

## 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.

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 TCS in patients who need large amounts of potent TCS for vast body areas 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 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.<sup>1</sup>

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<sup>2</sup>), 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. 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 running COVID-19 pandemic, as indicated by recommendations from the European Taskforce for Atopic Dermatitis.<sup>3,4</sup> 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<sup>5</sup>, other published literature and medical considerations, and may differ from the legal licensing status and access routes, which are not uniform in European countries.

## **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; 800-807.
- [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; 1501-1507.
- [3] Thyssen JP, Vestergaard C, Barbarot S, de Bruin-Weller MS, Bieber T, Taieb A, 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.
- [4] Wollenberg A, Flohr C, Simon D, Cork MJ, Thyssen JP, Bieber T, 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.
- [5] Drucker AM. Systemic immunomodulatory treatments for atopic dermatitis: a living systematic review and network meta-analysis. 2020. <https://eczematherapies.com/research/>.