Received: 15 April 2024 | Accepted: 8 May 2024

DOI: 10.1111/jdv.20132

JEADV JOURNAL OF THE EUROPEAN ACADEMY OF DERMATOLOGY & VENEREOLOGY

LETTER TO THE EDITOR

Combination of Janus kinase inhibitor and biologic for recalcitrant severe atopic dermatitis

Dear Editor,

Targeted immune inhibitors (biologics) and Janus kinase (JAK) inhibitors have revolutionized the management of moderate-to-severe atopic dermatitis (AD).[1,2] However, some patients remain insufficiently controlled with these new systemic immunomodulatory treatments (SITs). Little is known about efficacy and safety of combining the two types of drug classes in patients with recalcitrant or difficult-to-treat AD.[3–5]

We retrospectively collected data from February 2022 to January 2024 from a real-life monocentric cohort of adults and adolescents treated with a combination of a JAK inhibitor (JAKi) and a biologic, for poor-responding severe AD, defined by a validated Investigator Global Assessment scale for Atopic Dermatitis (vIGA-AD) of ≥3 despite a well-conducted treatment with either a JAKi or a biologic only. The primary outcome was the percentage of patients who achieved a vIGA-AD of 0 (clear) or 1 (almost clear) and/or an improvement of at least 75% of SCORing Atopic Dermatitis (SCORAD 75), and a reduction in Peak Pruritus Numeric Rating Scale (PP-NRS) of ≥4 from baseline, during the follow-up. All adverse events were reported during the study. The study and data collection were approved by the institutional review boards of Cliniques universitaires Saint-Luc and Université catholique de Louvain. Written informed consent was obtained from all study participants.

Four patients (three adults and one adolescent) were enrolled, with a median ± interquartile range (IQR) follow-up duration of 10.3 ± 12.7 months. Patients' characteristics are detailed in Table 1. All patients presented with severe recalcitrant AD before combined therapy (median vIGA-AD 4, SCORAD 52, PP-NRS 7.5), despite ongoing treatment with tralokinumab ($n = 2$) or upadacitinib ($n = 2$). All patients had been shifted from biologic to JAKi or vice-versa prior to considering a combination. The shift from tralokinumab to dupilumab was not proposed for patient 3 and 4 for various reasons including the need, in terms of quality of life, for rapid symptoms relief after several unsuccessful treatment attempts, or the unavailability of dupilumab for teenagers at the time in Belgium. The four patients reached the primary outcome within a median of 2.5 months, with a combination of tralokinumab and upadacitinib (Figure 1). Combination was discontinued after reaching the endpoint (two stopped tralokinumab and two stopped upadacitinib). All patients relapsed but repeat-treatment was effective in all cases.

No major adverse events were reported. No treatment-induced conjunctivitis nor injection-site reactions were observed. Altered lipid status was detected in 3/4 patients and transaminitis in one patient.

For patients with difficult-to-treat AD, guidelines for use of these new agents in combination with each other are not established. This real-life study suggests effectiveness and safety of combined SITs for these patients.

Studies reporting such combinations only focused on poor responders to dupilumab, for whom rescue therapy with a JAKi was initiated.[3–5] To the best of our knowledge, the current study is the first to report experience of tralokinumab and upadacitinib combination therapy.

Combining two SITs probably results in better blockage of interleukin-13 and, more broadly, of other cytokines involved. The benefit of such a combination in these refractory patients may be linked to the association of a biologic for long-term control with a faster-acting treatment.

The 'treat-retreat strategy', demonstrated to be effective in two of our patients re-treated with tralokinumab, has previously been proven effective with upadacitinib.[6] Relapse was observed in all cases when one SIT was discontinued, proving the effectiveness of the combination rather than the failure of each individual SIT.

Limitations of this study are the small size of the patient cohort, and the retrospective and monocentric design.

In conclusion, current approved monotherapies are insufficient for some patients with difficult-to-treat AD, probably due to the heterogeneous nature of this disease. Concomitant association of a biologic and a JAKi is an innovative option for treating refractory AD. Accessibility, particularly in terms of reimbursement for such associations, remains a limiting factor. Moreover, benefits and risks of combined treatment should be further investigated and carefully evaluated for each patient.

TABLE 1 Patients' demographics and clinical characteristics.

Patient n°	Sex	Age (years)	Co-morbidities	Previous systemic treatments	vIGA-AD before SIT 1	SIT 1	Reason for combined treatment	Scores before combined therapy	Combined therapy (SIT 1 + SIT 2)	Primary outcome	Attempt to discontinue combined treatment	Follow-up duration since combined therapy (months)
1	M	28	*Atopic*: RC *Non-atopic*: arterial hypertension	CyA (8 months), Dupilumab (4 months)	4	Upa	No clinical improvement after 19 months with Upa, failure of shift (Dupi)	vIGA-AD 3, SCORAD 56.6, PP-NRS 8	Upa 30 mg + Tralo	vIGA-AD 0/1: Yes SCORAD 75: Yes ≥4 points reduction in PP-NRS: Yes Reached after 3 months	vIGA-AD 2 7 days after stopping Upa, successful re-treatment	6.0
2	M	42	*Atopic*: A, RC *Non-atopic*: pulmonary sarcoidosis, Ehlers-Danlos syndrome, osteoporosis	Systemic GC (rescue therapy), CyA (10 months), Dupi (4 months), Bari 4 mg (9 months)	3	Tralo	No clinical improvement after 3 months with Tralo, failure of shifts (Bari, Dupi)	vIGA-AD 4, SCORAD 52.0, PP-NRS 9	Tralo + Upa 30 mg	vIGA-AD 0/1: Yes SCORAD 75: Yes ≥4 points reduction in PP-NRS: Yes Reached after 1 month	vIGA-AD 3 1 month after stopping Tralo, successful re-treatment	19.8
3	M	26	*Atopic*: RC, FA *Non-atopic*: none	Systemic GC (rescue therapy), CyA (7 months), Bari 4 mg (4 months)	4	Tralo	No clinical improvement after 5.5 months with Tralo, failure of shift (Bari)	vIGA-AD 4, SCORAD 31.9, PP-NRS 7	Tralo + Upa 30 mg	vIGA-AD 0/1: Yes SCORAD 75: Yes ≥4 points reduction in PP-NRS: Yes Reached after 2 months	vIGA-AD 3 9 months after stopping Tralo, successful re-treatment	14.7
4	F	15	*Atopic*: A, RC *Non-atopic*: none	Systemic GC (rescue therapy), CyA (4 months), Nemo (14 months)	4	Upa	No clinical improvement after 10 months with Upa, failure of shift (Nemo)	vIGA-AD 3, SCORAD not available, PP-NRS 4	Upa 15mg[a] + Tralo	vIGA-AD 0/1: Yes SCORAD 75: NA ≥4 points reduction in PP-NRS: Yes Reached after 6 months	vIGA-AD 2 10 days after stopping Upa, successful re-treatment	5.8

Abbreviations: A, asthma; Abro, abrocitinib; Bari, baricitinib; CyA, cyclosporine A; Dupi, dupilumab; F, female; FA, food allergy; GC, glucocorticoids; M, male; Nemo, nemolizumab; PP-NRS, Peak Pruritus Numeric Rating Scale; RC, rhinoconjunctivitis; SCORAD, SCORing Atopic Dermatitis; SCORAD 75, SCORAD score improvement of at least 75%; SIT, systemic immunomodulatory treatment; Upa, upadacitinib; vIGA-AD, validated Investigator Global Assessment scale for Atopic Dermatitis.

[a]Recommended dose for age and weight.

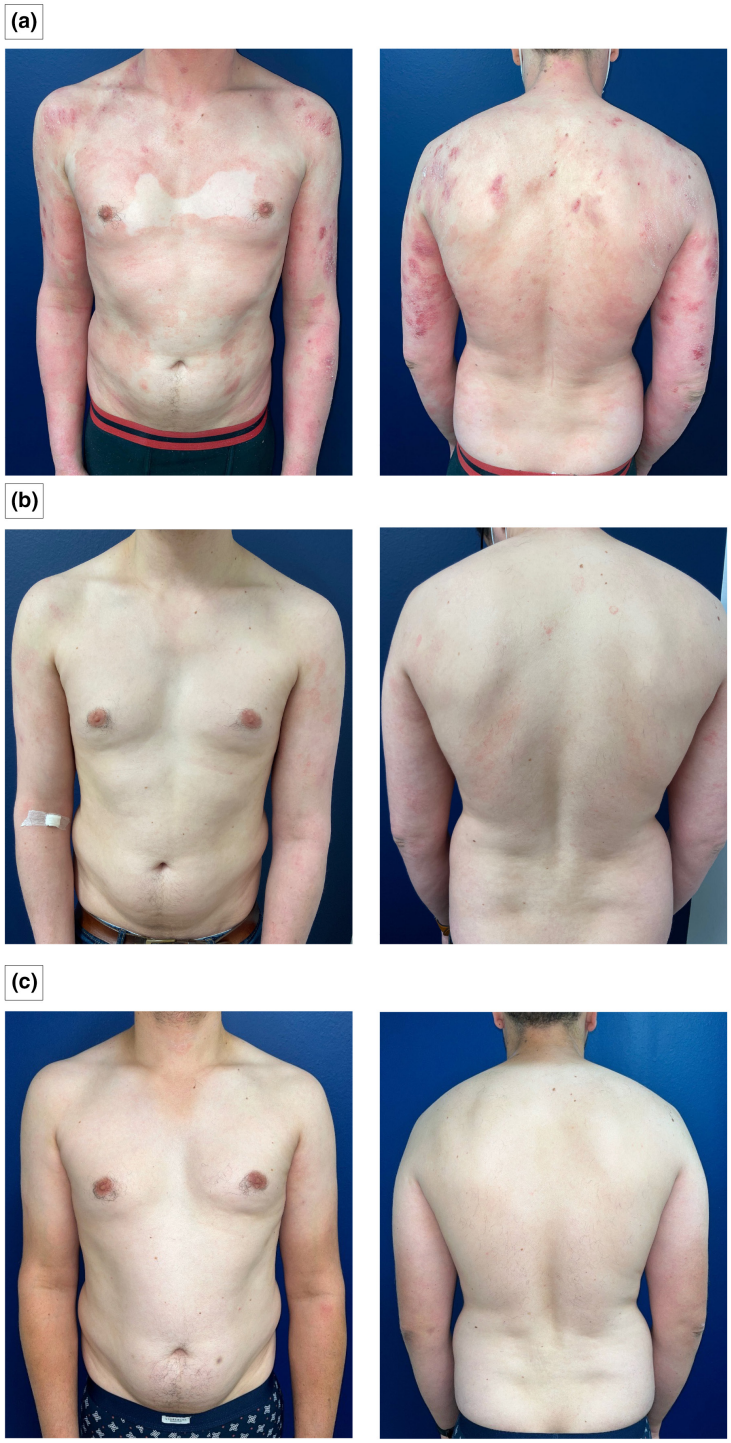

FIGURE 1 Patient 1 - Severe atopic dermatitis before treatment with upadacitinib (vIGA-AD 4) (a), insufficient clinical improvement with upadacitinib monotherapy (vIGA-AD 3) (b), clearance of eczema and relief from pruritus after 3 months with combined upadacitinib and tralokinumab therapy (vIGA-AD 0) (c). vIGA-AD, validated Investigator Global Assessment scale for Atopic Dermatitis.

ACKNOWLEDGEMENTS

Medical writing: We thank Dr. Mariana Andrade, M.D. (Andrade-Evrard SRL), who provided editorial assistance. Fees were funded by the authors.

FUNDING INFORMATION

Axel De Greef has a Ph.D. fellowship of the Fund for Scientific Research (F.R.S) – FNRS. The funder had no role in the design and conduct of the study; collection, management,

analysis and interpretation of the data; preparation, review or approval of the manuscript; and decision to submit the manuscript for publication.

CONFLICT OF INTEREST STATEMENT

Axel De Greef and Marie Baeck disclose their past participation on the tralokinumab advisory boards organized by LEO Pharma. Marie Baeck discloses her past participation on the upadacitinib advisory boards organized by AbbVie. Axel De Greef and Marie Baeck have previously participated as speakers in events sponsored by AbbVie. The authors declare that the current study was conducted in an independent manner.

DATA AVAILABILITY STATEMENT

Data sharing is not applicable to this article as no new data were created or analyzed in this study.

ETHICS STATEMENT

The patients in this manuscript have given written informed consent to publication of their case details.

Axel De Greef[1,2]
Marie Baeck[1,2]

[1]*Dermatology Department, Cliniques universitaires Saint-Luc, UCLouvain, Brussels, Belgium*
[2]*Institute of Experimental and Clinical Research (IREC), Pneumology, ENT and Dermatology Pole (LUNS), Université catholique de Louvain (UCLouvain), Brussels, Belgium*

Correspondence
Axel De Greef, Department of Dermatology, Cliniques universitaires Saint-Luc (UCLouvain), Avenue Hippocrate 10, B-1200 Brussels, Belgium.
Email: axel.degreef@saintluc.uclouvain.be

ORCID

Axel De Greef https://orcid.org/0000-0003-0713-8283
Marie Baeck https://orcid.org/0000-0003-0499-7939

REFERENCES

1. McLornan DP, Pope JE, Gotlib J, Harrison CN. Current and future status of JAK inhibitors. Lancet. 2021;398(10302):803–16. https://doi.org/10.1016/S0140-6736(21)00438-4
2. Schneider S, Li L, Zink A. The new era of biologics in atopic dermatitis: a review. Dermatol Pract Concept. 2021;11(4):e2021144. https://doi.org/10.5826/dpc.1104a144
3. Yang N, Chen L, Shao J, Jiang F, Liu J, Li Z. Dupilumab with concomitant Janus kinase inhibitor: a novel treatment strategy for atopic dermatitis with poor response to dupilumab. Br J Dermatol. 2022;187(5):828–30. https://doi.org/10.1111/bjd.21776
4. Peterson DM, Vesely MD. Remission of severe atopic dermatitis with dupilumab and rescue tofacitinib therapy. JAAD Case Rep. 2021;10:4–7. https://doi.org/10.1016/j.jdcr.2021.01.020
5. Shahriari N, Strober B, Shahriari M. JAK-inhibitors as rescue therapy in dupilumab-refractory severe atopic dermatitis: a case series of 6 patients. JAAD Case Rep. 2023;33:81–3. https://doi.org/10.1016/j.jdcr.2023.01.020
6. Figueras-Nart I. Is the treat-retreat strategy a viable option for atopic dermatitis patients undergoing Janus kinase inhibitor treatment? A report on two successful cases with upadacitinib. J Eur Acad Dermatol Venereol. 2024;38(1):e54–e55. https://doi.org/10.1111/jdv.19430