Original Article

Switching From Dupilumab to Tralokinumab or Janus Kinase Inhibitors in Cases of Ocular and/or Facial Adverse Events in Patients With Atopic Dermatitis: A Multicenter Retrospective Study

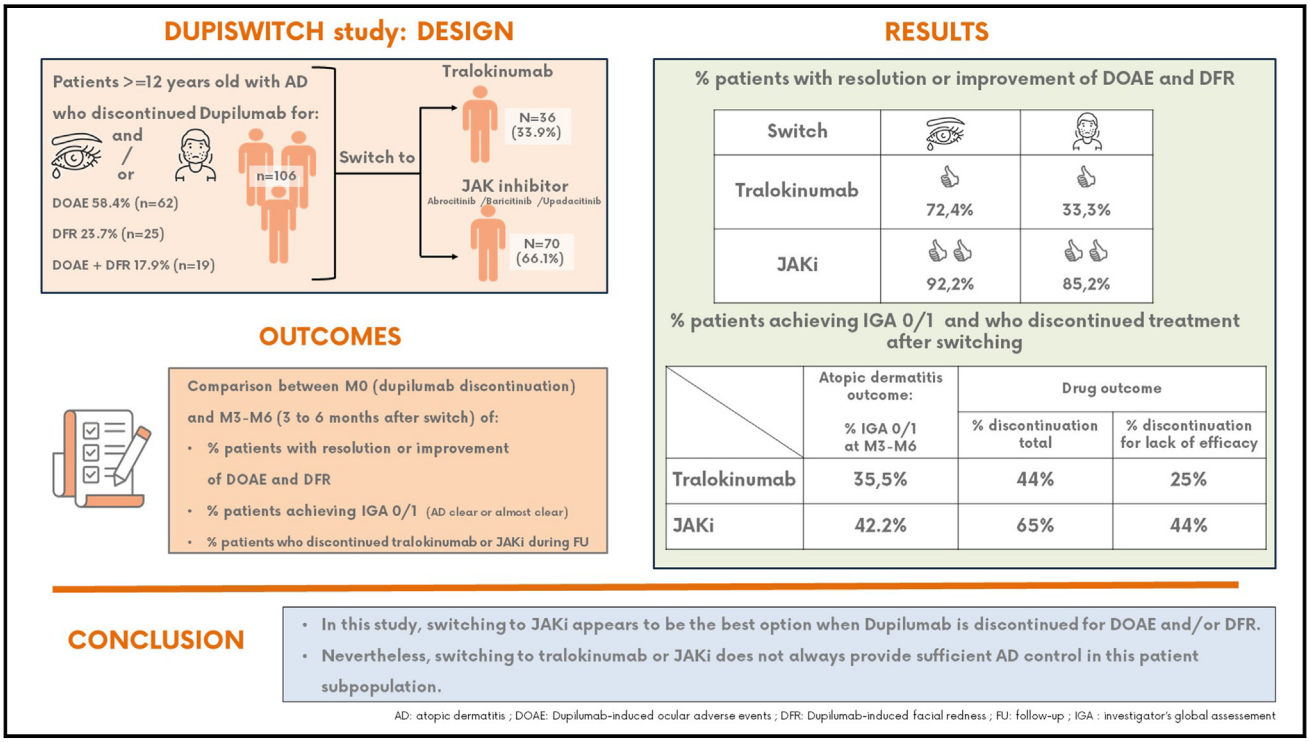
Alexandre Beyrouti, MD[a,*], Juliette Deuze[b,*], Eric Fontas, MD, PhD[c], Aurore Foureau, MS[d], Sébastien Barbarot, MD, PhD[d], Hélène Aubert, MD[d], Claire Bernier, MD[d], Marie Le Moigne, MD[d], Thierry Passeron, MD, PhD[a], Feriel Boukari, MD[a], Margaux Garnier, MD[a], Marie Jachiet, MD[e], Florence Tetart, MD[f], Julien Seneschal, MD, PhD[g], Clémentine Toussaint, MD[g], Emmanuel Mahé, MD[h], Camille Leleu, MD[i], Marie Masson Regnault, MD[j], Justine Pasteur, MD[k], Audrey Nosbaum, MD, PhD[l], Antoine Badaoui, MD[m], Anne-Claire Fougerousse, MD[m], Pauline Pralong, MD[n], Manuelle Viguier, MD, PhD[o], Catherine Droitcourt, MD, PhD[p], Claire Abasq, MD[q], Stéphanie Mallet, MD[r], Nadia Raison-Peyron, MD[s], Delphine Staumont-Sallé, MD, PhD[b,†], and Thomas Hubiche, MD[a,†], on behalf of the French Atopic Dermatitis Network (FRADEN) from the Groupe de Recherche sur l'Eczéma Atopique (GREAT) Research Group *Nice, Lille, Nantes, Paris, Rouen, Bordeaux, Argenteuil, Dijon, Périgueux, Clermont-Ferrand, Pierre Bénite, Saint-Mandé, Grenoble, Reims, Rennes, Brest, Marseille, and Montpellier, France*

What is already known about this topic? Dupilumab discontinuation for ocular adverse events or facial redness in patients with atopic dermatitis is frequent; however, real-life data on outcomes of these adverse events after switching to tralokinumab or Janus kinase inhibitors are limited.

What does this article add to our knowledge? Switching to tralokinumab or Janus kinase inhibitors is efficient for managing dupilumab-induced adverse events but does not always provide sufficient control of atopic dermatitis in this patient subpopulation.

How does this study impact current management guidelines? Janus kinase inhibitors appear to be the best option when dupilumab is discontinued for ocular adverse events or facial redness.

VISUAL SUMMARY



Abbreviations used
AD- Atopic dermatitis
AE- Adverse event
DFR- Dupilumab-induced facial redness
DOAE- Dupilumab-induced ocular adverse event
IGA- Investigator's Global Assessment
JAKi- Janus kinase inhibitor
OAE- Ocular adverse event

BACKGROUND: Patients with atopic dermatitis (AD) may discontinue dupilumab owing to dupilumab-induced ocular adverse events (DOAEs) or dupilumab-induced facial redness (DFR).
OBJECTIVE: To evaluate DOAE and DFR outcomes after switching to tralokinumab or Janus kinase inhibitor (JAKi).
METHODS: This retrospective study included 106 patients discontinuing dupilumab because of DOAEs and/or DFR. The primary outcome was the proportion of patients with resolution of adverse events or improvement between dupilumab discontinuation (M0) and 3 to 6 months of tralokinumab or JAKi (M3-M6) treatment; the secondary outcome was the percentage of patients with controlled AD defined by Investigator's Global Assessment scores of 0/1 at M3 to M6.
RESULTS: Proportions of patients with DOAE (92% vs 72%; $P = .0244$) and DFR (85% vs 33%; $P = .0006$) resolution or improvement were higher with JAKi than with tralokinumab. Proportions of patients reaching an Investigator's Global Assessment score of 0/1 increased from M0-M3 through M6 (22% vs 42%; $P = .0067$) in the JAKi group and remained similar (32% vs 35%) in the tralokinumab group. However, 57% discontinued the new treatment after 8 months on average, mainly owing to lack of efficacy.
CONCLUSIONS: Janus kinase inhibitor appears to be more efficient than tralokinumab in managing dupilumab-induced AE; however, both strategies may fail to control AD. © **2024 American Academy of Allergy, Asthma & Immunology (J Allergy Clin Immunol Pract 2024;■:■-■)**

Key words: *Atopic dermatitis; Dupilumab; Tralokinumab; Janus kinase inhibitors; Baricitinib; Upadacitinib; Abrocitinib; Dupilumab-induced ocular adverse events; Dupilumab-induced facial redness*

INTRODUCTION

Dupilumab, a human IgG_4 antibody that binds to the common alpha chain of interleukin (IL)-4 and IL-13 receptors, is a reference treatment for moderate to severe atopic dermatitis (AD).[1,2] The efficacy and safety of dupilumab have been well documented in randomized trials and real-life studies[3-8]; however, 10% to 20% of patients discontinue dupilumab after 2 years of treatment, often because of adverse events (AEs).[7,9-11] In real-life studies, up to 19% of patients with AD treated with dupilumab developed dupilumab-induced ocular AEs (DOAEs).[12,13] These DOAEs cause dupilumab discontinuation in up to 24% of patients.[11] Dupilumab-induced facial redness (DFR), defined as *de novo* or exacerbated facial redness with dupilumab use, affects 10% of patients in real life,[14-16] and up to 11% of these patients discontinue dupilumab.[11-14] Thus, exploring alternative treatments for patients who experience dupilumab-associated AEs is necessary. Tralokinumab, a human monoclonal IgG_4 antibody that specifically binds to IL-13, and Janus kinase inhibitors (JAKis), which are small molecules that inhibit the JAK—signal transducer and activator of transcription pathway, have recently demonstrated efficacy in treating moderate to severe AD in clinical trials[17-20] and real-life studies.[21-24] Tralokinumab caused conjunctivitis in 7% of patients in clinical trials, with less than 2% of cases resulting in discontinuation.[25] However, the lower prevalence of ocular AEs (OAEs) with tralokinumab than with dupilumab needs to be verified in real-life practice. Small case studies suggest that DOAEs do not recur after switching from dupilumab to tralokinumab.[26,27] By contrast, JAKis do not cause OAEs.[22-24] Limited evidence indicates the potential benefits of switching to tralokinumab or JAKi to alleviate DFR.[28,29] Thus, a gap in evidence exists regarding the management of patients requiring dupilumab discontinuation owing to these AEs. In this study, we aimed to evaluate the evolution of these AEs and the control of AD when switching to tralokinumab or a JAKi after dupilumab discontinuation owing to DFR or DOAEs.

METHODS

Study design and population

We conducted a multicenter retrospective study from July 2023 to December 2023 within the French Atopic Dermatitis Network and the French Group of Research in Atopic Dermatitis. This study included patients aged 12 years or more who were receiving dupilumab for AD,[30] were experiencing DOAEs or DFR (new onset or worsening), and who consequently received tralokinumab or a JAKi (baricitinib, upadacitinib, or abrocitinib) within 6 months of dupilumab discontinuation. All treatments for AD and dupilumab-induced AEs were prescribed at the dermatologist's discretion. The DOAE and DFR treatments were optimized before dupilumab discontinuation. Treatment with tralokinumab or JAKi was selected

[a]Department of Dermatology, University Hospital of Nice, Côte d'Azur University, Nice, France
[b]Department of Dermatology-Venerology, Centre Hospitalier Universitaire Lille, U1286 Inserm INFINITE, Université de Lille, Lille, France
[c]Department of Clinical Research, Cimiez Hospital, Centre Hospitalier Universitaire Nice, Université Côte d'Azur, Nice, France
[d]Department of Dermatology, Hotel-Dieu Centre Hospitalier Universitaire Nantes, Nantes Université, Nantes, France
[e]Faculty of Medicine, Assistance Publique-Hôpitaux de Paris, Department of Dermatology, Saint-Louis Hospital, University of Paris, Paris, France
[f]Department of Dermatology-Venerology and Ophthalmology, Rouen University Hospital, Rouen, France
[g]National Reference Center for Rare Skin Diseases, CNRS UMR5164, Immuno-ConCept, Université de Bordeaux, Bordeaux, France
[h]Department of Dermatology, Hôpital Victor Dupouy, Argenteuil, France
[i]Department of Dermatology, Centre Hospitalier Universitaire Dijon, Dijon, France
[j]Department of Dermatology, Hôpital Privé Francheville, Périgueux, France
[k]Department of Dermatology, Centre Hospitalier Universitaire Clermont-Ferrand, Clermont-Ferrand, France
[l]Department of Allergology and Clinical Immunology, Centre Hospitalier Lyon Sud, Hospices Civils de Lyon, Pierre Bénite, France
[m]Department of Dermatology, Hôpital d'Instruction des Armées Bégin, Saint-Mandé, France

by the dermatologists based on their opinion; the reasons leading to the choice of treatment were not collected.

We conducted this study with the approval of the Groupe Nantais d'Ethique dans le Domaine de la Santé Ethics Committee (Approval No. 23-90-07-100). All patients provided consent for the use of their deidentified records, based on French legislation. This study follows the Strengthening the Reporting of Observational Studies in Epidemiology guidelines.

Data collection

Dermatologists collected data at four time points: at the initiation and discontinuation of dupilumab (M0), initiation of tralokinumab or JAKi, and 3 to 6 months after initiation of the new treatment (M3 to M6). The washout period corresponds to the duration without systemic treatment between dupilumab interruption and introduction of tralokinumab or JAKi. A dedicated questionnaire was used to collect these data: the description and outcome of DOAEs and DFR, the Investigator's Global Assessment (IGA) score (0-4), AEs observed with tralokinumab or JAKi use, and discontinuation of tralokinumab or JAKi and corresponding reasons.

Outcomes

The primary outcome was the proportion of patients with resolution or improvement of these AE between dupilumab discontinuation (M0) and 3 to 6 months of treatment with tralokinumab or JAKi (M3 to M6); the secondary outcome was the percentage of patients with controlled AD defined by IGA scores of 0/1 at M3 to 6. We also compared the tralokinumab and JAKi discontinuation rates during follow-up.

Subgroup analysis

We conducted a subgroup univariate analysis, including age, sex, and duration of the washout period greater than 6 weeks between dupilumab discontinuation and tralokinumab or JAKi initiation to identify the predictive factors associated with the outcome of the AEs of interest.

Statistical analysis

Descriptive results of continuous variables are expressed as means (±SDs) and as the absolute number and relative frequencies for categorical data. We compared characteristics between patients in the tralokinumab and JAKi groups using χ^2 test (or Fisher exact test for a small sample) and t test (or Wilcoxon rank sum test when normality was not assessed). We compared the proportions of resolution or improvement of each AE between the tralokinumab and JAKi groups. The AEs of interest were compared between groups using χ^2 test (or Fisher exact test for small samples). Evolution of the IGA score between M0 and M3 to M6 in the tralokinumab and JAKi groups was studied using McNemar tests. The association between potential predictive factors and good evolution (ie, resolution or improvement) of each AE in each treatment group was evaluated using first-instance univariate logistic regression models. All risk factors associated with a good evolution ($P < .20$) were then introduced in the multivariate logistic regression model. Two-sided $P < .05$ was considered statistically significant. We conducted statistical analyses using SAS Enterprise Guide (version 7.1, 2017, SAS Institute, Inc, Cary, NC).

RESULTS

Baseline characteristics of patients

We included 106 patients (mean age, 37 years) from 18 hospitals. Overall, 19 patients (18%) had discontinued dupilumab owing to DFR and DOAEs, 62 (58%) exclusively owing to DOAEs, and 25 (24%) exclusively owing to DFR. On dupilumab discontinuation (M0), 24 patients (25%) had IGA scores of 0/1 (mean ± SD, 2.1 ± 1) (Table I). Thirty-six patients switched to tralokinumab (initial dose: 600 mg, followed by 300

[n]Department of Allergology, Centre Hospitalier Universitaire Grenoble, Grenoble, France
[o]Department of Dermatology-Venerology, Centre Hospitalier Universitaire Robert-Debré, Reims, France
[p]Department of Dermatology, University Hospital Center of Rennes, Rennes, France
[q]Department of Dermatology, Brest University Hospital, Brest, France
[r]Department of Dermatology, Assistance Publique—Hôpitaux de Marseille, La Timone University Hospital, Marseille Center University, Marseille, France
[s]Department of Dermatology, Centre Hospitalier Universitaire Montpellier, Montpellier, France
*These authors contributed equally to this work.
†These authors contributed equally to this work.

Conflicts of interest: D. Staumont-Sallé is an investigator, consultant, and/or speaker for AbbVie, Almirall, Amgen, AstraZeneca, Eli Lilly, Galderma, Leo Pharma, Novartis, Pfizer, Sanofi-Regeneron, and UCB. T. Hubiche is an investigator, consultant, and/or speaker for AbbVie, Amgen, Bayer, Eli Lilly, Leo Pharma, OMpharma, Novartis, Pierre Fabre, Pfizer, and Sanofi-Regeneron. S. Barbarot is an investigator or speaker for AstraZeneca, Almirall, Sanofi-Genzyme, AbbVie, Galderma, Alexion, Novartis, Janssen, Leo Pharma, Pfizer, Eli Lilly, and UCB Pharma. H. Aubert is an investigator, consultant, and/or speaker for AbbVie, Almirall, UCB, Leo Pharma, Medac, Novartis, Pfizer, and Sanofi-Regeneron. T. Passeron has received grants and/or honoraria from AbbVie, ACM Pharma, Almirall, Amgen, Astellas, Bristol Myers Squibb, Calypso, Celgene, Galderma, Genzyme/Sanofi, GlaxoSmithKline, Incyte, Janssen, LEO Pharma, Eli Lilly, Novartis, Pfizer, Sun Pharmaceuticals, UCB, and Vyne Therapeutics; and is the cofounder of NIKAIA Pharmaceuticals. M. Jachiet has received honoraria as an advisor, speaker, and/or research speaker from Sanofi-Genzyme, AbbVie, Lilly, Pfizer, Leo Pharma, AstraZeneca, and GlaxoSmithKline. F. Tetart has received honoraria as an advisor and speaker from Sanofi-Genzyme, Lilly, Leo Pharma, AbbVie, Pfizer, and Novartis. J. Seneschal has received grants and/or honoraria from AbbVie, Almirall Bristol Myers Squibb, Eli Lilly, Leo Pharma, Pfizer, Pierre Fabre, and Sanofi. E. Mahé has received grants and/or honoraria from Sanofi, AbbVie, Biolane, and Almirall. J. Pasteur is an investigator, consultant, and/or speaker for AbbVie, Almirall, BMS, Eli Lille, Leo Pharma, Medac, Novartis, Pfizer, and Sanofi-Regeneron. A. Nosbaum has received honoraria as an advisor, speaker, and/or research from Sanofi-Genzyme, AbbVie, Eli Lilly, Pfizer, Leo Pharma, Almirall, Medac, Galderma, and Pierre Fabre. A. Badaoui is a consultant for Sanofi, AbbVie, Lilly, and Léo. P. Pralong is a consultant and/or speaker for AbbVie, Leo Pharma, Novartis, and Sanofi-Regeneron. M. Viguier has received travel fees for attending medical conferences; and is an investigator, consultant, and/or speaker for Janssen Cilag, AbbVie, Almirall, Eli Lilly, Leo Pharma, Novartis, Pfizer, Medac, Nordic, UCB, Bristol Myers Squibb, and Boehringer-Ingelheim. C. Droitcourt has received honoraria as an advisor, speaker, and/or research from Sanofi-Genzyme, Eli Lilly, Novartis, and UCB-Pharma. C. Abasq has received honoraria as an advisor, speaker, and/or research from Sanofi-Genzyme, AbbVie, Leo Pharma, and Eli Lilly. S. Mallet is an investigator, consultant, and/or speaker for AbbVie, Eli Lilly, Leo Pharma, Novartis, MSD, Pierre Fabre, Pfizer, and Sanofi-Regeneron. N. Raison-Peyron has received personal fees from Sanofi-Regeneron. M. Masson Regnault has received travel fees for attending medical conferences and has been a consultant and/or speaker for Janssen Cilag, AbbVie, Almirall, Eli Lilly, Leo Pharma, Novartis, Pfizer, Sanofi-Regeneron, UCB Pharma, and Bristol Myers Squibb. The rest of the authors declare that they have no relevant conflicts of interest.

Received for publication August 7, 2024; revised November 25, 2024; accepted for publication December 3, 2024.
Available online ■■

Corresponding author: Thomas Hubiche, MD, Department of Dermatology, Centre Hospitalier Universitaire de Nice, 151 Route de Saint Antoine de Ginestière, 06200 Nice, France. E-mail: hubiche.t@chu-nice.fr.

2213-2198

https://doi.org/10.1016/j.jaip.2024.12.001

TABLE I. Baseline characteristics of patients

Data	n	Total (n = 106)	n	Tralokinumab (n = 36)	n	JAKi (n = 70)	*P*
Age, y (mean [SD])	106	37 (13)	36	41 (13)	70	35 (13)	.0263
Sex	106		36		70		.4762
Male		61 (58%)		19 (53%)		42 (60%)	
Female		45 (42%)		17 (47%)		28 (40%)	
Duration of dupilumab treatment, mo (mean [SD])	106	16 (14)	36	18 (16)	70	16 (13)	.2907
Time between dupilumab discontinuation and introduction of new treatment, wk (mean [SD])	105	4 (6)	36	4 (6)	69	4 (6)	.3351
Discontinuation owing to Dupilumab ocular adverse events	106	81 (76%)	36	29 (81%)	70	52 (74%)	.4715
Discontinuation owing to dupilumab facial redness	106	44 (41%)	36	15 (42%)	70	29 (41%)	.9812
Switched to	106		36		70		—
Tralokinumab		36 (34%)		36 (100%)		0	
JAKi		70 (66%)		0		70 (100%)	
Choice of JAKi	70						—
Abrocitinib		2 (3%)		—		2 (3%)	
Baricitinib		44 (63%)		—		44 (63%)	
Upadacitinib		24 (34%)		—		24 (34%)	
IGA score when starting dupilumab (mean [SD])	95	3.4 (0.8)	32	3.2 (0.8)	63	3.5 (0.8)	.0665
IGA score at dupilumab discontinuation	95		31		64		
IGA score (mean [SD])		2.3 (1.1)		2.2 (1.3)		2.4 (1.1)	.5000
IGA score of 0/1, n (%)		71 (75%)		10 (32%)		14 (22%)	.4116

IGA, Investigator's Global Assessment; *JAKi*, Janus kinase inhibitor.

mg biweekly), whereas 70 switched to a JAKi; 44 patients received baricitinib (39 patients at 4 mg/d and one at 2 mg/d), 24 received upadacitinib (13 patients at 30 mg/d, five starting at 15 mg and reaching 30 mg/d, and four at 15 mg/d, and two received abrocitinib at 200 mg/d). Most patients (84%) received the maximum dose of JAKi. Patients who received tralokinumab were 6 years older than patients who received JAKi (mean age, 41 and 35 years, respectively). Reasons for dupilumab discontinuation in the tralokinumab group were: DOAEs only, 58% (n = 21); DFR only, 19% (n = 7); and DFR and DOAEs, 22% (n = 8). In contrast, those in the JAKi group were: DOAEs only, 58% (n = 41), DFR only, 26% (n = 18), and DFR and DOAEs, 16% (n = 11). The proportion of patients with IGA scores of 0/1 at M0 was similar between groups (10/31 patients [32%] in the tralokinumab group vs 14/64 [22%] in the JAKi group; $P = .41$) (Table I).

Adverse event outcomes after switching from dupilumab to tralokinumab or JAKi

Among 51 patients with DOAEs who switched to JAKi, 47 (92%) had a favorable AE evolution (ie, improvement or resolution), compared with 21 of 29 (72%) who switched to tralokinumab ($P = .0244$). Among patients with DFR, 23 of 27 (85%) with JAKi similarly had a favorable AE evolution, compared with five of 15 (33%) treated with tralokinumab ($P = .0006$) (Table II and Figure 1). Only one patient had *de novo* conjunctivitis under tralokinumab, which improved under topical treatment. All other ophthalmologic and facial AEs reported with tralokinumab or JAKi use were induced by and persisted since dupilumab treatment.

Atopic dermatitis outcome after switching from dupilumab to tralokinumab or a JAKi

The IGA score did not significantly improve with tralokinumab after switching from dupilumab: 11 of 31 patients (35%) achieved an IGA score of 0/1 at M3 to M6, whereas 10 of 31 (32%) in this group achieved this score at the time of dupilumab discontinuation (M0). Among the JAKi-treated patients, 22% (14 of 64 patients) achieved an IGA score of 0/1 at M0, which increased significantly to 42% (27 of 64 patients) at M3 to M6 ($P = .0067$). The proportion of patients with an IGA score of 0/1 at M3 to M6 was 59% (13 of 22 patients) and 34% (14 of 41 patients) among patients treated with upadacitinib and baricitinib, respectively; the difference was not significant ($P = .056$) (Table II). Among the two patients treated with abrocitinib, one had an IGA score of 3 at M0 and M3 to M6, whereas the other had an IGA score of 4 at M0 and 2 at M3 to M6 (Table II and Figure 1).

Safety and discontinuation of tralokinumab and JAKis

During the follow-up (mean, 16 months; SD, 11 months), 60 of 104 patients (57%; missing data, n = 2) discontinued the new treatment after 8 months on average (SD, 7 months). Of 36 patients, 16 (44%) discontinued tralokinumab after 4 months (SD, 2 months) during the follow-up (mean, 8 months; SD, 5 months) because of a lack of efficacy (nine of 16; 56%), OAEs (six of 16, 37%), or facial redness (two of 16; 12%) (Table III). A total of 44 of 68 JAKi-treated patients (65%; (missing data for two of 70 patients) discontinued treatment after 9 months (SD, 7 months) on average during the follow-up (19 months; SD, 18

TABLE II. Patient outcomes (dupilumab ocular adverse events, dupilumab facial redness, and IGA score) after switching to tralokinumab or JAKi

Data	n	Total (n = 106)	n	Tralokinumab(n = 36)	n	JAKi (n = 70)	*P*
Dupilumab ocular adverse events outcomes							
Improvement/resolution at M3-M6	80		29	21 (72%)	51	47 (92%)	.0244
Evolution between M0 and M3-M6	80		29		51		
Worse		8 (10%)		5 (17%)		3 (6%)	
Stable		4 (5%)		3 (10%)		1 (2%)	
Improvement		36 (45%)		11 (38%)		25 (49%)	
Resolution		32 (40%)		10 (34%)		22 (43%)	
Dupilumab facial redness outcomes							
Improvement/resolution at M3-M6	42		15	5 (33%)	27	23 (85%)	.0006
Evolution between M0 and M3-M6	42		15		27		
Worse		1 (2%)		1 (7%)		0	
Stable		13 (31%)		9 (60%)		4 (2%)	
Improvement		18 (43%)		3 (20%)		15 (56%)	
Resolution		10 (24%)		2 (13%)		8 (30%)	
IGA							
Comparison of proportion of patients achieving IGA score of 0/1 between M0 and M3-M6							
Tralokinumab group				32% vs 35%			1.00
JAKi group						22% vs 42%	.0067
IGA score at new treatment initiation (mean [SD])	98	2.4 (1.1)	33	2.3 (1.2)	65	2.5 (1.1)	.6277
IGA score at M3-M6 (mean [SD])	95	1.8 (1.1)	31	1.9 (1.2)	64	1.8 (1.1)	.6936

IGA, Investigator's Global Assessment; *JAKi*, Janus kinase inhibitor; *M0*, dupilumab discontinuation; *M3-M6*, 3-6 mo after initiating tralokinumab or JAKi.

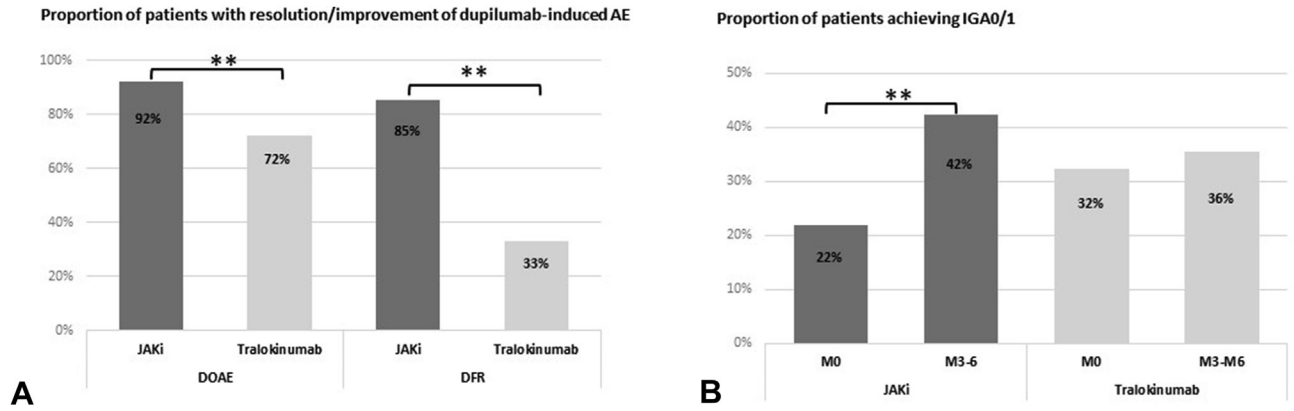


FIGURE 1. Proportions of patients with (**A**) resolution/improvement, based on adverse event (AE) type 3−6 months after tralokinumab (M3-M6), and (**B**) Investigator's Global Assessment (IGA) scores of 0/1 at dupilumab discontinuation (M0) and M3 to M6 in tralokinumab and Janus kinase inhibitor (JAKi) groups. $^{**}P < .05$. *DFR*, dupilumab facial redness; *DOAE*, dupilumab-induced ocular AE.

months), primarily because of a lack of efficacy (30 of 44 patients; 68%). Most discontinuations occurred in the baricitinib group (35 of 44 patients), with 26 discontinuations because of a lack of efficacy. Seven of 22 patients discontinued upadacitinib; only two of these patients discontinued owing to a lack of efficacy. The two patients treated with abrocitinib discontinued treatment because of a lack of efficacy. Other causes of discontinuation are detailed in Table III.

Predictive factors of AE outcomes

The univariate subgroup analysis, including age, sex, and washout period (ie, without systemic treatment, between dupilumab discontinuation and tralokinumab or JAKi introduction) identified no predictive factors. A washout period of less than 6 weeks between dupilumab discontinuation and new treatment was not associated with the persistence of AEs in the tralokinumab (odds ratio = 1.33 [0.28-6.44]; $P = .7204$) or JAKi (OR = 1.20 [0.21-6.84]; $P = .8373$) groups.

DISCUSSION

This study highlights the potential benefits of switching to tralokinumab or JAKi after dupilumab discontinuation owing to DOAEs or DFR. The strengths of our study include the real-life

TABLE III. Safety and treatment outcome under tralokinumab and JAKi

Data	n	Total (n = 106)	n	Tralokinumab (n = 36)	n	JAKi (n = 70)
Safety						
Injection site AE	36	0	36	0		
Blood test abnormalities related to tralokinumab or JAKi	104	4 (4%)	36	0	68	4 (6%)
Treatment outcomes						
Discontinuation during follow-up	104	60 (57%)	36	16 (44%)	68	44 (65%)
Reasons for discontinuation	60		16		44	
Lack of efficacy		39 (65%)		9 (56%)		30 (68%)
Efficacy		2 (3%)		0		2 (4%)
Ocular AE*		7 (12%)		6 (37%)		1 (2%)
Head and neck AE		4 (7%)		2 (12%)		2 (4%)
Patient's choice†		6 (10%)		2 (12%)		4 (9%)
Other reason‡		7 (12%)		2 (12%)		5 (11%)

AE, adverse event; *JAKi*, Janus kinase inhibitor.

*JAKi group (upadacitinib): one patient with corneal abscess. Tralokinumab group: one patient with upadacitinib) keratitis, two with conjunctivitis, and three with dry eyes.

†Tralokinumab group: one because of weariness of injections and one because of a lack of efficacy. JAKi group: three because of good efficacy (two treated with baricitinib and one with upadacitinib) and one because of fear during the coronavirus disease pandemic (baricitinib).

‡Tralokinumab group: one because of rosacea and one because of mood disorder (tralokinumab). JAKi group: one because of stroke (upadacitinib), one because of hypercholesterolemia (baricitinib), one because of elevated liver enzymes (baricitinib), one because of herpes zoster infection (upadacitinib), and two because of headaches.

setting, inclusion of a large patient sample, and evaluation by trained dermatologists, many of whom have conducted previous studies on AEs associated with dupilumab use.[11,13,16]

The populations of patients treated with tralokinumab or JAKi were similar. The JAKi group patients were 6 years younger on average than the tralokinumab group patients, likely because of warnings regarding JAKi use in older patients. The predominance of baricitinib (63%) could be attributed to its earlier approval and reimbursement in France.

Concerning DOAEs, both treatments led to a favorable evolution but with a significantly better response with JAKi than with tralokinumab in our experience. Tralokinumab also causes DOAEs,[17] possibly more often in real-life settings than in clinical trials.[13] Nevertheless, two small case series showed that DOAE do not recur after switching to tralokinumab.[26,27] In our study, 15 of 36 patients (42%) experienced OAEs with tralokinumab use contributing to its discontinuation in six of 36 patients (17%).[13] We acknowledge that OAEs reported under tralokinumab in our study may be persistent since dupilumab use. However, we assumed that patients received optimized treatment for OAEs before dupilumab discontinuation. Moreover, the mean washout period was 4 weeks in our study, and most DOAEs are reported to resolve within 4 weeks of dupilumab discontinuation.[27] Furthermore, our subgroup analysis did not reveal washout duration to be a predictive factor for AE evolution. A recent retrospective cohort study focusing on DOAE outcome after switching to tralokinumab or JAKi identified conjunctivitis duration, personal history of asthma, or switching to JAKi to be associated with DOAE resolution.[31] IL-4 but also IL-13 inhibition is involved in the pathophysiology of DOAE.[32] Specific blockage of the IL-13 pathway with tralokinumab might explain the more frequent persistence of DOAEs in the tralokinumab group[25]; however, this hypothesis should be investigated further.

The improvement of DFR was also better with JAKi than with tralokinumab, in our experience. The mechanisms underlying DFR probably involve pathways other than the T_H2 immune response (eg, T_H17 or T_H22 polarization as well as dysbiosis with the suspected pathogenic role of *Malassezia* and *Demodex*).[13,16,29,33] Bangert et al[33] demonstrated that DFR is characterized by a T_H22 immune signature. The IL-22 pathway is mediated through TYK2 and JAKi and might explain the better outcome of DFR under JAKi treatment. Moreover, tralokinumab may be responsible for head and neck exacerbation or *de novo* facial redness, similar to dupilumab, although this hypothesis needs to be verified in real life.

Concerning AD control, only patients who had switched to JAKi had significantly improved IGA scores after M3 to M6. Our results (42% of JAKi-treated patients achieved an IGA score of 0/1 at M3 to M6) are concordant with those of the Heads Up clinical trial[34] and with data from real-life registries.[21-24] We believe that the effectiveness of JAKi in controlling AD might have been even better if more patients had received JAK1-selective inhibitors such as upadacitinib and abrocitinib, because meta-analyses have shown these JAKis to be more effective than baricitinib.[35,36] At M3 to M6, the proportion of patients achieving an IGA score of 0/1 was lower in the tralokinumab group (35%) versus the JAKi group (42%). This result is consistent with that of a meta-analysis showing the superiority of upadacitinib (30 mg) and abrocitinib (200 mg) over biologics.[35] However, studies have reported the effectiveness of tralokinumab in real-life practice in naive or in dupilumab- or JAKi-refractory patients.[22-24,37] The assessment of efficacy at M3 to M6 in our study may have been too premature to appreciate the efficacy of tralokinumab compared with that of JAKi.

We observed a relatively high rate (57%) of treatment discontinuation: 44% and 65% in the tralokinumab and JAKi groups, respectively. The lack of efficacy in controlling AD was the most frequently reported cause of discontinuation in both groups, which suggests that patients experiencing DOAEs and/or DFR are a difficult-to-treat AD subpopulation. Paradoxically, more patients discontinued JAKi than tralokinumab, whereas JAKi was more efficient in controlling AE and AD. This discrepancy could be explained by a shorter delay in the response expected with JAKi and a longer follow-up in the JAKi group than in the tralokinumab group. Thus, more patients had the opportunity to discontinue new treatment. In two real-life case series, tralokinumab was discontinued because of no clinical improvement in 10% to 40% of patients after an average treatment duration of 14 weeks.[38,39] Moreover, in our study, the

high discontinuation rate in the JAKi group could be explained by the high proportion of patients receiving baricitinib, which is less effective than upadacitinib or abrocitinib in controlling AD in real-life cases.[21] Approximately one in four patients discontinued JAKi for AEs other than OAEs and facial redness, which was similar to our previous observations in real-life settings.[21] There was one case of stroke with upadacitinib treatment, with no further information.

Our study had some limitations, including its retrospective design, missing data, and differences in representation and follow-up duration between treatments because of market access. The average follow-up (8 months) under tralokinumab or JAKi treatment did not capture long-term outcomes. Moreover, we acknowledge the possibility that OAEs and DFR may be partly attributed to the natural evolution of AD, which we attempted to limit via patient evaluation by dermatologists trained to diagnose AEs of interest. Finally, the choice of tralokinumab or JAKi at the dermatologists' discretion may have influenced AE outcomes.

Our study suggests that switching to JAKi is the best option when dupilumab is discontinued for DOAEs or DFR. The implementation of registries with long-term prospective follow-up and the development of research to compare therapeutic strategies will be essential, given the proliferation of newly available treatments.

REFERENCES

1. Wollenberg A, Kinberger M, Arents B, Aszodi N, Avila Valle G, Barbarot S, et al. European guideline (EuroGuiDerm) on atopic eczema: part I – systemic therapy. J Eur Acad Dermatol Venereol 2022;36:1409-31.
2. Davis DM, Drucker AM, Alikhan A, Bercovitch L, Cohen DE, Darr JM, et al. Guidelines of care for the management of atopic dermatitis in adults with phototherapy and systemic therapies. J Am Acad Dermatol 2024;90:e43-56.
3. Simpson EL, Bieber T, Guttman-Yassky E, Beck LA, Blauvelt A, Cork MJ, et al. Two phase 3 trials of dupilumab versus placebo in atopic dermatitis. N Engl J Med 2016;375:2335-48.
4. Blauvelt A, de Bruin-Weller M, Gooderham M, Cather JC, Weisman J, Pariser D, et al. Long-term management of moderate-to-severe atopic dermatitis with dupilumab and concomitant topical corticosteroids (Liberty AD Chronos): a 1-year, randomised, double-blinded, placebo-controlled, phase 3 trial. Lancet 2017;389:2287-303.
5. Deleuran M, Thaçi D, Beck LA, de Bruin-Weller M, Blauvelt A, Forman S, et al. Dupilumab shows long-term safety and efficacy in patients with moderate to severe atopic dermatitis enrolled in a phase 3 open-label extension study. J Am Acad Dermatol 2020;82:377-88.
6. Faiz S, Giovannelli J, Podevin C, Jachiet M, Bouaziz JD, Reguiai Z, et al. Effectiveness and safety of dupilumab for the treatment of atopic dermatitis in a real-life French multicenter adult cohort. J Am Acad Dermatol 2019;81:143-51.
7. Spekhorst LS, de Graaf M, Zuithoff NP, van den Reek JM, Kamsteeg M, Boesjes CM, et al. Dupilumab drug survival and associated predictors in patients with moderate to severe atopic dermatitis: long-term results from the Daily Practice BioDay Registry. JAMA Dermatol 2022;158:1048-56.
8. Musters AH, Van Lookeren FL, Van Der Gang LF, Middelkamp-Hup MA, Bosma AL, Jessurun NT, et al. Real-world reported adverse events related to systemic immunomodulating therapy in patients with atopic dermatitis: results from the TREAT NL (TREatment of ATopic eczema, the Netherlands) registry. J Eur Acad Dermatol Venereol 2024;38:530-42.
9. Khosravi H, Zhang S, Anderson AM, Ferris LK, Choudhary S, Patton T. Dupilumab drug survival, treatment failures, and insurance approval at a tertiary care center in the United States. J Am Acad Dermatol 2020;82:1023-4.
10. Georgakopoulos JR, Felfeli T, Drucker AM, Jo CE, Piguet V, Yeung J. Two-year efficacy, safety, and drug survival of dupilumab for atopic dermatitis: a real-world Canadian multicenter retrospective study. JAAD Int 2021;4:67-9.
11. Marniquet ME, Seneschal J, Darrigade AS, Staumont-Sallé D, Jachiet M, Nosbaum A, et al. Reasons for discontinuation of dupilumab in adult atopic dermatitis in clinical practice. Br J Dermatol 2022;186:733-5.
12. Halling AS, Loft N, Silverberg JI, Guttman-Yassky E, Thyssen JP. Real-world evidence of dupilumab efficacy and risk of adverse events: a systematic review and meta-analysis. J Am Acad Dermatol 2021;84:139-47.
13. Costedoat I, Wallaert M, Gaultier A, Vasseur R, Vanhaecke C, Viguier M, et al. Multicenter prospective observational study of dupilumab-induced ocular events in atopic dermatitis patients. J Eur Acad Dermatol Venereol 2023;37:1056-63.
14. Waldman RA, DeWane ME, Sloan B, Grant-Kels JM. Characterizing dupilumab facial redness: a multi-institution retrospective medical record review. J Am Acad Dermatol 2020;82:230-2.
15. Jo CE, Finstad A, Georgakopoulos JR, Piguet V, Yeung J, Drucker AM. Facial and neck erythema associated with dupilumab treatment: a systematic review. J Am Acad Dermatol 2021;84:1339-47.
16. Soria A, Du-Thanh A, Seneschal J, Jachiet M, Staumont-Sallé D, Barbarot S, et al. Development or exacerbation of head and neck dermatitis in patients treated for atopic dermatitis with dupilumab. JAMA Dermatol 2019;155:1312-5.
17. Wollenberg A, Blauvelt A, Guttman-Yassky E, Worm M, Lynde C, Lacour JP, et al. Tralokinumab for moderate-to-severe atopic dermatitis: results from two 52-week, randomized, double-blind, multicentre, placebo-controlled phase III trials (ECZTRA 1 and ECZTRA 2). Br J Dermatol 2021;184:437-49.
18. Guttman-Yassky E, Teixeira HD, Simpson EL, Papp KA, Pangan AL, Blauvelt A, et al. Once-daily upadacitinib versus placebo in adolescents and adults with moderate-to-severe atopic dermatitis (Measure Up 1 and Measure Up 2): results from two replicate double-blind, randomised controlled phase 3 trials. Lancet 2021;397:2151-68.
19. Simpson EL, Lacour JP, Spelman L, Galimberti R, Eichenfield LF, Bissonnette R, et al. Baricitinib in patients with moderate-to-severe atopic dermatitis and inadequate response to topical corticosteroids: results from two randomized monotherapy phase III trials. Br J Dermatol 2020;183:242-55.
20. Simpson EL, Sinclair R, Forman S, Wollenberg A, Aschoff R, Cork M, et al. Efficacy and safety of abrocitinib in adults and adolescents with moderate-to-severe atopic dermatitis (JADE MONO-1): a multicentre, double-blind, randomised, placebo-controlled, phase 3 trial. Lancet 2020;396:255-66.
21. Vanlerberghe J, Dezoteux F, Martin C, Jachiet M, Soria A, Tétart F, et al. Effectiveness and tolerance of Janus kinase inhibitors for the treatment of recalcitrant atopic dermatitis in a real-life French multicenter adult cohort. J Am Acad Dermatol 2023;88:900-4.
22. Pereyra-Rodríguez JJ, Herranz P, Ruiz-Villaverde R, Elosua-González M, Galán-Gutiérrez M, Figueras-Nart I, et al. Treatment of severe atopic dermatitis with tralokinumab in clinical practice: short-term effectiveness and safety results. Clin Exp Dermatol 2023;48:991-7.
23. Boesjes CM, Kamphuis E, Zuithoff NP, Bakker DS, Loman L, Spekhorst LS, et al. Daily practice experience of baricitinib treatment for patients with difficult-to-treat atopic dermatitis: results from the BioDay Registry. Acta Derm Venereol 2022;102:adv00820.
24. De Greef A, Ghislain PD, De Montjoye L, Baeck M. Real-life effectiveness and tolerance of upadacitinib for severe atopic dermatitis in adolescents and adults. Adv Ther 2023;40:2509-14.
25. Wollenberg A, Beck LA, de Bruin Weller M, Simpson EL, Imafuku S, Boguniewicz M, et al. Conjunctivitis in adult patients with moderate-to-severe atopic dermatitis: results from five tralokinumab clinical trials. Br J Dermatol 2022;186:453-65.
26. Achten R, Dekkers C, Bakker D, van Luijk C, de Graaf M, van Wijk F, et al. Switching from dupilumab to tralokinumab in atopic dermatitis patients with ocular surface disease: preliminary case series. Clin Exp Allergy 2023;53:586-9.
27. Licata G, Tancredi V, Pezzolo E, Pertusi G, Tolino E, Arisi M, et al. Efficacy and safeness of tralokinumab in patients with atopic dermatitis who developed conjunctivitis under dupilumab: a case series. J Eur Acad Dermatol Venereol. Published April 5, 2023. https://doi.org/10.1111/jdv.19108
28. Uchida H, Kamata M, Egawa S, Nagata M, Fukaya S, Hayashi K, et al. Newly developed erythema and red papules in the face and neck with detection of demodex during dupilumab treatment for atopic dermatitis improved by discontinuation of dupilumab, switching to upadacitinib or treatment with oral ivermectin: a report of two cases. J Eur Acad Dermatol Venereol 2023;37:e300-2.
29. Kozera E, Flora A, Stewart T, Gill K, Xu J, De La Vega MA, et al. Dupilumab-associated head and neck dermatitis resolves temporarily with itraconazole therapy and rapidly with transition to upadacitinib, with Malassezia-specific immunoglobulin E levels mirroring clinical response. J Am Acad Dermatol 2023;88:255-7.
30. Hanifin JM, Rajka G. Diagnostic features of atopic dermatitis. Acta Derm Venereol Suppl (Stockh) 1980;92:44-7.
31. Reguiai Z, Becherel PA, Perrot JL, Boulard C, Fougerousse AC, Begon E, et al. Evolution of dupilumab-associated conjunctivitis in patients with atopic dermatitis after switching dupilumab to tralokinumab or Janus kinase inhibitors (RESO-ADOC study). J Eur Acad Dermatol Venereol 2024;38:2149-55.

32. Barnett BP, Afshari NA. Dupilumab-associated mucin deficiency (DAMD). Transl Vis Sci Technol 2020;9:29.
33. Bangert C, Alkon N, Chennareddy S, Arnoldner T, Levine JP, Pilz M, et al. Dupilumab-associated head and neck dermatitis shows a pronounced type 22 immune signature mediated by oligoclonally expanded T cells. Nat Commun 2024;15:2839.
34. Blauvelt A, Ladizinski B, Prajapati VH, Laquer V, Fischer A, Eisman S, et al. Efficacy and safety of switching from dupilumab to upadacitinib versus continuous upadacitinib in moderate-to-severe atopic dermatitis: results from an open-label extension of the phase 3, randomized, controlled trial (Heads Up). J Am Acad Dermatol 2023;89:478-85.
35. Drucker AM, Morra DE, Prieto-Merino D, Ellis AG, Yiu ZZ, Rochwerg B, et al. Systemic immunomodulatory treatments for atopic dermatitis: update of a living systematic review and network meta-analysis. JAMA Dermatol 2022;158:523-32.
36. Wan H, Jia H, Xia T, Zhang D. Comparative efficacy and safety of abrocitinib, baricitinib, and upadacitinib for moderate-to-severe atopic dermatitis: a network meta-analysis. Dermatol Ther 2022;35:e15636.
37. Lasheras-Pérez MA, Palacios-Diaz RD, Pozuelo-Ruiz M, Torres-Navarro I, Botella-Estrada R, Rodriguez-Serna M. Switching from dupilumab to tralokinumab in patients with atopic dermatitis due to inefficacy or side effects. Int J Dermatol 2024;63:105-7.
38. Schlösser AR, Shareef M, Olydam J, Nijsten TE, Hijnen DJ. Tralokinumab treatment for patients with moderate-to-severe atopic dermatitis in daily practice. Clin Exp Dermatol 2023;48:510-7.
39. De Greef A, Ghislain PD, Bulinckx A, Coster A, de Halleux C, Damsin T, et al. Real-life experience of tralokinumab for the treatment of adult patients with severe atopic dermatitis: a multicentric prospective study. Clin Drug Investig 2023;43:299-306.