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Title: Effectiveness and tolerance of Janus kinase inhibitors for the treatment of recalcitrant atopic dermatitis in a real-life French multicenter adult cohort

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Body of manuscript:

JAK inhibitors (JAKis) are newly available drugs for the treatment of moderate-to-severe atopic dermatitis (AD). Their efficacy and safety have been demonstrated in clinical trials[1-4], but there is little published data from real-life practice. Upadacitinib (UPADA), a JAK1-selective inhibitor, has been available for use in France in adolescents and adults with moderate-to-severe AD in accordance with the French Early Access Program for patients who failed treatment due to

inefficiency or intolerance or alternate treatments were contraindicated (e.g., cyclosporine (CyA), dupilumab). A second JAKi, baricitinib (BARI) which targets JAK1/JAK2, has been available since March 2021 in adult AD patients after failed cyclosporine (CyA) treatment. We assessed the effectiveness and tolerance of JAKis in real life by conducting a multicenter retrospective cohort that included the first AD patients who received UPADA and BARI from March 2021 to January 2022. The primary outcome was the percentage of patients obtaining an Investigator's Global Assessment (IGA) score at 0, 1 or -2 at 3 (± 1) months (M3) compared with baseline. The secondary outcomes were Scoring Atopic Dermatitis (SCORAD), Eczema Area and Severity Index (EASI), Pruritus Numerical Rating Scale (PNRS), and Dermatological Life Quality Index (DLQI) scores at M3 and at 6 (± 1) months (M6). All adverse events (AEs) during the study period were recorded. 100 patients were enrolled from 18 centers: 54 treated with UPADA at 15 mg/day, 12 with UPADA at 30 mg/day, and 34 with BARI at 4 mg/day. Patient characteristics are detailed in **Supplementary Table I (https://data.mendeley.com/datasets/5zw326gw6v/1)**. Most patients had severe AD (median IGA at baseline, 3; IQR 3;4) and had previously received a mean number of 3 types of systemic drugs before JAKi introduction (methotrexate in 56.6%, CyA in 72% and dupilumab in 78%), interrupted for inefficacy and/or poor tolerance. An IGA score at 0, 1 or -2 compared with baseline was reached at M3 for 33/54 (61.1%), 11/12 (91.7%) and 14/34 (41.2%) patients receiving UPADA 15 mg, UPADA 30 mg or BARI 4 mg, respectively. The median decrease in PNRS at M3 was -3 (IQR -5.5;-1.5), -5 (-7;-1) and -2 (-3;0) in patients receiving UPADA 15 mg (data available for 24 patients), UPADA 30 mg (6 patients) and BARI 4 mg (19 patients), respectively. Other outcomes measured at month 3 and month 6 are shown in **Table I**. The median follow-up duration was 3 months (IQR 3;6). Overall, 60 patients presented at least 1 AE, the most frequent being increased blood levels of cholesterol (23.2%) or triglycerides (18.2%), facial papular eruption (12.9%), increased ALAT and/or ASAT (11.1%) and herpes infection (6.4%) **(Table II)**. No thromboembolic events were observed. JAKis were stopped in 18 patients (9 patients taking UPADA 15 mg, 1 taking UPADA 30 mg and 8 taking BARI 4 mg), primarily for drug inefficacy (9/21) and/or for AE (6/21) **(Supplementary Table**

II) (https://data.mendeley.com/datasets/5jy3c6jrrr/1). In summary, this real-life study highlighted the effectiveness of JAKis in a population of AD patients recalcitrant to conventional systemics and biologics and demonstrated a good short-term safety profile.

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Table I. Efficacy outcomes reported at 3 months (M3) and 6 months (M6) in patients treated with JAKi.

	Outcomes at M3								Outcomes at M6							
	All patients		Upadacitinib 15 mg		Upadacitinib 30 mg		Baricitinib 4 mg		All patients		Upadacitinib 15 mg #		Upadacitinib 30 mg		Baricitinib 4 mg	
	N	Number of patients achieving score (%)	N	Number of patients achieving score (%)	N	Number of patients achieving score (%)	N	Number of patients achieving score (%)	N	Number of patients achieving score (%)	N	Number of patients achieving score (%)	N	Number of patients achieving score (%)	N	Number of patients achieving score (%)
IGA 0, 1 or 2	100	58 (58%)	54	33 (61.1%)	12	11 (91.7%)	34	14 (41.2%)	30	12 (40%)	24	9 (37.5)	4	3 (75.0)	2	0
SCORAD50	53	28 (52.8%)	30	17 (56.7%)	9	7 (77.8%)	14	4 (28.6%)	17	5 (29.4%)	12	3 (25%)	3	2 (66.7%)	2	0
SCORAD75	53	9 (17.0%)	30	4 (13.3%)	9	4 (44.4%)	14	1 (7.1%)	17	2 (11.8%)	12	1 (8.3%)	3	1 (33.3%)	2	0
SCORAD90	53	5 (9.4%)	30	3 (10%)	9	2 (22.2%)	14	0	17	1 (5.9%)	12	0	3	1 (33.3%)	2	0
EASI50	24	13 (54.2%)	14	6 (42.9%)	7	6 (85.7%)	3	1 (33.3%)	10	5 (50%)	8	3 (37.5%)	2	2 (100%)	0	-
EASI75	24	9 (37.5%)	14	5 (35.7%)	7	4 (57.1%)	3	0	10	5 (50%)	8	3 (37.5%)	2	2 (100%)	0	-
EASI90	24	5 (20.8%)	14	1 (7.1%)	7	4 (57.1%)	3	0	10	1 (10%)	8	0	2	1 (50%)	0	-
	N	**Absolute value compared with baseline**	N	**Absolute value compared with baseline**	N	**Absolute value compared with baseline**	N	**Absolute value compared with baseline**	N	**Absolute value compared with baseline**	N	**Absolute value compared with baseline**	N	**Absolute value compared with baseline**	N	**Absolute value compared with baseline**
Median PNRS (Q1;Q3)	49	-3 (-5;-1)	24	-3 (-5.5;-1.5)	6	-5 (-7;-1)	19	-2 (-3;0)	14	-3.5 (-5;0)	12	-3.5 (-5.5;-1.5)	1	3 (3;3)	1	-5 (-5;-5)
Median DLQI (Q1;Q3)	15	-5 (-9;-3)	13	-5 (-8;-3)	2	-11 (-15;-7)	0	-	10	-6.5 (-15;-1)	8	-2 (-12;0)	2	-17 (-19;-15)	0	-

Because the follow-up time was not standardized among the different centers, the IGA, SCORAD, EASI, PNRS and DLQI scores at three months (M3) were defined by the highest (or worst) scores recorded after either two, three or four months of treatment. The same scores at six months (M6) were defined by the highest (or worst) scores recorded after either five, six or seven months of treatment.

including 13 patients who received upadacitinib 15 mg from M0 to at least M3 and then 30 mg; 4 patients (30.7%) obtained an IGA score of 0-2 at M6.

N: Number of patients with available data. IGA: Investigator's Global Assessment. SCORAD: Scoring Atopic Dermatitis. EASI: Eczema Area and Severity Index. PNRS: Pruritus Numerical Rating Scale. DLQI: Dermatological Life Quality Index. Q1: first quartile. Q3: third quartile. SCORAD50/75/90: Patients achieving 50/75/90% amelioration of SCORAD compared to baseline. EASI 50/70/90: Patients achieving 50/75/90% amelioration of EASI compared to baseline.

Table II Adverse events reported during the follow-up period in patients treated with JAK inhibitors.

Adverse event (AE)	All patients		Upadacitinib 15 mg		Upadacitinib 30 mg		Baricitinib 4 mg	
	N patients with data available	Patients, n (%)	N patients with AE	Patients, n (%)	N patients with AE	Patients, n (%)	N patients with AE	Patients, n (%)
At least 1 adverse event	100	60 (60.0)	54	35 # (64.8)	12	6 (50.0)	34	19 (55.9)
At least 1 biological adverse event	99	44 (44.4)	53	25 (47.2)	12	2 (16.7)	34	17 (50.0)
At least 1 clinical adverse event	100	30 (30.0)	54	19 (35.2)	12	4 (33.3)	34	7 (20.6)
Increased* LDL cholesterol or total cholesterol	99	23 (23.2)	53	13 (24.5)	12	1 (8.3)	34	9 (26.5)
Increased* triglycerides	99	18 (18.2)	53	12 (22.6)	12	1 (8.3)	34	5 (14.7)
Facial papular eruptions	93	12 [1] (12.9)	53	9 (17)	9	3 (33.3)	31	0
Increased ALAT and/or ASAT §	99	11 (11.1)	53	6 (11.3)	12	2 (16.7)	34	3 (8.8)
Increased* CPK §	99	8 (8.1)	53	6 (11.3)	12	2 (16.7)	34	0
HSV infections	94	6 (6.4)	54	4 (7.4)	9	2 (22.2)	31	0
Headaches	93	5 (5.4)	54	4 (7.4)	9	0	30	1 (3.3)
Upper airway infections	95	3 (3.2)	54	0	10	0	31	3 (9.7)
Lymphopenia	99	3 (3.0)	53	3 (5.7)	12	0	34	0
Nausea	95	2 (2.1)	54	1 (1.9)	10	0	31	1 (3.2)
Increased* creatinine clearance §	99	2 (2.0)	53	0	12	0	34	2 (5.9)
Neutropenia §	99	2 (2.0)	53	2 (3.8)	12	0	34	0
Diarrhea	95	1 (1.1)	54	0	10	1 (10)	31	1 (3.2)
Abdominal pain	95	1 (1.1)	54	1 (1.9)	10	0	31	0
Cough	93	1 (1.1)	54	1 (1.9)	8	0	31	0
Herpes zoster	95	1 (1.1)	54	1 (1.9)	10	0	31	0
Fever	95	1 (1.1)	54	0	10	1 (10)	31	0
Weight increase	95	1 (1.1)	54	1 (1.9)	10	0	31	0
Anemia §	99	1 (1.0)	53	1 (1.9)	12	0	34	0
Thrombocytosis §	99	1 (1.0)	53	0	12	0	34	1 (2.9)
Other clinical abnormalities [2]	95	15 (15.7)	54	7 (12.3)	10	2 (20)	31	6 (19.4)
Other biological abnormalities [3] §	99	12 (12.1)	53	6 (11.3)	12	1 (8.3)	34	5 (14.7)

including 13 patients who received upadacitinib 15 mg from M0 to at least M3 and then 30 mg; 4 patients (30.7%) obtained an IGA score of 0-2 at M6.

* increased according to local laboratory threshold values

[1] including 6 acne and 6 papulopustular eruptions

[2] including myalgia, asthenia, urticaria, chronic leg ulceration, wart, dermatophytosis, chest pain, dyspnea, molluscum contagiosum, folliculitis, gonalgia, urinary tract infection, facial edema, scalp pruritus, impetigo, dyspepsia, and dizziness.

[3] including C reactive protein elevation, monocytosis, hyperbasophilia, and eosinophilia.

225 § all cases asymptomatic

226 N: Number of patients with available data. LDL: low-density lipoprotein. ALAT (alanine aminotransferase) and/or
227 ASAT (aspartate aminotransferase). CPK: creatine phosphokinase

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