib versus other drugs, see Evidence Report* | | |

Upadacitinib is licensed for AE in adolescents (12 years and above) and adults.

*Mechanisms of action and efficacy* Upadacitinib is a selective and reversible JAK inhibitor. There is one phase 2 trial including 167 adult patients that investigated three different doses of upadacitinib (30, 15 and 7.5 mg/day) for AE compared to placebo.[85] The trial was conducted over 16 weeks. Upadacitinib was superior to placebo for all dosage groups in EASI [mean change (SE) 74% (6.1%) for 30 mg, 62% (6.1%) for 15 mg, 39% (6.2%) for 7.5 mg and 23% (6.4%) for placebo ($P = 0.03$, <0.001, <0.001)]. There were also significant improvements seen with regard to the SCORAD index, NRS pruritus and POEM scores. The trials published since have shown similar efficacy.[86–88]

In a direct head-to-head trial enrolling adult AE patients randomized to receive upadacitinib ($n = 348$) and dupilumab ($n = 344$) 247 patients receiving upadacitinib (71.0%) and 210 patients receiving dupilumab (61.1%) achieved EASI-75 at 16 weeks ($P = 0.006$). All ranked secondary end points also demonstrated the superiority of upadacitinib *vs* dupilumab, including improvement in Worst Pruritus NRS as early as week 1, achievement of EASI-75 as early as week 2, and EASI-100 at week 16. Rates of serious infection, eczema herpeticum, herpes zoster, and laboratory-related adverse events were higher for patients who received upadacitinib, whereas rates of conjunctivitis and injection-site reactions were higher for patients who received dupilumab.

*Dosage: acute flare, short term, long term* Upadacitinib is licensed at the 15 and 30 mg doses for AE, and at 15 mg for rheumatoid arthritis, psoriatic arthritis and ankylosing spondilitis. Follow-up until week 52 is now available, showing long-term efficacy and safety profiles similar to the 16 week trials.[89] There is no study that has looked at acute flare treatment, and there are currently early phase AE trials in children >6 months.

*Safety* The cumulative incidence rates of adverse events were 78.6% for 30 mg, 76.2% for 15 mg, 73.8% for 7.5 mg and 62.5% for placebo in the phase 2 trial and have been similar in the studies reported since.[85] Upper respiratory tract infections and acne were the most frequently reported adverse events for Upadacitinib. The cumulative incidence rates of severe adverse events were 0% for 30 mg, 2.4% for 15 mg, 4.8% for 7.5 mg and 2.4% for placebo. Low withdrawal rates were reported in the placebo and upadacitinib groups ($n < 5$ for each group).

*Monitoring* The manufacturer advises that patients are screened for viral hepatitis B and C and TB. Lipid and liver profiles need to be measured at baseline and regularly following treatment initiation. Screening and monitoring for any haematological abnormalities are also advised, no later than 12 weeks.

In practice, we recommend the same baseline screening and treatment monitoring investigations for all JAK inhibitors. For baseline screening, this is a full blood count, renal, liver and lipid profile as well as creatinine phosphokinase levels and hepatitis and TB screen, including a chest radiograph.

For monitoring purposes, we recommend a full blood count, renal, liver and lipid profile as well as creatinine phosphokinase level at 4 weeks into treatment and then three-monthly while on therapy.

*Combination with other treatments* No studies assessing the use of upadacitinib with other systemic therapies in AE patients have been published to date, but the combination therapy with MTX is an established combination regimen in the management of rheumatoid arthritis, albeit only with the 15 mg once a day dose.[90]

*Special considerations* AE patients with concomitant inflammatory diseases, such as rheumatoid arthritis, psoriatic arthritis and ankylosing spondylitis are likely to experience benificial effects, as upadacitinib is already licensed for this indication.[91]

## Other systemic treatment

### Alitretinoin

| | | |
|---|---|---|
| We **suggest** alitretinoin for AE patients with severe chronic hand eczema, who are candidates for systemic treatment, duely considering its teratogenicity. | ↑ | >75%<br>(14/15)<br>Expert consensus |
| Alitretinoin: in label for adults with severe chronic hand eczema unresponsive to topical corticosteroids; dosage adults 10 - 30 mg per day | | |

*Mechanisms of action and efficacy* Alitretinoin is a retinoid binding both retinoic acid (RAR) and retinoic X (RXR) receptors, thus delivering anti-inflammatory and antiproliferative effects. It is licensed in some European countries for the treatment of chronic hand eczema irrespectively of its pathogenesis.

There is one large, multicenter randomized, placebo-controlled clinical trial involving 1032 patients with chronic hand eczema, about one-third of which were probably atopic hand eczema patients.[92] Improvement of eczema was seen in 75% of the patients. The patient group suffering from atopic hand eczema was not analysed separately, and extrapalmar symptoms have not been assessed in this trial.

Six patients with AE and prominent hand involvement were treated with alitretinoin for 12 weeks in an uncontrolled, open-label trial.[93] Both, palmar and extrapalmar lesions improved during the trial, as shown by the modified Total Lesion Symptom Score (mTLSS) hand eczema score and the SCORAD.

*Dosage: acute flare, short term, long term* According to the mode of action, alitretinoin is suitable for long-term treatment. An alitretinoin treatment course should be planned for 3 to 6 months.

The dosage of alitretinoin is 10–30 mg per day.

*Safety* As alitretinoin is highly teratogenic, all women of childbearing potential must adhere to a strict birth control programme.

*Monitoring* Before and during therapy: liver enzymes [aspartate aminotransferase (ASAT), alanine aminotransferase (ALAT), gamma-glutamyl transpeptidase (GGT)], cholesterol, triglycerides, basal thyroid stimulating hormone (TSH), free thyroxine (fT4) peripheral blood levels; pregnancy test in women with childbearing potential.

*Combination with other treatments* Concomitantly to alitretinoin, topical therapy with corticosteroids, calcineurininhibitors and emollients can be applied.

*Special considerations* A retrospective analysis of children treated with alitretinoin because of hand eczema and other diagnoses including two severe AE patients, revealed that the response to alitretinoin was moderate in one subject, whereas the other patient failed to improve even after extending treatment to up to 11 months.[94]

## Acknowledgement

Open Access funding enabled and organized by Projekt DEAL.

## Data availability statement

Data sharing not applicable to this article as no datasets were generated or analysed during the current study.

## References

1 Kaminski-Hartenthaler A, Meerpohl JJ, Gartlehner G *et al.* GRADE guidelines: 14. Going from evidence to recommendations: the significance and presentation of recommendations. *Z Evid Fortbild Qual Gesundhwes* 2014; **108**: 413–420.
2 Drucker AM, Ellis AG, Bohdanowicz M *et al.* Systemic immunomodulatory treatments for patients with atopic dermatitis: a systematic review and network meta-analysis. *JAMA Dermatol* 2020; **156**: 659–667.
3 Drucker AM. Systemic immunomodulatory treatments for atopic dermatitis: a living systematic review and network meta-analysis. 2020.
4 Silverberg JI, Simpson EL, Armstrong AW, de Bruin-Weller MS, Irvine AD, Reich K. Expert perspectives on key parameters that impact interpretation of randomized clinical trials in moderate-to-severe atopic dermatitis. *Am J Clin Dermatol* 2022; **23**: 1–11.

5 Wollenberg A, Christen-Zäch S, Taieb A *et al*. ETFAD/EADV eczema task force 2020 position paper on diagnosis and treatment of atopic dermatitis in adults and children. *J Eur Acad Dermatol Venereol* 2020; **34**: 2717–2744.
6 Schünemann H, Brożek J, Guyatt G, Oxman A. Handbook for grading the quality of evidence and the strength of recommendations using the GRADE approach. 2013.
7 Schmitt J, Spuls PI, Thomas KS *et al*. The Harmonising outcome measures for eczema (HOME) statement to assess clinical signs of atopic eczema in trials. *J Allergy Clin Immunol* 2014; **134**: 800–807.
8 Stadler PC, Renner ED, Milner J, Wollenberg A. Inborn error of immunity or atopic dermatitis: when to be concerned and how to investigate. *J Allergy Clin Immunol Pract* 2021; **9**: 1501–1507.
9 Thyssen JP, Vestergaard C, Barbarot S *et al*. European task force on atopic dermatitis: position on vaccination of adult patients with atopic dermatitis against COVID-19 (SARS-CoV-2) being treated with systemic medication and biologics. *J Eur Acad Dermatol Venereol* 2021; **35**: e308–e311.
10 Wollenberg A, Flohr C, Simon D *et al*. European task force on atopic dermatitis statement on severe acute respiratory syndrome coronavirus 2 (SARS-Cov-2) infection and atopic dermatitis. *J Eur Acad Dermatol Venereol* 2020; **34**: e241–e242.
11 Lennard L. The clinical pharmacology of 6-mercaptopurine. *Eur J Clin Pharmacol* 1992; **43**: 329–339.
12 Roekevisch E, Spuls PI, Kuester D, Limpens J, Schmitt J. Efficacy and safety of systemic treatments for moderate-to-severe atopic dermatitis: a systematic review. *J Allergy Clin Immunol* 2014; **133**: 429–438.
13 Thomsen SF, Karlsmark T, Clemmensen KK *et al*. Outcome of treatment with azathioprine in severe atopic dermatitis: a 5-year retrospective study of adult outpatients. *Br J Dermatol* 2015; **172**: 1122–1124.
14 Garritsen FM, Roekevisch E, van der Schaft J, Deinum J, Spuls PI, de Bruin-Weller MS. Ten years experience with oral immunosuppressive treatment in adult patients with atopic dermatitis in two academic centres. *J Eur Acad Dermatol Venereol* 2015; **29**: 1905–1912.
15 van der Schaft J, van Zuilen AD, Deinum J, Bruijnzeel-Koomen CA, de Bruin-Weller MS. Serum creatinine levels during and after long-term treatment with cyclosporine a in patients with severe atopic dermatitis. *Acta Derm Venereol* 2015; **95**: 963–967.
16 Gerbens LAA, Hamann SAS, Brouwer MWD, Roekevisch E, Leeflang MMG, Spuls PI. Methotrexate and azathioprine for severe atopic dermatitis: a 5-year follow-up study of a randomized controlled trial. *Br J Dermatol* 2018; **178**: 1288–1296.
17 Meggitt SJ, Gray JC, Reynolds NJ. Azathioprine dosed by thiopurine methyltransferase activity for moderate-to-severe atopic eczema: a double-blind, randomised controlled trial. *Lancet* 2006; **367**: 839–846.
18 Meggitt SJ, Reynolds NJ. Azathioprine for atopic dermatitis. *Clin Exp Dermatol* 2001; **26**: 369–375.
19 Taylor AE, Shuster S. Skin cancer after renal transplantation: the causal role of azathioprine. *Acta Derm Venereol* 1992; **72**: 115–119.
20 Vestergaard C, Wollenberg A, Barbarot S *et al*. European task force on atopic dermatitis position paper: treatment of parental atopic dermatitis during preconception, pregnancy and lactation period. *J Eur Acad Dermatol Venereol* 2019; **33**: 1644–1659.
21 Meggitt SJ, Anstey AV, Mohd Mustapa MF, Reynolds NJ, Wakelin S. British Association of Dermatologists' guidelines for the safe and effective prescribing of azathioprine 2011. *Br J Dermatol* 2011; **165**: 711–734.
22 Janssen NM, Genta MS. The effects of immunosuppressive and anti-inflammatory medications on fertility, pregnancy, and lactation. *Arch Intern Med* 2000; **160**: 610–619.
23 Noguera-Morel L, Knöpfel N, Torrelo A, Hernández-Martín A. A retrospective study of systemic treatment of severe atopic dermatitis with azathioprine: effectiveness and tolerance in 11 pediatric patients. *Actas Dermosifiliogr* 2019; **110**: 227–231.
24 Schmitt J, Schmitt N, Meurer M. Cyclosporin in the treatment of patients with atopic eczema - a systematic review and meta-analysis. *J Eur Acad Dermatol Venereol* 2007; **21**: 606–619.
25 Seger EW, Wechter T, Strowd L, Feldman SR. Relative efficacy of systemic treatments for atopic dermatitis. *J Am Acad Dermatol* 2019; **80**: 411–6.e4.
26 Dal Bello G, Maurelli M, Schena D, Girolomoni G, Gisondi P. Drug survival of dupilumab compared to cyclosporin in moderate-to-severe atopic dermatitis patients. *Dermatol Ther* 2020; **33**: e13979.
27 Goujon C, Viguier M, Staumont-Sallé D *et al*. Methotrexate versus cyclosporine in adults with moderate-to-severe atopic dermatitis: a phase III randomized noninferiority trial. *J Allergy Clin Immunol Pract* 2018; **6**: 562–9.e3.
28 Berth-Jones J, Finlay AY, Zaki I *et al*. Cyclosporine in severe childhood atopic dermatitis: a multicenter study. *J Am Acad Dermatol* 1996; **34**: 1016–1021.
29 Rhen T, Cidlowski JA. Antiinflammatory action of glucocorticoids--new mechanisms for old drugs. *N Engl J Med* 2005; **353**: 1711–1723.
30 La Rosa M, Musarra I, Ranno C *et al*. A randomized, double-blind, placebo-controlled, crossover trial of systemic flunisolide in the treatment of children with severe atopic dermatitis. *Curr Ther Res* 1995; **56**: 720–726.
31 Saag KG, Koehnke R, Caldwell JR *et al*. Low dose long-term corticosteroid therapy in rheumatoid arthritis: an analysis of serious adverse events. *Am J Med* 1994; **96**: 115–123.
32 Richter B, Neises G, Clar C. Glucocorticoid withdrawal schemes in chronic medical disorders. A systematic review. *Endocrinol Metab Clin North Am* 2002; **31**: 751–778.
33 Alqarni AM, Zeidler MP. How does methotrexate work? *Biochem Soc Trans* 2020; **48**: 559–567.
34 Weatherhead SC, Wahie S, Reynolds NJ, Meggitt SJ. An open-label, dose-ranging study of methotrexate for moderate-to-severe adult atopic eczema. *Br J Dermatol* 2007; **156**: 346–351.
35 Goujon C, Bérard F, Dahel K *et al*. Methotrexate for the treatment of adult atopic dermatitis. *Eur J Dermatol* 2006; **16**: 155–158.
36 Lyakhovitsky A, Barzilai A, Heyman R *et al*. Low-dose methotrexate treatment for moderate-to-severe atopic dermatitis in adults. *J Eur Acad Dermatol Venereol* 2010; **24**: 43–49.
37 Schram ME, Roekevisch E, Leeflang MM, Bos JD, Schmitt J, Spuls PI. A randomized trial of methotrexate versus azathioprine for severe atopic eczema. *J Allergy Clin Immunol* 2011; **128**: 353–359.
38 El-Khalawany MA, Hassan H, Shaaban D, Ghonaim N, Eassa B. Methotrexate versus cyclosporine in the treatment of severe atopic dermatitis in children: a multicenter experience from Egypt. *Eur J Pediatr* 2013; **172**: 351–356.
39 Deo M, Yung A, Hill S, Rademaker M. Methotrexate for treatment of atopic dermatitis in children and adolescents. *Int J Dermatol* 2014; **53**: 1037–1041.
40 Taieb Y, Baum S, Ben Amitai D, Barzilai A, Greenberger S. The use of methotrexate for treating childhood atopic dermatitis: a multicenter retrospective study. *J Dermatolog Treat* 2019; **30**: 240–244.
41 Shah N, Alhusayen R, Walsh S, Shear NH. Methotrexate in the treatment of moderate to severe atopic dermatitis: a retrospective study. *J Cutaneous Med Surg* 2018; **22**: 484–487.
42 Ortiz Z, Shea B, Suarez-Almazor ME, Moher D, Wells GA, Tugwell P. The efficacy of folic acid and folinic acid in reducing methotrexate gastrointestinal toxicity in rheumatoid arthritis. A metaanalysis of randomized controlled trials. *J Rheumatol* 1998; **25**: 36–43.
43 Dogra S, Mahajan R. Systemic methotrexate therapy for psoriasis: past, present and future. *Clin Exp Dermatol* 2013; **38**: 573–588.
44 Weinblatt ME. Methotrexate in rheumatoid arthritis: a quarter century of development. *Trans Am Clin Climatol Assoc* 2013; **124**: 16–25.
45 Allison AC. Mechanisms of action of mycophenolate mofetil. *Lupus* 2005; **14**(Suppl 1): s2–s8.
46 Phan K, Smith SD. Mycophenolate mofetil and atopic dermatitis: systematic review and meta-analysis. *J Dermatolog Treat* 2020; **31**: 810–814.
47 Dias-Polak D, Bergman R, Avitan-Hersh E. Mycophenolate mofetil therapy in adult patients with recalcitrant atopic dermatitis. *J Dermatolog Treat* 2019; **30**: 49–51.

48 Simpson EL, Bieber T, Guttman-Yassky E *et al*. Two phase 3 trials of Dupilumab versus placebo in atopic dermatitis. *N Engl J Med* 2016; **375**: 2335–2348.
49 Beck LA, Thaçi D, Hamilton JD *et al*. Dupilumab treatment in adults with moderate-to-severe atopic dermatitis. *N Engl J Med* 2014; **371**: 130–139.
50 Beck LA, Thaçi D, Deleuran M *et al*. Dupilumab provides favorable safety and sustained efficacy for up to 3 years in an open-label study of adults with moderate-to-severe atopic dermatitis. *Am J Clin Dermatol* 2020; **21**: 567–577.
51 Wollenberg A, Beck LA, Blauvelt A *et al*. Laboratory safety of dupilumab in moderate-to-severe atopic dermatitis: results from three phase III trials (LIBERTY AD SOLO 1, LIBERTY AD SOLO 2, LIBERTY AD CHRONOS). *Br J Dermatol* 2020; **182**: 1120–1135.
52 Akinlade B, Guttman-Yassky E, de Bruin-Weller M *et al*. Conjunctivitis in dupilumab clinical trials. *Br J Dermatol* 2019; **181**: 459–473.
53 Wollenberg A, Ariens L, Thurau S, van Luijk C, Seegräber M, de Bruin-Weller M. Conjunctivitis occurring in atopic dermatitis patients treated with dupilumab-clinical characteristics and treatment. *J Allergy Clin Immunol Pract* 2018; **6**: 1778–80.e1.
54 Blauvelt A, de Bruin-Weller M, Gooderham M *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.
55 Guttman-Yassky E, Blauvelt A, Eichenfield LF *et al*. Efficacy and safety of Lebrikizumab, a high-affinity interleukin 13 inhibitor, in adults with moderate to severe atopic dermatitis: a phase 2b randomized clinical trial. *JAMA Dermatol* 2020; **156**: 411–420.
56 Simpson EL, Flohr C, Eichenfield LF *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**: 863–71.e11.
57 Ruzicka T, Hanifin JM, Furue M *et al*. Anti-Interleukin-31 receptor a antibody for atopic dermatitis. *N Engl J Med* 2017; **376**: 826–835.
58 Silverberg JI, Pinter A, Pulka G *et al*. Phase 2B randomized study of nemolizumab in adults with moderate-to-severe atopic dermatitis and severe pruritus. *J Allergy Clin Immunol* 2020; **145**: 173–182.
59 Silverberg JI, Pinter A, Alavi A *et al*. Nemolizumab is associated with a rapid improvement in atopic dermatitis signs and symptoms: subpopulation (EASI $\geq$ 16) analysis of randomized phase 2B study. *J Eur Acad Dermatol Venereol* 2021; **35**: 1562–1568.
60 Kabashima K, Matsumura T, Komazaki H, Kawashima M. Trial of Nemolizumab and topical agents for atopic dermatitis with pruritus. *N Engl J Med* 2020; **383**: 141–150.
61 Wollenberg A, Thomsen SF, Lacour J-P, Jaumont X, Lazarewicz S. Targeting immunoglobulin E in atopic dermatitis: a review of the existing evidence. *World Allergy Organ J* 2021; **14**: 100519.
62 Metz M, Maurer M. Omalizumab in chronic urticaria. *Curr Opin Allergy Clin Immunol* 2012; **12**: 406–411.
63 Bieber T, de la Salle H, Wollenberg A *et al*. Human epidermal Langerhans cells express the high affinity receptor for immunoglobulin E (fc epsilon RI). *J Exp Med* 1992; **175**: 1285–1290.
64 Chan S, Cornelius V, Cro S, Harper JI, Lack G. Treatment effect of Omalizumab on severe pediatric atopic dermatitis: the ADAPT randomized clinical trial. *JAMA Pediatr* 2019; **174**: 29–37.
65 Belloni B, Ziai M, Lim A *et al*. Low-dose anti-IgE therapy in patients with atopic eczema with high serum IgE levels. *J Allergy Clin Immunol* 2007; **120**: 1223–1225.
66 Wang HH, Li YC, Huang YC. Efficacy of omalizumab in patients with atopic dermatitis: a systematic review and meta-analysis. *J Allergy Clin Immunol* 2016; **138**: 1719–22.e1.
67 Corren J, Casale TB, Lanier B, Buhl R, Holgate S, Jimenez P. Safety and tolerability of omalizumab. *Clin Exp Allergy* 2009; **39**: 788–797.
68 Cruz AA, Lima F, Sarinho E *et al*. Safety of anti-immunoglobulin E therapy with omalizumab in allergic patients at risk of geohelminth infection. *Clin Exp Allergy* 2007; **37**: 197–207.
69 Popovic B, Breed J, Rees DG *et al*. Structural characterisation reveals mechanism of IL-13-Neutralising monoclonal antibody Tralokinumab as inhibition of binding to IL-13Rα1 and IL-13Rα2. *J Mol Biol* 2017; **429**: 208–219.
70 Wollenberg A, Blauvelt A, Guttman-Yassky E *et al*. Tralokinumab for moderate-to-severe atopic dermatitis: results from two 52-week, randomized, double-blind, multicentre, placebo-controlled phase III trials (ECZTRA 1 and ECZTRA 2). *Br J Dermatol* 2021; **184**: 437–449.
71 Silverberg JI, Toth D, Bieber T *et al*. Tralokinumab plus topical corticosteroids for the treatment of moderate-to-severe atopic dermatitis: results from the double-blind, randomized, multicentre, placebo-controlled phase III ECZTRA 3 trial. *Br J Dermatol* 2021; **184**: 450–463.
72 Solimani F, Meier K, Ghoreschi K. Emerging topical and systemic JAK inhibitors in dermatology. *Front Immunol* 2019; **10**: 2847.
73 Amano W, Nakajima S, Kunugi H, Numata Y, Kitoh A, Egawa G, Dainichi T, Honda T, Otsuka A, Kimoto Y, Yamamoto Y, Tanimoto A, Matsushita M, Miyachi Y, Kabashima K The Janus kinase inhibitor JTE-052 improves skin barrier function through suppressing signal transducer and activator of transcription 3 signaling. *J Allergy Clin Immunol* 2015; **136**: e7, 667, 677.e7.
74 Oetjen LK, Mack MR, Feng J *et al*. Sensory neurons co-opt classical immune signaling pathways to mediate chronic itch. *Cell* 2017; **171**: 217–228.e13.
75 Eichenfield LF, Flohr C, Sidbury R *et al*. Efficacy and safety of Abrocitinib in combination with topical therapy in adolescents with moderate-to-severe atopic dermatitis: the JADE TEEN randomized clinical trial. *JAMA Dermatol* 2021; **157**: 1165–1173.
76 Bieber T, Simpson EL, Silverberg JI *et al*. Abrocitinib versus placebo or Dupilumab for atopic dermatitis. *N Engl J Med* 2021; **384**: 1101–1112.
77 Blauvelt A, Silverberg JI, Lynde CW *et al*. Abrocitinib induction, randomized withdrawal, and retreatment in patients with moderate-to-severe atopic dermatitis: results from the JAK1 atopic dermatitis efficacy and safety (JADE) REGIMEN phase 3 trial. *J Am Acad Dermatol* 2021; **86**: 02343-4.
78 Simpson EL, Silverberg JI, Nosbaum A *et al*. Integrated safety analysis of Abrocitinib for the treatment of moderate-to-severe atopic dermatitis from the phase II and phase III clinical trial program. *Am J Clin Dermatol* 2021; **22**: 693–707.
79 Reich K, Kabashima K, Peris K *et al*. Efficacy and safety of Baricitinib combined with topical corticosteroids for treatment of moderate to severe atopic dermatitis: a randomized clinical trial. *JAMA Dermatol* 2020; **156**: 1333–1343.
80 Silverberg JI, Simpson EL, Wollenberg A *et al*. Long-term efficacy of Baricitinib in adults with moderate to severe atopic dermatitis who were treatment responders or partial responders: an extension study of 2 randomized clinical trials. *JAMA Dermatol* 2021; **157**: 691–699.
81 A study of Baricitinib (LY3009104) in children and adolescents with atopic dermatitis (BREEZE-AD-PEDS). 2019.
82 Bieber T, Thyssen JP, Reich K *et al*. Pooled safety analysis of baricitinib in adult patients with atopic dermatitis from 8 randomized clinical trials. *J Eur Acad Dermatol Venereol* 2021; **35**: 476–485.
83 Taylor PC, Takeuchi T, Burmester GR *et al*. Safety of baricitinib for the treatment of rheumatoid arthritis over a median of 4.6 and up to 9.3 years of treatment: final results from long-term extension study and integrated database. *Ann Rheum Dis* 2022; **81**: 335–343.
84 Fleischmann R, Schiff M, van der Heijde D *et al*. Baricitinib, methotrexate, or combination in patients with rheumatoid arthritis and no or limited prior disease-modifying Antirheumatic drug treatment. *Arthritis Rheumatol* 2017; **69**: 506–517.
85 Guttman-Yassky E, Thaci D, Pangan AL *et al*. Upadacitinib in adults with moderate to severe atopic dermatitis: 16-week results from a randomized, placebo-controlled trial. *J Allergy Clin Immunol* 2020; **145**: 877–884.

86 Simpson EL, Sinclair R, Forman S *et al*. Efficacy and safety of abrocitinib in adults and adolescents with moderate-to-severe atopic dermatitis (JADE MONO-1): a multicentre, double-blind, randomised, placebo-controlled, phase 3 trial. *Lancet* 2020; **396**: 255–266.
87 Guttman-Yassky E, Teixeira HD, Simpson EL *et al*. Once-daily upadacitinib versus placebo in adolescents and adults with moderate-to-severe atopic dermatitis (measure up 1 and measure up 2): results from two replicate double-blind, randomised controlled phase 3 trials. *Lancet* 2021; **397**: 2151–2168.
88 Reich K, Teixeira HD, de Bruin-Weller M *et al*. Safety and efficacy of upadacitinib in combination with topical corticosteroids in adolescents and adults with moderate-to-severe atopic dermatitis (AD up): results from a randomised, double-blind, placebo-controlled, phase 3 trial. *Lancet* 2021; **397**: 2169–2181.
89 Silverberg JI, de Bruin-Weller M, Bieber T *et al*. Upadacitinib plus topical corticosteroids in atopic dermatitis: week 52 AD up study results. *J Allergy Clin Immunol* 2022; **149**: 977–987.
90 Fleischmann RM, Genovese MC, Enejosa JV *et al*. Safety and effectiveness of upadacitinib or adalimumab plus methotrexate in patients with rheumatoid arthritis over 48 weeks with switch to alternate therapy in patients with insufficient response. *Ann Rheum Dis* 2019; **78**: 1454–1462.
91 Blauvelt A, Teixeira HD, Simpson EL *et al*. Efficacy and safety of Upadacitinib vs Dupilumab in adults with moderate-to-severe atopic dermatitis: a randomized clinical trial. *JAMA Dermatol* 2021; **157**: 1047–1055.
92 Ruzicka T, Lynde CW, Jemec GB *et al*. Efficacy and safety of oral alitretinoin (9-cis retinoic acid) in patients with severe chronic hand eczema refractory to topical corticosteroids: results of a randomized, double-blind, placebo-controlled, multicentre trial. *Br J Dermatol* 2008; **158**: 808–817.
93 Grahovac M, Molin S, Prinz JC, Ruzicka T, Wollenberg A. Treatment of atopic eczema with oral alitretinoin. *Br J Dermatol* 2010; **162**: 217–218.
94 Luchsinger I, Vogler T, Schwieger-Briel A *et al*. Safe and effective use of alitretinoin in children with recalcitrant hand eczema and other dermatoses - a retrospective analysis. *J Eur Acad Dermatol Venereol* 2020; **34**: 1037–1042.