Switching between JAK Inhibitors in Patients with Atopic Dermatitis: Unanswered Questions in Daily Clinical Practice

Dear Editor,

Data on switching between agents in patients with atopic dermatitis (AD) are scarce (1-3). We report the case of a patient with severe AD and inadequate response to upadacitinib who showed a complete response after switching to abrocitinib. A 23-year-old male patient with severe AD was enrolled in the Measure Up double-blind, placebo-controlled, phase 3 randomized clinical trial. At baseline, the Eczema Area Severity Index (EASI) was 50.6, the Investigator's Global Assessment (IGA) was 4, the affected Body Surface Area (BSA) was 80%, and the Worst Pruritus-Numeric Rating Scale (WP-NRS) was 10/10 (Figure 1). At week 124, the patient discontinued participation in the trial, while EASI was 9.2, IGA 3, BSA 20%, and WP-NRS 5/10 at the time.

After one month off treatment, and while expecting unblinding, the patient again presented with exacerbation of AD, since EASI was 45.6, IGA 4, BSA 80%, and WP-NRS 10/10. At that point of time, access to both dupilumab and tralokinumab was not available in Greece, while upadacitinib was avoided due to inadequate patient satisfaction, partly due to recurrent ocular herpes simplex infections during the previous upadacitinib treatment. The patient was prescribed abrocitinib 200 mg daily. One month after initiation of therapy, the patient achieved complete control of the disease (EASI 0.0, IGA 0, BSA 0%, and WP-NRS 0/10) (Figure 2). This has been maintained with no reported adverse events after 12 months of continuous treatment. After unblinding, the patient was confirmed to have received 15 mg of upadacitinib daily during his participation in the clinical trial.

When to switch agents in the treatment of patients with severe AD if the response is not adequate, and what agent to switch to, is an issue that is not clearly defined. Data available from the JADE EXTEND study concluded that patients failing to achieve efficacy outcomes with dupilumab can benefit from

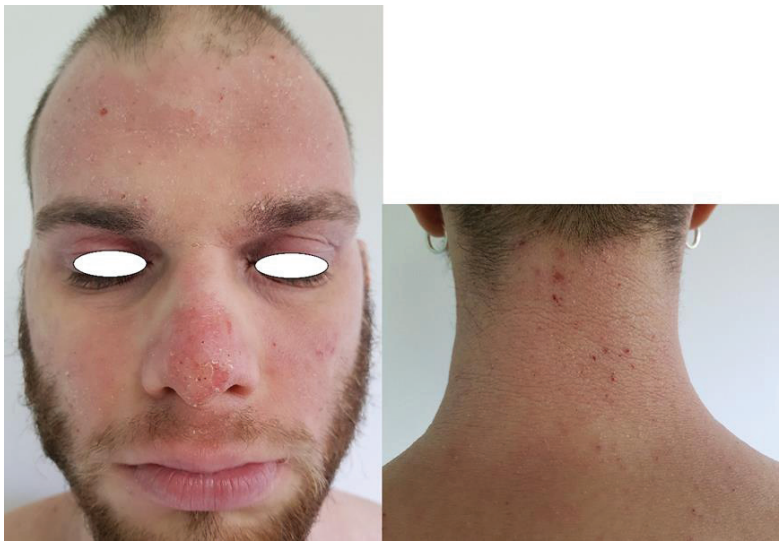

Figure 1. Patient at baseline before starting treatment with upadacitinib 15 mg.

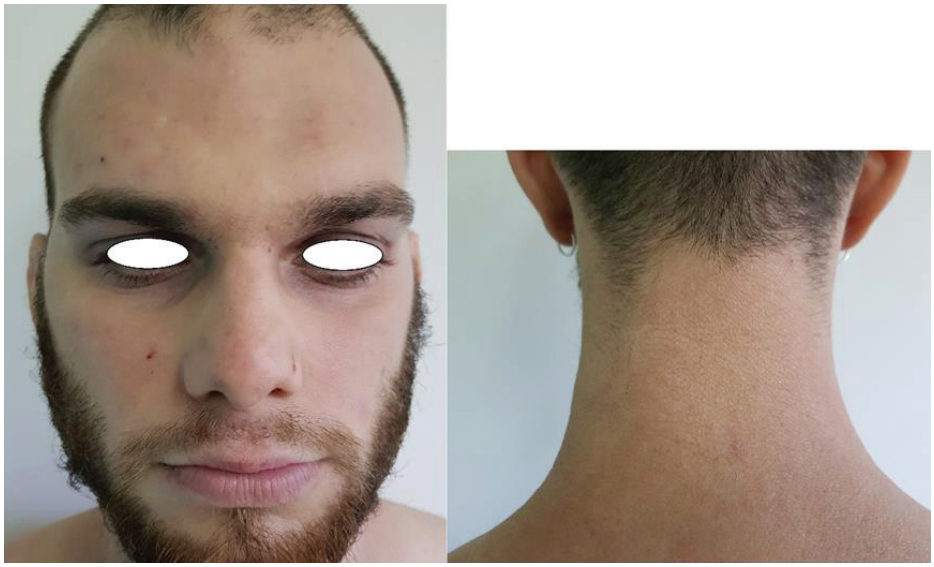

Figure 2. Patient after one month of treatment with 200 mg of abrocitinib.

switching to both doses of abrocitinib (1). However, a number of patients in this study did not achieve efficacy outcomes even after treatment with 200 mg of abrocitinib. Furthermore, sub-population analysis of the JADE EXTEND study, evaluating difficult-to-achieve patient-oriented outcomes such as Patient Oriented Eczema Measure (POEM) ≤2 and Dermatology Life Quality Index (DLQI) ≤1, further emphasized that switching might be beneficial for a significant number of patients, but unmet need was still evident for some of them (4).

The literature lacks data on switching between Janus kinase (JAK) inhibitors in AD. Treat-to-target might be different for early control of the disease, as baricitinib and upadacitinib were assessed at 16 weeks, while abrocitinib was assessed at 12 weeks in the pivotal studies. Regarding the present case, the different clinical response obtained cannot be clearly defined since abrocitinib and upadacitinib are both selective JAK1 inhibitors. Consequently, the targeted inflammatory pathways and the expected regulation of immune functionality could be similar. We may assume that the high dose of abrocitinib vs. the low dose of upadacitinib could have accounted for the improved response. However, it is impossible to assess whether clinical outcomes would have been comparable with the administration of the full dose of upadacitinib 30 mg daily or whether usage of a half-dose of abrocitinib 100 mg daily would have also resulted in inadequate response in the same patient. Switching within the same class of treatment agents has also been a heavily-debated issue for psoriasis for many years; however, recent data suggest that switching between interleukin (IL)-17A antagonists may be of benefit to some patients, although the underlying mechanism of action is still under investigation (5,6).

Treatment modification in inadequate response could include: up-dosing, adding classical treatments like methotrexate to the JAK inhibitor, switching to monoclonals, or switching to another JAK inhibitor, taking into account published metanalyses of the efficacy of novel agents. Consequently, there is an unmet need to determine an algorithmic step-by-step approach of treat-to-target and switching or adding treatment in the current landscape of AD therapy. Different policies of reimbursement in different countries, along with a lack of comparative studies, may complicate adding such recommendations to existing treatment guidelines.

References:

1. Shi VY, Bhutani T, Fonacier L, Deleuran M, Shumack S, Valdez H, *et a*l. Phase 3 efficacy and safety of abrocitinib in adults with moderate-to-severe atopic dermatitis after switching from dupilumab (JADE EXTEND). J Am Acad Dermatol. 2022;87:351-8.
2. Gao DX, Kahn JS, Cohen SR, Griffiths DM, Fiumara K, Lam A, et al. Results of Switching From Tofacitinib to Upadacitinib in Patients With Atopic Dermatitis: A Retrospective Medical Record Review. Dermatitis. 2021;32:e165-e166.
3. Hayama K, Fujita H. Improvement of dupilumab-associated conjunctivitis after switching to upadacitinib in a patient with atopic dermatitis. Dermatol Ther. 2022;35:e15575.
4. Makris M, Gregoriou S, Koulias C, Zhang F, Clibborn C, Myers DE, *et al.* Abrocitinib in the Treatment of Moderate-to-Severe Atopic Dermatitis

Not Responding Adequately to Dupilumab Treatment: An Analysis of Patient-Reported Outcomes in JADE EXTEND. Poster presented at the European Academy of Allergy and Clinical Immunology (EAACI) Hybrid Congress; July 1-3, 2022; Prague, Czech Republic.

5. Georgakopoulos JR, Phung M, Ighani A, Lam K, Yeung J. Biologic switching between interleukin 17A antagonists secukinumab and ixekizumab: a 12-week, multicenter, retrospective study. J Eur Acad Dermatol Venereol. 2019;33:e7-e8.
6. Georgakopoulos JR, Phung M, Ighani A, Yeung J. Efficacy and safety of switching to ixekizumab in secukinumab nonresponders with plaque psoriasis: A multicenter retrospective study of interleukin 17A antagonist therapies. J Am Acad Dermatol. 2018;79:155-7.

Styliani Mastraftsi, Michail Bakakis, Aikaterini Tsiogka, Ileana Afroditi Kleidona, Stamatios Gregoriou

National and Kapodistrian University of Athens, Faculty of Medicine, 1st Department of Dermatology and Venereology, Andreas Sygros Hospital for Skin and Venereal Diseases, Athens, Greece

Corresponding author:
Styliani Mastraftsi, MD
5, Ionos Dragoumi str.
16121, Athens, Greece
stmastraftsi@yahoo.com,

Received: July 3, 2023
Accepted: August 10, 2023