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Real-life management of atopic dermatitis patients with an inadequate response to on-label use of dupilumab

Rémi Strizzolo, MD[a], Julien Seneschal, MD, PhD[b], Angèle Soria, MD, PhD[c], Delphine Staumont-Sallé, MD, PhD[d], Sébastien Barbarot, MD, PhD[e], Manuelle Viguier, MD, PhD[f], Marie Jachiet, MD[g], Audrey Nosbaum, MD, PhD[h], Aude Clément, MD[h], Marie Tauber, MD, PhD[i], Stéphanie Mallet, MD[j] and Aurélie Du-Thanh, MD, PhD[a]*, on behalf of the French Atopic Dermatitis Network from the GREAT Research group

ABSTRACT

In patients with moderate to severe atopic dermatitis (AD) showing an inadequate response to dupilumab 300mg/2weeks, few real-life studies reported the response to alternative regimen maintaining dupilumab.

To assess and analyze the response to an increased dose of dupilumab or its combination with cyclosporin A (CsA), methotrexate (MTX), or itraconazole (ITRA), all adult AD patients from 7 French University Hospitals were retrospectively included if they achieved an inadequate response to dupilumab 300mg/2weeks and were subsequently treated with an increased dose of dupilumab (300mg every 7 or 10 days), or a combination of dupilumab 300mg/2weeks with CsA, MTX or ITRA. The response after 3 months, along with epidemiological, clinical, and therapeutic baseline characteristics, were collected.

Overall, 68.75% of the 48 included patients achieved an improved response, including 45.8% of complete response (CR). No strategy proved significantly better. Patients showing an initial no response never achieved a further CR versus 52.4% of patients with an initial partial response ($p = 0.025$). Digestive intolerance and tachycardia led to MTX and ITRA discontinuation in 3 patients. Increasing the dose of dupilumab or combining it with CsA, MTX, or ITRA could be alternative and safe options, to be evaluated in further medico-economic studies.

Keywords: Dermatitis, Atopic, Dupilumab, Cyclosporine, Methotrexate, Itraconazole

INTRODUCTION

Dupilumab has demonstrated its good safety profile and efficacy over time in patients with moderate to severe atopic dermatitis (AD) in pivotal[1] and real-life studies.[2] Few real-life studies describe the management of patients with an inadequate response to on-label use of dupilumab, despite published algorithms propose to increase the dose, or to combine with immunosuppressive drugs,[3,4] or to switch for oral Janus Kinase inhibitors (JAKi).[5,6]

[a]Dermatology Department, University Hospital of Montpellier, Montpellier, France
*Corresponding author. Department of Dermatology, University Hospital of Montpellier, 80 avenue Augustin Fliche, 34295 Montpellier, France. E-mail: a-du_thanh@chu-montpellier.fr
Full list of author information is available at the end of the article

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We conducted a multicenter retrospective study to i) assess the response to increased dose of dupilumab or combination with other systemic agents and ii) analyze epidemiological and clinical factors associated with this response.

POPULATION AND METHODS

This study was conducted in 7 French University Hospitals. We included all adult AD patients between March 2017 and March 2021 with an inadequate response to dupilumab 300 mg every 2 weeks and were subsequently treated with any of the following strategies: increasing the dose of dupilumab (300mg every 7 or 10 days); combination of dupilumab 300 mg every 2 weeks with cyclosporin A (CsA), methotrexate (MTX), or itraconazole (ITRA). Response was assessed after 3–6 months of any treatment option; thus data were collected between November 2020 and June 2021 from medical files. A complete response (CR) was defined as achieving an Investigator's Global Assessment (IGA) score of 0/1 or improvement $\geq$ 2 points, and/or a Dermatology Life Quality Index (DLQI)<10, and/or reaching a 75% improvement of the eczema area scoring index (EASI75). An inadequate response was defined as a partial response (PR) (IGA = 2 and/or 10$\leq$DLQI<20 and/or a 25–50% decrease in EASI and/or *de novo* or worsening head-and-neck dermatitis (HAND)) or no response (NR) (IGA>2 and/or DLQI$\geq$20 and/or a 0–25% decrease in EASI).

Additionally, we collected the following data: age, gender, weight, previous treatments, initial response to dupilumab, and practicians' alleged reason for choosing any of the above-mentioned therapeutic options.

Statistics analysis

The categorical variables are presented with their associated numbers and compared using the Fisher's test. The quantitative variables are presented with their means and extreme values of the series (lower, higher) and compared *via* a Student's *t*-test (or Wilcoxon Mann Whitney test if the conditions of validity were not met) for comparisons with 2 groups and ANOVA (or Kruskal Wallis if the conditions of validity were not met) for comparisons with more than 2 groups. The results of the statistical tests of comparison are presented as p-values. A difference was considered significant if the p-value was less than 0.05.

RESULTS

Forty-eight patients were included (30 men): 42 patients had shown a PR (87.5%) and 6 had shown NR (12.5%) after 3 months of dupilumab 300mg/2 weeks. Their baseline characteristics are presented in Table 1. To be noted, 21.4% of the PR patients had a *de novo* or worsening HAND. As shown in Table 2, 21 patients received an increased dose of dupilumab (300mg/7 or 10 days), and 27

Age, mean (range), years	36 (19–64)
Sex ratio M/F	1.67
Weight, mean (range), kg	70.8 (45–118)
Baseline SCORAD at dupilumab initiation, mean (range) n = 39	53 (18–94)
Baseline IGA at dupilumab initiation, mean (range) n = 38	3.3 (2–4)
Baseline EASI at dupilumab initiation, mean (range) n = 23	19.4 (2.1–49)
Baseline DLQI at dupilumab initiation, mean (range) n = 35	15.8 (1–30)
Previous treatment with cyclosporin A, number of patients (%)	37 (77.1)
Previous treatment with methotrexate, number of patients (%)	22 (45.8)
Previous treatment with phototherapy, number of patients (%)	28 (58.3)

Table 1. Baseline characteristics of the 48 patients with an initial inadequate response after 3 months of dupilumab 300mg/2weeks. *M male, F female, SCORAD SCORing Atopic Dermatitis, IGA Investigator's Global Assessment, EASI Eczema Area and Severity Index, DLQI Dermatology Life Quality Index, n number of patients with available data.*

Number of patient	Gender	Age, years	Weight, kg	Treatment prior to dupilumab			Scores at dupilumab initiation				Initial response to dupilumab (M3)	De novo or worsening of a HAND in patients with partial response to dupilumab (M3)	Treatment options	Response to the treatment options (M3)	Subsequent treatment with JAKi, mg/day
				MTX	Photo-therapy	CsA	SCORAD	DLQI	EASI	IGA					
1	m	23	63			1	na	na	na	2	PR		Combination of dupilumab with CsA	CR	
2	m	31	65			1	33.1	9	na	na	PR	yes	Combination of dupilumab with MTX	CR	
3	m	27	75			1	50.3	25	na	4	PR		Combination of dupilumab with MTX	NR	upadacitinib 30
4	m	48	80		1	1	47	19	na	4	NR		Combination of dupilumab with CsA	PR	
5	m	60	70		1	1	60	13	na	na	NR		Combination of dupilumab with MTX	PR	upadacitinib 30
6	m	26	80			1	51.6	7	na	na	PR		Increased dose of dupilumab	CR	
7	f	48	95		1		56	23	na	na	PR	yes	Combination of dupilumab with ITRA	NR	
8	f	33	64	1		1	na	na	na	3	PR		Increased dose of dupilumab	CR	
9	m	57	59		1	1	67	na	na	na	PR		Increased dose of dupilumab	CR	
10	m	38	95			1	18	na	na	na	PR		Combination of dupilumab with CsA	CR	
11	m	28	84				29.2	na	na	na	PR		Combination of dupilumab with ITRA	NR	
12	m	39	70	1			51	14	16	3	PR	yes	Combination of dupilumab with ITRA	NR	

(continued)

Number of patient	Gender	Age, years	Weight, kg	Treatment prior to dupilumab			Scores at dupilumab initiation				Initial response to dupilumab (M3)	De novo or worsening of a HAND in patients with partial response to dupilumab (M3)	Treatment options	Response to the treatment options (M3)	Subsequent treatment with JAKi, mg/day
				MTX	Photo-therapy	CsA	SCORAD	DLQI	EASI	IGA					
13	f	36	51	1	1	1	45	24	2.1	2	PR		Combination of dupilumab with MTX	NR	
14	m	21	60	1	1	1	46	27	na	3	PR		Increased dose of dupilumab	PR	
15	f	32	56		1		na	3	17.6	3	PR		Increased dose of dupilumab	CR	
16	m	51	83	1	1		26	3	14.7	2	PR	yes	Combination of dupilumab with ITRA	CR	
17	m	30	63	1	1	1	94	30	49	4	PR		Combination of dupilumab with CsA	CR	
18	f	39	93	1		1	55	25	19	4	PR		Increased dose of dupilumab	CR	
19	m	34	85	1		1	50	23	11	3	NR		Increased dose of dupilumab	PR	
20	f	27	53		1		63		22.8	3	RP		Increased dose of dupilumab	NR	upadacitinib 30
21	f	61	88	1	1	1	70	25	20	4	RP	yes	Combination of dupilumab with ITRA	CR	
22	f	26	53		1	1	47	20	17	4	RP		Combination of dupilumab with CsA	PR	
23	f	44	55	1	1		38	25	12	3	RP	yes	Combination of dupilumab with ITRA	CR	
24	m	36	95	1	1	1	55	26	18	4	RP		Increased dose of dupilumab	NR	baracitinib 4
25	m	26	63		1	1	30.5	5	5	2	RP	yes	Combination of dupilumab with ITRA	PR	

26	m	40	70		1	1	26	6	4.5	2	RP		Combination of dupilumab with MTX	CR	
27	f	24	63			1	72.5	21	25.2	4	RP		Combination of dupilumab with MTX	CR	
28	f	49	69		1		60	12	10.4	4	RP		Combination of dupilumab with MTX	PR	
29	m	26	62	1	1	1	71.5	14	16.4	4	RP	yes	Combination of dupilumab with MTX	PR	
30	m	34	88	1	1	1	na	na	na	4	NR		Combination of dupilumab with MTX	NR	
31	m	32	79	1		1	68.3	4	36.3	3	PR		Increased dose of dupilumab	CR	
32	f	22	65			1	42	8	29.6	3	PR		Increased dose of dupilumab	NR	upadacitinib 30
33	m	22	78	1		1	38	3	na	na	NR		Increased dose of dupilumab	NR	
34	f	35	90	1		1	48	na	na	na	NR		Increased dose of dupilumab	NR	
35	m	42	69	1	1	1	na	na	na	3	PR		Increased dose of dupilumab	CR	
36	f	45	78	1	1	1	82	16	na	3	PR		Increased dose of dupilumab	NR	upadacitinib 30
37	m	56	118				41	18	na	3	PR		Increased dose of dupilumab	CR	
38	m	19	46			1	64	8	na	3	PR		Combination of dupilumab with MTX	CR	
39	m	44	48		1	1	68	21	na	3	PR		Combination of dupilumab with MTX	CR	
40	m	64	75	1	1		63	7	na	3	PR		Combination of dupilumab with MTX	CR	
41	f	37	45	1	1	1	30	7	na	2	PR		Combination of dupilumab with MTX	CR	upadacitinib 30

(continued)

Number of patient	Gender	Age, years	Weight, kg	Treatment prior to dupilumab			Scores at dupilumab initiation				Initial response to dupilumab (M3)	De novo or worsening of a HAND in patients with partial response to dupilumab (M3)	Treatment options	Response to the treatment options (M3)	Subsequent treatment with JAKi, mg/day
				MTX	Photo-therapy	CsA	SCORAD	DLQI	EASI	IGA					
42	m	21	62			1	na	na	na	na	PR	yes	Combination of dupilumab with ITRA	PR	
43	m	51	67		1	1	76	29	34.4	4	PR		Increased dose of dupilumab	PR	upadacitinib 30
44	f	29	66	1	1	1	69	5	18.5	4	PR		Increased dose of dupilumab	NR	upadacitinib 30
45	f	52	68	1	1	1	66	na	24	4	PR		Increased dose of dupilumab	NR	upadacitinib 30
46	m	21	50			1	na	na	22.5	4	PR		Increased dose of dupilumab	NR	upadacitinib 30
47	m	31	80				na	29	na	4	PR		Increased dose of dupilumab	CR	
48	f	15	64		1	1	na	na	na	3	PR		Combination of dupilumab with MTX	PR	

Table 2. (Continued) Characteristics of the patients and response to treatment options. *m male, f female, na data not available, CR complete or almost complete response, PR partial response, NR no response, CsA cyclosporin A, MTX methotrexate, ITRA itraconazole, M month, JAKi Janus Kinase inhibitors, HAND head and neck dermatitis, SCORAD scoring atopic dermatitis, EASI eczema area and severity index, IGA investigator's global assessment*

received a combination of dupilumab 300mg/2 weeks with 1 of the following drugs: CsA (3–5mg/kg every day or twice a week) in 5 patients previously prescribed with CsA; MTX (mean dosage 13.1mg/week, range 10–20) in 14 patients including 5 previously prescribed with MTX; ITRA (28.5–200mg/day) in 8 ITRA-naïve patients. Patients with a *de novo* or worsening HAND were more likely to be prescribed with additional ITRA. Patients with a higher baseline EASI at dupilumab initiation were more likely to be prescribed with additional CsA, whereas patients who were prescribed with additional MTX had a lower EASI. Patients with a higher weight at dupilumab initiation were less likely to be prescribed with additional MTX than an increased dose of dupilumab (Table S1).

Overall, 68.75% of the included patients achieved at least a PR, including 45.8% of CR. The mean duration of treatment was 5.8 months (range, 1–24). Increasing the dosage of dupilumab resulted in 14.3% of PR and 42.8% of CR. Combination with CsA resulted in 40% of PR and 60% of CR. Combination with MTX resulted in 28.6% of PR and 50% of CR. Combination with ITRA resulted in 25% of PR and 37.5% of CR.

Age, gender, weight, or severity scores (IGA, DLQI) before dupilumab first initiation did not influence the response. However, patients showing an initial NR never achieved a CR to further options (versus 52.4% of patients with an initial PR, $p = 0.025$) (Table S2).

Three patients discontinued combination therapy due to adverse events including drug-induced colitis and digestive intolerance with MTX ($n = 1$), digestive intolerance with ITRA ($n = 1$) and an episode of tachycardia with ITRA ($n = 1$). Of these, only 1 had achieved a CR to the additional MTX and was subsequently treated with a JAKi.

DISCUSSION

In this French retrospective multicentric study of 48 AD patients with an inadequate response after 3 months of dupilumab 300mg/2weeks, up to 45.8% of the patients achieved a CR to alternative regimen maintaining dupilumab, either increasing its dose or combining with MTX, CsA or ITRA, though none proved significantly better. Digestive intolerance and tachycardia led to treatment discontinuation in 3 patients with MTX and ITRA.

In NR patients after 3 months of dupilumab 300mg/2weeks, no further CR could be achieved after 3 months of any alternative regimen, and a PR could be achieved in only half of them. This result may prompt for an earlier-than-6-months switch of dupilumab towards alternative treatments like JAKi. Indeed, a maintained but no additional efficacy of dupilumab was shown after 16 weeks in long-term studies.[1]

Patients prescribed with a combination therapy of dupilumab and CsA showed at least a PR and no adverse effects in a short-term follow-up. CsA had already been prescribed in these 5 patients prior to dupilumab, according with on-label use of dupilumab in France, and had been interrupted because of PR or NR and/or clinical or biological adverse effects. In a recent drug survival study, only 16% of AD patients discontinued CsA because of adverse effects, none of them serious.[7] Moreover, adding CsA might reduce dupilumab-induced conjunctivitis. However, the duration of CsA treatment should not be over 1 year; thus the combination of dupilumab and MTX could be an interesting alternative, even in patients who had shown a PR or NR to MTX prior to dupilumab. Interestingly, out of the 5 patients previously prescribed with MTX prior to dupilumab, 2 had a CR with the combination of dupilumab with MTX, 2 showed NR and 1 had digestive adverse effects. This result is in line with a previous study showing that MTX was efficient and well tolerated in AD patients.[8] However, the combination of dupilumab and MTX in our study was prescribed in patients with a lower mean EASI score (see Table S1: 11.7 vs 13.5 to 33, $p = 0.02$). This result suggests that this combination could rather be proposed to patients with milder disease. The combination of dupilumab with ITRA was almost exclusively proposed to patients with *de novo* or worsening dupilumab-associated HAND, according to the results of a previous study.[9] Despite an acceptable PR and CR rate of 62.5% in our study, a recent study[10] showed that patients prescribed with such a combination achieved a shorter and less good response than those prescribed with a JAKi treatment. Increasing the dose of dupilumab by narrowing the time interval between injections

showed at least a PR in 57.1% of patients, almost exclusively in patients with an initial PR to dupilumab 300mg/2weeks. This result is not different from the other therapeutic options combining dupilumab with MTX, CsA or ITRA, but it dramatically increases costs.

In this study, no combination therapy of dupilumab with JAKi was reported. Such a combination was rarely reported in the literature,[11] although achieving a better response in severe AD patients than the combination of dupilumab with CsA or systemic steroids.[4]

Limitations of this study include small sample size and a retrospective nature. The so-called "end-of-dose" effect, which refers to the relapse of pruritus or AD skin lesions shortly before next administration of dupilumab, was not assessed in this study, although it may be predictive of a better response to the narrowing of injections interval. Also the occurrence of a dupilumab-induced conjunctivitis was not under the scope of our study, while it could have altered the practicians' decision to choose combination therapy over increasing the dose of dupilumab, despite a previous study reported a similar rate of adverse events between weekly versus every-two-weeks injections.[12] The data in this study were mostly collected before the wide use of JAKi in AD in France, and the latter have dramatically modified the management of AD patients, providing a strict monitoring of their contraindications and adverse effects.

CONCLUSION

This retrospective study suggests that increasing the dose of dupilumab or combining dupilumab with CsA, MTX or ITRA may be safe options prior to a switch toward JAKi or in case of their contraindication. Additional treatments may be chosen upon particular phenotypes of AD or adverse effects of dupilumab monotherapy, such as HAND. Further studies are necessary to determinate the most favorable patients' profiles for each option and evaluate their comparative costs.

Abbreviations

AD, atopic dermatitis; CsA, cyclosporin A; DLQI, dermatology life quality index; EASI, eczema area and severity index; HAND, head and neck dermatitis; IGA, investigator's global assessment; ITRA, itraconazole; JAKi, Janus Kinase inhibitors; MTX, methotrexate; SCORAD, Scoring atopic dermatitis.

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Data availability statement

All data are available upon reader's request to the corresponding author.

Authors contribution

R Strizzolo made substantial contributions to conception and design, acquisition of data, analysis and interpretation of data; drafted the article; gave final approval of the version to be published.
J Seneschal made substantial contributions to conception and design, acquisition of data, analysis and interpretation of data; revised the article critically for important intellectual content; gave final approval of the version to be published.
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data; revising the article critically for important intellectual content; gave final approval of the version to be published. A Du-Thanh made substantial contributions to conception and design, acquisition of data, analysis and interpretation of data; drafted the article and revised it critically for important intellectual content; gave final approval of the version to be published.

Ethics statement
This study was approved by the Montpellier University institutional review board (IRB-MTP_2023_04_202100936).

Authors' consent for publication
I, the corresponding author, on behalf of all my co-authors, confirm our consent for publication.

Confirmation of unpublished work
This manuscript is original, has not been published before, is not currently being considered for publication elsewhere.

Declaration of competing interest
R Strizzolo reports no competing interest.
J Seneschal reports the following competing interests: Principal investigator or consultant or speaker for AbbVie, Almirall, Lilly, Sanofi, LeoPharma, Pierre Fabre, Pfizer; support for attending meetings from AbbVie.
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Appendix A. Supplementary data
Supplementary data to this article can be found online at https://doi.org/10.1016/j.waojou.2024.100923.

Author details
[a]Dermatology Department, University Hospital of Montpellier, Montpellier, France. [b]CHU de Bordeaux, National Reference Center for Rare Skin Diseases, CNRS UMR5164, ImmunoConCept, Univ. Bordeaux, Bordeaux, France. [c]Sorbonne Université, Department of Dermatology and Allergology, AP-HP, Tenon Hospital, 75020, Paris, France. [d]CHU Lille, Service de Dermatologie, Univ Lille, INSERM U1286, Lille Inflammation Translational Research Institute (INFINITE), F-59000, Lille, France. [e]Department of Dermatology, CHU Nantes, UMR 1280 PhAN, INRA, Nantes Université, Nantes, France. [f]Department of Dermatology-Venerology, University Hospital of Reims Champagne-Ardenne, Robert-Debré Hospital, Reims, France. [g]Department of Dermatology, Saint-Louis Hospital, APHP, Paris, France. [h]Centre Hospitalier Lyon Sud, Service d'Allergologie et Immunologie Clinique, Hospices Civils de Lyon, Pierre Bénite, France. [i]Department of Dermatology-Venerology, Toulouse, France. [j]Dermatology department, Aix-Marseille Université, FR-13885 Marseille, France.

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