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An approach for the transition from systemic immunosuppressants to dupilumab

Dear Editor,

Atopic dermatitis (AD) is a complex and heterogeneous chronic inflammatory skin disease. A subset of patients requires systemic immunosuppressants including cyclosporine A (CsA), azathioprine (AZA), mycophenolate mofetil (MMF)/mycophenolic acid (MPA) and methotrexate (MTX).¹ Dupilumab is the first biologic for treatment of AD, mostly started in patients with insufficient effectiveness or side effects of systemic immunosuppressants. In daily practice, approximately 65% of patients are still using systemic immunosuppressants when starting dupilumab.² Although a significant reduction in itch can be present by week 2, clinically relevant AD improvement continues until at least 8–12 weeks of dupilumab treatment.^{2,3} Additionally, abrupt discontinuation of systemic

immunosuppressants is unpreferable due to a possible rebound phenomenon.^{1,3–6} We found that tapering the immunosuppressants after the start of dupilumab results in a seamless transition between therapies. In our patients ($n = 88$), we did not find side effects resulting from this combination treatment.^{2,5}

Based on clinical experience in 44 patients, we propose an approach for the transition from conventional systemic immunosuppressants (excluding oral corticosteroids) to dupilumab (Table 1, Fig. 1). This approach is only applicable in the absence of serious side effects. The timing of consultations (live/telemedicine) can be adjusted to local protocols. We recommend to assess disease control at every visit using Atopic Dermatitis Control Tool (ADCT) or Recap of atopic eczema (RECAP).^{7,8} However, it should not replace physician's and patient's shared decision-making. Note that this is a clinical guideline based on expert opinion and that decisions can be affected by many factors, e.g. current symptoms, season, patient's mental state, relative patient burden of signs and symptoms, and experiences with tapering the immunosuppressant. We therefore only aim to provide guidance, but no strict cut-off levels for achieving disease control. Additionally, a prospective study on the utility of this approach would be of added value for validating this transition approach.

For all systemic immunosuppressants, we recommend to maintain the dose that was used at the start of dupilumab for the first 8 weeks. After 8 weeks, the dose of the immunosuppressant can be reduced in case of disease control. From that moment, the approach differs for patients using CsA and other immunosuppressants in order to prevent a rebound phenomenon in CsA-treated patients. In patients treated with MTX/AZA/MMF/MPA, the dose can be reduced to ~50% until the next visit (at approximately 12 weeks). In good responders, we suggest to discontinue the immunosuppressant after 12 weeks of dupilumab treatment (applicable in ~40% of our patients). Due to the high risk of a rebound phenomenon, we propose tapering more gradually in CsA-treated patients. In case of disease control after 8 weeks, the dose can be reduced to ~75% of the dose at the start of dupilumab treatment. In good responders, the CsA dose will be reduced to ~50% after 10 weeks of treatment and subsequently ~25% after 12 weeks of treatment. CsA can be discontinued in good responders after approximately 14 weeks of treatment (applicable in ~60% of our patients).

In case of insufficient disease control at a visit, immunosuppressants will be continued at the same dose until the next visit. Additionally, topical treatment using moisturizers, topical corticosteroids and calcineurin inhibitors should be optimized. Dupilumab discontinuation or continuation of the systemic immunosuppressants on the long term at the lowest possible dose should be considered when: (i) disease control is not reached after two subsequent visits with a similar dose, (ii) patients are treated with dupilumab for at least 12 weeks, and (iii) topical treatment is optimal. With many new drugs being developed, this might be also the point where a switch to a different drug can be considered.

Table 1 Approach for transition from conventional immunosuppressants to dupilumab monotherapy

Week 0–8		✓ Disease control ✓ Week 8 – . . .	✗ No disease control ✗
CsA	Maintain dose [eg 2dd 100 mg (week 0–8)]	Every 2 weeks (week 10, 12, 14, 16, 18) 25% dose reduction (of dose at the start) Earliest discontinuation: 14 weeks of dupilumab treatment [e.g. 2dd 75 mg (week 8–10) – 2dd 50 mg (week 10–12) – 2dd 25 mg (week 12–14) – discontinue (week 14)]	Current dose used for (≈) <8 weeks: Continue immunosuppressant at same dose for another 4 weeks Current dose used for (≈) >8 weeks: Consider continuation of concomitant immunosuppressant at the lowest possible, effective dose on the long term and/or Consider discontinuation of dupilumab treatment
MTX AZA MPA MMF	Maintain dose [eg MTX 15 mg weekly (week 0–8)]	Every 4 weeks (week 12, 16, 20, 24, 28) 50% dose reduction (of dose at the start) Earliest discontinuation: 12 weeks of dupilumab treatment [e.g. 7.5 mg weekly (week 8–12) – discontinue (week 12)]	

All steps are guided by the assessed disease control and physicians' and patients' shared decision-making. Atopic Dermatitis Control Tool (ADCT) or Recap of atopic eczema (RECAP) can be used to determine disease control. Note that this is a general approach for several systemic immunosuppressants used in the treatment of moderate-to-severe AD, including CsA, MTX, AZA, MPA and MMF. Some formulations will not allow, e.g. 50% of the original dose, or doses may not be effective. We suggest to make a rational treatment decision based on experience with the specific immunosuppressant.

In conclusion, we propose a practical treatment approach for the transition from systemic immunosuppressants to dupilumab based on shared decision-making.

Conflicts of interest

L.E.M. de Wijs, H.B. Thio and A.C.M. Kunkeler have none to declare. J.P. Thyssen attended advisory boards for Eli Lilly, Regeneron, Pfizer, LEO Pharma, AbbVie and Sanofi Genzyme; received speaker honorarium from LEO Pharma, AbbVie,

Regeneron and Sanofi Genzyme; and received research grants from Regeneron and Sanofi Genzyme. C. Vestergaard has acted as speaker and/or investigator for Sanofi Genzyme, AbbVie, LEO Pharma, Galapagos, Pierre Fabre Dermo-Cosmetique and Novartis. D.J. Hijnen has been an investigator for AbbVie, LEO Pharma, Galderma, MedImmune/AstraZeneca, Novartis and Sanofi/Regeneron; and consultant for Regeneron/Sanofi, LEO Pharma, MedImmune/AstraZeneca, Novartis, Incyte, Janssen, Pfizer and Lilly. T. Biedermann has been an institution investigator for AbbVie, LEO Pharma, Novartis, Sanofi/Regeneron, Janssen, Pfizer and Lilly; consultant for Alk-Abelló, Mylan, Novartis and Sanofi/Regeneron; and received honorarium for talks or research grant from Alk-Abelló, Celgene, Mylan, Novartis, Phadia/Thermo Fisher and Sanofi/Regeneron.

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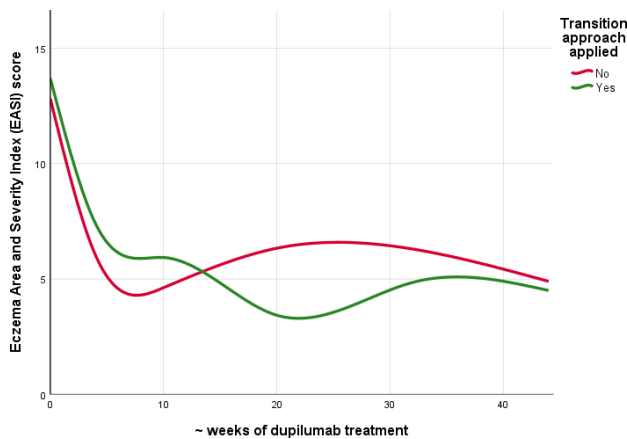


Figure 1 Disease severity of patients with and without the use of the proposed transition approach. *Green line*: Eczema Area and Severity Index (EASI) scores for AD patients ($n = 44$) with concomitant systemic immunosuppressants that were slowly tapered and discontinued after at least 12–14 weeks of dupilumab treatment, according to the transition approach described in the current article. *Red line*: EASI scores for AD patients ($n = 61$) that discontinued immunosuppressants at the start or in the first 12–14 weeks of dupilumab treatment. EASI scores were measured at baseline, after approximately 4 weeks, 8–12 weeks, 16–24 weeks, 28–36 weeks and 40–48 weeks of treatment.

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Primary cutaneous follicle centre lymphoma, spindle cell type, presenting with multicentre figural erythema and complete remission after intralesional injections of ultra-low-dose Interferon alpha-2a

To the Editor,

A 56-year-old man presented with a 4-year history of multiple itchy, annular, erythematous macules and plaques with

centrifugal growth, located on his right abdomen and left flank (Fig. 1a). He had no previous history of skin diseases and denied any other symptoms.

Histological analysis of a skin biopsy specimen revealed dermal lymphocytic infiltrates with partly spindle-shaped centrocytes and centroblasts, small T-lymphocytes and few eosinophils. The B cells expressed CD20, bcl-2 and bcl-6. Immunostaining with Ki-67 showed a proliferative activity of 60%. Physical examination, laboratory tests, chest, abdominal and pelvic computed tomography and bone marrow biopsy showed no evidence for extracutaneous manifestations. The clinical, histological and immunophenotypical data led to the diagnosis of primary cutaneous follicle centre lymphoma (PCFCL), spindle cell type.

A 21-day course of doxycycline 200 mg/die was given without significant improvement.¹ Due to the multifocal lesions, neither radiation therapy nor surgical excision were reasonable treatment alternatives. We decided on a course of intralesional interferon alpha-2a (INF α -2a) at a dose of 3 million units (MU) every 3–7 weeks. The dosage of 3 MU was divided in 5–7 injection areas, and the plaques improved significantly not only on the injection sites but also between the injected areas (Fig. 1b). The treatment was repeated four times and induced nearly complete remission after a cumulative dose of 15 MU (Fig. 1c,d). Because of a mild clinical relapse after 4 months, three more injections were performed at similar intervals of 2–7 weeks, and a complete remission was achieved after 24 MU. Mild flu-like symptoms were treated with paracetamol.

Primary cutaneous follicle centre lymphoma (PCFCL) is an indolent primary cutaneous B-cell lymphoma. It manifests most commonly in the head and neck area of adults. Clinical manifestations on the trunk were originally described as reticulohistiocytoma of the dorsum or Crosti's lymphoma.² Occasionally, PCFCL can present with a predominant spindle cell

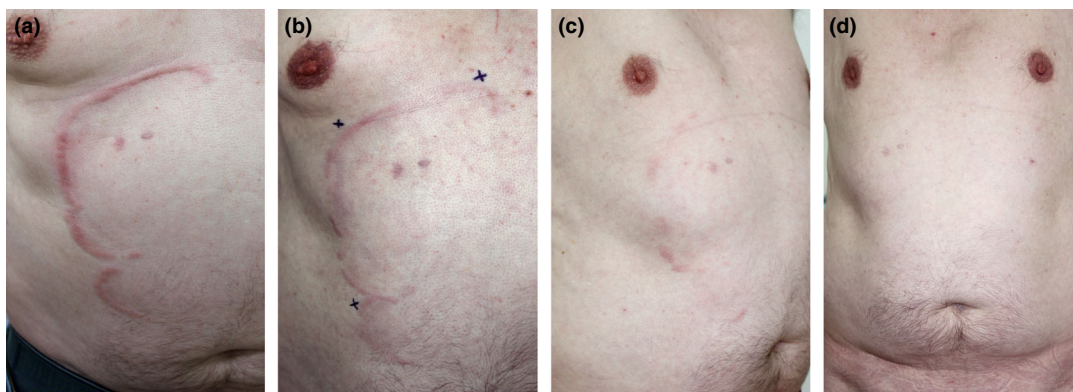


Figure 1 Clinical course under intralesional therapy with interferon alpha-2a. (a) Annular indurated erythema before therapy. (b) The marks show the injection sites before the second injection. (c) Clinical presentation after the third injection. (d) Complete remission after the fifth injection.