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 programs of the various new biologics and small molecules are providing much better levels of evidence than what is available for the longer existing drugs due to more robust RCT evidence.

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 over prolonged periods to control their AE.

Candidates for systemic treatment may be either patients with a high composite score such as a SCORAD above 50 (scale definition), or 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 scores such as physician-reported 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 basis to classify disease severity.[1]

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 a sufficient tool to make a final decision on commencing 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[2], and to ascertain that potential trigger factors such as allergic contact dermatitis and concomitant skin infections have been excluded, and behavioural as well as educational reasons for poor responses have been adequately addressed.

Systemic medications for AE:

Conventional immunomodulatory drugs, such as systemic corticosteroids (SCS), ciclosporin (CyA), azathioprine (AZA), mycophenolate mofetil (MMF), enteric-coated mycophenolate sodium (EC-MPS) and methotrexate (MTX) were used traditionally for difficult-to-treat AE. Most were not licensed for this indication. The newer medications, whose efficacy has been demonstrated in high-quality studies and are approved by the European Medicines Agency (EMA), include the Janus kinase (JAK) inhibitors abrocitinib (Abro), baricitinib (Bari), and upadacitinib (Upa), as well as the biologics targeting IL-13 tralokinumab (Tralo), lebrikizumab (Lebri), the IL-13/4 receptor dupilumab (Dupi), and the IL-31 receptor nemolizumab (NEMO).

The following recommendations for systemic drugs are based on the living systematic review by Drucker et al.[3, 4], other published literature and medical considerations as well as expert opinion, and may differ from the legal licensing status and access routes, which are not uniform in European countries.

	Drug	Recommendation	Strengh	Label ǂ	Dose ǂ	Appli-cation	Certainty of evidence (GRADE RATING) ǂǂ
Conventional immunomodulatory drugs	Ciclosporin	We **recommend** ciclosporin to achieve disease control in AE patients who are candidates for systemic treatment.	↑↑	≥ 16 years severe AE	adults: 2.5-5 mg/kg per day children: 2.5-5 mg/kg per day	oral	Network meta-analysis from 2022[4, 5]: Higher dose ⊕⊕⊕◯ MODERATE change in signs*, QoL* ⊕⊕◯◯ LOW itch Lower dose ⊕⊕⊕◯ MODERATE change in signs* ⊕⊕◯◯ LOW QoL, itch
	Methotrexate	We **suggest** methotrexate in AE patients who are candidates for systemic treatment.	↑	off-label	adults: 5-25 mg per week children: 0.3–0.4 mg/kg per week (see guideline text)	oral or s.c.	Network meta-analysis from 2022[4, 5]: ⊕⊕◯◯ LOW change in signs, Qol, itch
Interleukin-13-Inhibitors	Dupilumab	We **recommend** dupilumab in AE patients who are candidates for systemic treatment.	↑↑	≥ 6 months severe AE; ≥ 12 years moderate-severe AE	age- and weight-adjusted 200–600 mg Q2W-Q4Q (see guideline text)	s.c.	Network meta-analysis from 2024[4, 6]: ⊕⊕⊕⊕ HIGH EASI*, POEM*, PPNRS*, DLQI*
	Lebrikizumab	We **recommend** lebrikizumab in AE patients, who are candidates for systemic treatment.	↑↑	≥ 12 years moderate-severe AE	500 mg day 1 and 15 followed by 250 mg Q2W-Q4W, from week 24 onwards, generally Q4W (see guideline text)	s.c.	Network meta-analysis from 2024[4, 6]: ⊕⊕⊕⊕ HIGH POEM* ⊕⊕⊕◯ MODERATE EASI*, DLQI* ⊕⊕◯◯ LOW PPNRS*
	Tralokinumab	We **recommend** tralokinumab in AE patients, who are candidates for systemic treatment.	↑↑	≥ 12 years moderate-severe AE	600 mg day 1 followed by 300 mg Q2W-Q4W (see guideline text)	s.c	Network meta-analysis from 2024[4, 6]: ⊕⊕⊕⊕ HIGH POEM* ⊕⊕⊕◯ MODERATE PPNRS*, DLQI* ⊕⊕◯◯ LOW EASI*
Interleukin-31-Inhibitors	Nemolizumab	We **recommend** nemolizumab in AE patients, who are candidates for systemic treatment.	↑↑	≥ 12 years moderate-severe AE	60 mg day 1 followed by 30 mg Q4W-Q8W (see guideline text)	s.c	Network meta-analysis from 2025[3, 4]: ⊕⊕⊕◯ MODERATE EASI*, POEM*, DLQI*, PPNRS*
JAK-Inhibitors	Abrocitinib	We **recommend** abrocitinib in AE patients who are candidates for systemic treatment.	↑↑	≥ 12years moderate-severe AE	100-200 mg per day based on disease burden and risk factors adults age ≥ 65: 100 mg per day (see guideline text)	oral	Network meta-analysis from 2024[4, 6]: 100 mg ⊕⊕⊕⊕ HIGH EASI*, POEM* ⊕⊕⊕◯ MODERATE PPNRS*, DLQI* 200 mg ⊕⊕⊕⊕ HIGH EASI*, POEM*, DLQI* ⊕⊕⊕◯ MODERATE PPNRS*

	Baricitinib	We **recommend** baricitinib in AE patients who are candidates for systemic treatment.	↑↑	≥ 2 years moderate-severe AE	adults: 2 or 4 mg per day adults age ≥ 65: 2 mg per day children: 2-4 mg per day weight-adjusted (see guideline text)	oral	Network meta-analysis from 2024[4, 6]: 2 mg ⊕⊕⊕◯ MODERATE EASI*, POEM*, PPNRS*, DLQI* 4 mg ⊕⊕⊕⊕ HIGH POEM*, PPNRS* ⊕⊕⊕◯ MODERATE EASI*, DLQI*
	Upadacitinib	We **recommend** upadacitinib in AE patients who are candidates for systemic treatment	↑↑	≥ 12 years moderate-severe AE	adults: 15 or 30 mg per day adults age ≥ 65: 15 mg per day children (≥ 30 kg bw): 15 mg per day (see guideline text)	oral	Network meta-analysis from 2024[4, 6]: 15 mg ⊕⊕⊕⊕ HIGH EASI* ⊕⊕⊕◯ MODERATE POEM*, PPNRS* 30 mg ⊕⊕⊕⊕ HIGH EASI*, POEM*, PPNRS*

ǂ In accordance with SmPC and EMA approval. Cost coverage and approval may vary between countries
ǂǂ Short term (8-16 weeks) vs placebo; * = statistically significant superiority over placebo
AE = atopic eczema; DLQI = Dermatology Life Quality Index; EASI = Eczema Area and Severity Index; POEM = Patient-Oriented Eczema Measure; PPNRS = Peak Pruritus Numerical Rating Scale

Vaccination prior to the initiation of systemic treatment and during systemic treatment:

Vaccination before starting systemic therapy for AE is an important part of patient management, especially because many systemic treatments can suppress the immune system and potentially affect vaccine efficacy and safety. Systemic therapies, especially immunosuppressants, can increase susceptibility to infections, reduce vaccine effectiveness, and make live vaccines potentially dangerous. Updating necessary vaccinations should be considered before commencing therapy whenever possible. However, each systemic therapy class affects vaccination strategies differently.[7-9]

1. Administer vaccines ideally before starting treatment

- Live vaccines (e.g., measles, mumps, and rubella (MMR), varicella, yellow fever) should be administered at least 4 weeks before starting systemic therapy.
- Inactivated vaccines (e.g., influenza, COVID-19, pneumococcal, or inactivated zoster vaccination) can usually be given up to the start of therapy, though ideally ≥2 weeks before, to optimize the vaccine effect.

2. Assess vaccination history and immunity

- Serologic testing for measles, varicella, hepatitis B, etc. should be considered, if status is unclear and live vaccines are being considered.
- Ensure up-to-date status with:
    - Influenza (annually)
    - Pneumococcal (PCV20 or PCV15 + PPSV23)
    - Diphtheria, Tetanus, Pertussis (DTP) (every 10 years)
    - Hepatitis A & B (as indicated)
    - Human Papillomavirus (HPV) (as per age)

3. Vaccination during systemic therapy

- Avoid giving live vaccines during systemic immunosuppressive treatment.
- For JAK-Inhibitors or immunosuppressants, treatment may need to be interrupted for weeks before administering live vaccines (per product-specific recommendation).
- In specific situations a shorter interval may be discussed together with an infectious disease specialist.
- As all biologics, which are currently (November 2025) approved for the treatment of AE, are not considered immunosuppressive, inactivated vaccines can be given during treatment.
- Inactivated vaccines (non-live attenuated vaccines) can be safely used in patients receiving conventional immunomodulatory drugs or JAK-Inhibitors, but the immunogenicity of the vaccine may be reduced.
- As for live vaccinations and systemic therapy with biologics, we acknowledge that SmPCs generally recommend against their administration on treatment, and these should therefore only be used with careful consideration of the risks and benefits.

Switching systemic treatment:

Switching between systemic therapies in AE is a nuanced clinical decision that depends on treatment response, side effects, patient preferences, comorbidities, and pharmacologic factors (e.g., immunosuppression, drug half-life, vaccine timing). This guideline can only provide a general overview, as the exact decision-making process is complex.

Common reasons for switching to another therapy include:

- Insufficient response (partial or no improvement)
- Loss of efficacy over time
- Adverse effects or toxicity
- Patient burden or nonadherence (e.g., lab monitoring, injections)
- Change in clinical needs (e.g., comorbidities, pregnancy)
- Access/cost issues

1. From immunosuppressant to biologic

- Often direct switching is possible.
- Some clinicians let medication regimes overlap briefly to prevent flares of AE (especially from ciclosporin to dupilumab).
- For instance, continue ciclosporin for 2–4 weeks after starting dupilumab, then taper off. Similar overlap can be considered for other immunosuppressants.
- Watch for rebound of AE if immunosuppressant is stopped abruptly.

2. From biologic to JAK-Inhibitor

- Usually no washout needed; direct switching is common.
- Biologics have a long half-life (~21 days), but no significant immunosuppression, so overlapping medications are generally safe.

3. Between JAK-Inhibitors or from JAK- Inhibitors to biologic

- JAK-Inhibitors have short half-lives (hours to days).
- No need for overlapping medications in case of switching between JAK-Inhibitors.
- When switching from a JAK-Inhibitor to a biologic, an overlap of medications is usually helpful, especially in patients with high risk of flares.

4. Switching between biologics

- This is sometimes done, for example changing between IL-13 inhibitors (e.g. dupilumab → tralokinumab) or from IL-13 inhibitor to IL-31 inhibitors or vice versa.
- Direct switching is often performed with minimal issues.

Adaptation of frequency and interval in systemic therapy:

Adapting the treatment frequency and interval of systemic therapies (often off-label) for AE can help balance disease control with safety, tolerability, and patient convenience. This is often referred to as treatment optimization, maintenance adjustment, or step-down therapy once control is achieved.

Conventional immunomodulatory drugs:

- Tapering dose or frequency is common once control is achieved (often after 3–6 months)
- Long-term use may be limited due to safety issues (organ toxicity, lab monitoring)

Biologics:

- Interval extension in patients with sustained remission
- Can reduce cost, injection burden, and adverse events (e.g., conjunctivitis, facial erythema)
- Rebound risk is generally low, especially if AE is well-controlled
- Complete discontinuation is typically not pursued unless sustained remission has been achieved for several months.
- For tralokinumab, lebrikizumab and nemolizumab dose reduction is built into the label
    - **Tralokinumab**: After 16 weeks of treatment, patients who achieve good disease control may reduce intervals to **q4w.**
    - **Lebrikizumab**: After 16 weeks of treatment, patients achieving good disease control may reduce intervals to **q4w**. After 24 weeks, a mandatory interval reduction to **q4w** applies.
    - **Nemolizumab**: After 16 weeks, patients achieving good disease control may reduce intervals to **q8w.**
- Other adjustments to the intervals are off-label but common also for dupilumab

JAK-Inhibitors:

- More flexibility in dose adjustment vs biologics
- A typical approach is to start on the higher dose and then reduce to the lower licensed dose upon achieving good disease control.
- Note: JAK-Inhibitors have short half-lives (≈8–14 hours), so dose frequency (daily) cannot be changed safely, but dose size can

References

1. Schmitt J, Spuls PI, Thomas KS, Simpson E, Furue M, Deckert S 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(4):800–7.
2. 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(4):1501–7.
3. Drucker AM, Walwyn C, Chu C, Yiu ZZN, Rochwerg B, Di Giorgio S et al. Living network meta-analysis to compare nemolizumab against other available targeted systemic treatments for atopic dermatitis. *Br J Dermatol* 2025;193(3):548–52.
4. Drucker AM, Flohr C, Ellis AG, Prieto-Merino D, Rochwerg B, Bohdanowicz M et al. Systemic immunomodulatory treatments for atopic dermatitis: a living systematic review and network meta-analysis. 2025. Available at: https://eczematherapies.com/research/
5. Drucker AM, Morra DE, Prieto-Merino D, Ellis AG, Yiu ZZN, Rochwerg B et al. Systemic Immunomodulatory Treatments for Atopic Dermatitis: Update of a Living Systematic Review and Network Meta-analysis. *JAMA Dermatol* 2022;158(5):523–32.
6. Drucker AM, Lam M, Prieto-Merino D, Malek R, Ellis AG, Yiu ZZN et al. Systemic Immunomodulatory Treatments for Atopic Dermatitis: Living Systematic Review and Network Meta-Analysis Update. *JAMA Dermatol* 2024;
7. Eichenfield LF, Boguniewicz M, Lauren CT, Leung DYM, Levy ML, Schneider LC et al. Systemic Therapy for Atopic Dermatitis in Children and Adolescents: A US Expert Consensus. *Dermatology* 2024;240(5-6):897–909.
8. Fan R, Cohen JM. Vaccination Recommendations for Psoriasis and Atopic Dermatitis Patients on Biologic Therapy: A Practical Guide. *Yale J Biol Med* 2022;95(2):249–55.
9. Care AG-DoHaA. Australian Immunisation Handbook: Recommended timing of live vaccine administration for people receiving immunosuppressive therapies. 2025. Available at: https://immunisationhandbook.health.gov.au/resources/tables/table-recommended-timing-of-live-vaccine-administration-for-people-receiving-immunosuppressive-therapies? (last accessed 06.08.2025).