Effectiveness And Factors Associated With Minimal Disease Activity In Upadacitinib-treated Psoriatic Arthritis Patients: 24-week Results Of A Real-life Multicenter Study (UPREAL-PsA)

Valentino Paci[1], Antonio Carletto[2], Alen Zabotti[3], Roberta Ramonda[4], Maria Sole Chimenti[5], Lorenzo Dagna[6], Nicoletta Luciano[7], Anna Piccinelli[2], Ivan Giovannini[3], Giovanni Striani[4], Nicola Boffini[6], Gilda Sandri[8], Niccolò Possemato[9], Ilenia Pantano[10], Devis Benfaremo[1], Carlo Salvarani[8,9], Francesco Ciccia[10], Carlo Selmi[7,7+1], Gianluca Moroncini[1], Michele Maria Luchetti Gentiloni[1*]

*[1]Clinical Medicine and #Internal Medicine Residency Program, Department of Clinical and Molecular Sciences, Marche Polytechnic University and Internal Medicine Department, Azienda Ospedaliero Universitaria delle Marche, Ancona, Italy; [2]Department of Medicine, Rheumatology Operative Unit, AOUI Verona, Italy; [3]Rheumatology Institute, Department of Medicine, University of Udine, Azienda Sanitaria Universitaria Friuli Centrale, Italy; [4]Rheumatology Unit, Department of Medicine-DIMED, University of Padova, Italy; [5]Rheumatology, Allergology and Clinical Immunology, University of Rome "Tor Vergata", Roma, Italy; [6]Unit of Immunology, Allergy and Rare Diseases (UnIRAR), IRCCS San Raffaele Scientific Institute, Milano, Italy; [7]Department of Rheumatology and Clinical Immunology, IRCCS Humanitas Research Hospital, Rozzano; [7+1] Department of Biomedical Sciences, Humanitas University, Pieve Emanuele; [8]Department of Maternal, Infantile and Adult Medical and Surgical Sciences, University of Modena and Reggio Emilia, Modena, Italy; Rheumatology Unit, Azienda USL-IRCCS di Reggio Emilia, Reggio Emilia, Italy.; [10]Department of Precision Medicine, Rheumatology Unit, University della Campania L. Vanvitelli, Naples, Italy. ***Corresponding author: m.luchetti@staff.univpm.it**

Background

Psoriatic arthritis (PsA) is an immune-mediated musculoskeletal disease characterized by clinical heterogeneous manifestations (disease domains). This clinical peculiarity makes difficult the therapeutic choice and the "optimal" therapy should be broad and effective on each clinical manifestation of the disease.

Objective

Upadacitinib (UPA) is a selective JAK inhibitor recently approved for the treatment of psoriatic arthritis (PsA), and thus there are no available data on its performance in real-world clinical practice. In this observational study (UPREAL-PsA), we evaluated UPA's real-life effectiveness and safety in a large multicentric cohort of patients with PsA.

Methods

One-hundred twenty-six (126) patients with PsA treated with UPA at 10 Italian centres were evaluated at baseline, week 12 (w12), and week 24 (w24) for clinimetrics, laboratory tests, and adverse events.

PsA Patients Total number (%)		Females 86 (68.3)	Males 40 (31.7)	p	Bio-Naive 17 (13.5)	Bio-Failure 109 (86.5)	p	Ax (±Per) 54 (42.9)	Per (only) 72 (57.1)	p	Oligo 39(31.0)	Poly 85 (67.5)	p	Active PsO 52 (41.3)	Inactive PsO 74 (58.7)	p
Gender, female	86 (68.3)	86 (100)	0	<0.01	13 (76.5)	73 (67.0)	0.434	41 (75.9)	45 (62.5)	0.109	24 (61.5)	61 (71.8)	0.255	33 (63.5)	53 (71.6)	0.333
Gender, male	40 (31.7)	0 (0)	40 (100)	<0.01	4 (23.5)	36 (33.0)	0.434	13 (24.1)	27 (37.5)	0.109	15 (38.5)	24 (28.2)	0.255	19 (36.5)	21 (28.4)	0.333
Age, years ± SD	56.5±11.4	56.4±11.8	56.5±11	0.424	57.5±13.1	56.3±11.2	0.315	56.2±10.5	56.6±12.1	0.482	56.4±10.7	56.4±11.5	0.428	56.1±11.4	56.7±11.5	0.457
BMI, value ± SD	26.7±5.1	26.2±4.9	27.8±5.3	0.057	24.4±3.6	27.1±5.2	**0.027**	27.1±5.1	26.4±5.0	0.220	25.5±5.4	27.3±4.9	**0.038**	27.0±5.2	26.5±5.0	0.309
Cardiovascular Diseases[a]	40 (31.8)	27 (31.4)	13 (32.5)	0.451	4 (23.5)	36 (33.0)	0.219	23 (42.6)	17 (23.6)	**0.012**	13 (33.3)	25 (29.4)	0.331	16 (30.8)	24 (32.4)	0.422
Hypertension	27 (21.4)	20 (23.3)	7 (17.5)	0.464	3 (17.7)	24 (22.0)	0.683	15 (27.8)	12 (16.7)	0.133	10 (25.6)	16 (18.8)	0.387	8 (15.4)	19 (25.7)	0.166
Metabolic Diseases[b]	32 (25.4)	23 (26.7)	9 (22.5)	0.307	2 (11.8)	30 (27.5)	0.083	16 (29.6)	16 (22.2)	0.174	3 (7.7)	27 (31.7)	**<0.01**	12 (23.1)	20 (27.0)	0.309
Obesity	23 (18.3)	14 (16.3)	9 (22.5)	0.400	1 (5.9)	22 (20.2)	0.154	10 (18.5)	13 (18.1)	0.947	5 (12.8)	18 (21.2)	0.266	10 (19.2)	13 (17.6)	0.812
Diabetes type II	12 (9.5)	8 (9.3)	4 (10.0)	0.901	0 (0.0)	12 (11.0)	0.150	6 (11.1)	6 (8.3)	0.599	2 (5.1)	10 (11.8)	0.246	6 (11.5)	6 (8.1)	0.518
Depression/ Anxiety Disorder	18 (14.3)	13 (15.1)	5 (12.5)	0.964	2 (11.8)	16 (14.7)	0.901	11 (20.4)	7 (9.7)	0.089	6 (15.4)	12 (14.1)	0.447	5 (9.6)	13 (17.6)	0.384
Neoplastic Diseases[c]	7 (5.6)	4 (4.7)	3 (7.5)	0.260	0 (0.0)	7 (6.4)	0.143	4 (7.4)	3 (4.2)	0.218	4 (10.3)	3 (3.5)	0.067	4 (7.7)	3 (4.1)	0.192
Other Comorbidities[d]	98 (77.8)	69 (80.2)	29 (72.5)	0.168	11 (64.7)	87 (79.8)	**0.049**	44 (81.5)	54 (75.0)	0.195	30 (76.9)	67 (78.8)	**0.046**	44 (84.6)	54 (73.0)	0.132
Peripheral PsA	124 (98.4)	85 (98.8)	39 (97.5)	0.576	17 (100.0)	107 (98.2)	0.573	53 (98.1)	71 (98.6)	0.837	39(100.0)	85(100.0)	/	52 (100.0)	72 (97.3)	0.232
Axial PsA	54 (42.9)	41 (47.7)	13 (32.5)	0.109	2 (11.8)	52 (47.7)	**<0.01**	54 (100.0)	0 (0.0)	<0.01	17 (43.6)	36 (42.4)	0.897	21 (40.4)	33 (44.6)	0.638
Enthesitis	69 (54.8)	52 (60.5)	17 (42.5)	0.059	12 (70.6)	57 (52.3)	0.159	28 (51.9)	41 (56.9)	0.570	25 (64.1)	43 (50.6)	0.160	26 (50.0)	43 (58.1)	0.368
Dactylitis	30 (23.8)	19 (22.1)	11 (27.5)	0.507	3 (17.6)	27 (24.8)	0.521	12 (22.2)	18 (25.0)	0.717	5 (12.8)	23 (27.1)	0.078	13 (25.0)	17 (23.0)	0.793
Skin	78 (61.9)	52 (60.5)	26 (65.0)	0.626	10 (58.8)	63 (62.4)	0.779	35 (64.8)	43 (59.7)	0.560	23 (59.0)	54 (63.5)	0.627	52 (100.0)	27 (36.5)	**<0.01**
Nails	44 (34.9)	27 (31.4)	17 (42.5)	0.224	9 (52.9)	35 (32.1)	0.094	17 (31.5)	27 (37.5)	0.483	13 (33.3)	30 (35.3)	0.831	28 (53.8)	16 (21.6)	**<0.01**
Uveitis (ever).	6 (4.8)	4 (4.7)	2 (5.0)	0.932	0 (0.0)	6 (5.5)	0.322	4 (7.4)	2 (2.8)	0.227	2 (5.1)	4 (4.7)	0.919	3 (5.8)	3 (4.1)	0.656
IBD (ever)	6 (4.8)	4 (4.7)	2 (5.0)	0.932	1 (5.9)	5 (4.6)	0.816	4 (7.4)	2 (2.8)	0.227	2 (5.1)	3 (3.5)	0.674	3 (5.8)	3 (4.1)	0.656
DAPSA, mean ± SD	27.7±10.0	28.4±10.5	26.1±9.0	0.123	25.7±10.1	28.0±10.0	0.189	28.9±12.0	26.7±8.2	0.109	18.9±4.2	31.9±9.2	**<0.01**	28.5±10.4	27.0±9.8	0.203
ASDAS, mean ± SD	2.4±0.7	2.5±0.6	2.2±0.6	**0.011**	2.2±0.5	2.4±0.7	0.053	2.7±0.7	2.2±0.6	**<0.01**	2.2±0.6	2.5±0.7	**0.013**	2.5±0.6	2.3±0.7	0.072
Disease Duration, months median (IQR)	92 (132)	83 (131)	103 (122)	0.233	21 (42)	103 (122)	**<0.01**	108 (110)	69 (127)	**0.038**	106 (131)	83 (129)	0.085	103 (159)	83 (106)	0.111

Table 1. Characteristics of the UPREAL-PsA study patients at baseline. Clinical features of patients' cohort in UPREAL-PsA (Upadacitinib therapy in the real-life in patients with psoriatic arthritis). **a-d** Cardiovascular, Metabolic, Neoplastic and Other Comorbidities are fully listed in Table 1b. PsA: Psoriatic Arthritis; PsO: Psoriasis; BMI: Body Mass Index; Ax: Axial PsA; Per: Peripheral PsA; Oligo: Oligoarticular involvement; Poly: Polyarticular Involvement; IBD: Inflammatory Bowel Disease; DAPSA: Disease Activity in Psoriatic Arthritis; ASDAS-CRP: Ankylosing Spondylitis Disease Activity Score with the C-reactive protein; SD: Standard Deviation; IQR: Interquartile Range. Statistical analysis conducted by "Stata" software- Wilcoxon test, and the p express the comparisons between the two-previous columns. P significant (in bold) if <0.05

CONCLUSIONS

This is the first real-life study on the effectiveness of UPA in PsA patients, and we have confirmed its effectiveness and safety profile observed in Phase III trials. Importantly, we have identified clinical and demographic predictors of response to UPA at 6 months in real life, with the greatest UPA effectiveness shown in males, bio-naïve patients, and those with high baseline CRP.

Moreover, it is noteworthy that UPA in real life demonstrated consistent efficacy in patients with axial inflammation up to the 24-week follow up and in patients who could be considered difficult to treat, as those refractory to bDMARDs.

RESULTS

Among the enrolled patients, 124/126 (98%) had peripheral involvement and 54/126 (43%) had prevalent axial inflammation. Sixteen (13%) were refractory to conventional synthetic DMARDS, and 113 (87%) had been intolerant/refractory to one or more biologic DMARDs.

At baseline, patients showed high disease clinical activity (DAPSA 27.7±10.0; ASDAS-CRP 2.4±0.7), particularly women, and patients with polyarticular involvement, metabolic comorbidities, higher body-mass-index and elevated C reactive protein (CRP) (Table 1).

At w24, UPA significantly improved DAPSA, ASDAS, LEI, and PASI scores in 66 (52%) patients. MDA status was achieved in 47% of patients (Fig.1, Table 2, A-B).

An analysis of clinical responses in patient subgroups (Fig. 2, A-B) revealed that: ***i***) normal CRP, oligoarticular and bio-naïve groups showed a rapid clinical improvement at week 12, maintaining the improved scores at week 24, while high CRP, polyarticular and bio-failure groups experienced a further significant improvement from week 12 to week 24; ***ii)*** patients with cardiovascular or metabolic comorbidities show improvement at week 12, which was maintained at week 24. ***iii)*** both female and male patients showed significant improvement at week 12 and continue to experience further significant improvement from week 12 to 24.

Finally, **the multivariate logistic regression analysis** demonstrated that male gender (OR 2.54, 95% CI 1.03-6.25 p=0.043), bio-naïve patients (OR 4.13, 95% CI 1.34-12.71, p=0.013), and patients with high baseline CRP levels (OR 2.49, 95% CI 1.02-6.12, p=0.046) had the highest probability of achieving MDA response at week 24.

UPA was discontinued in 13 (10%) patients for inefficacy or non-serious adverse events (AE). No life-threatening serious AE was observed during the 24-week follow up.

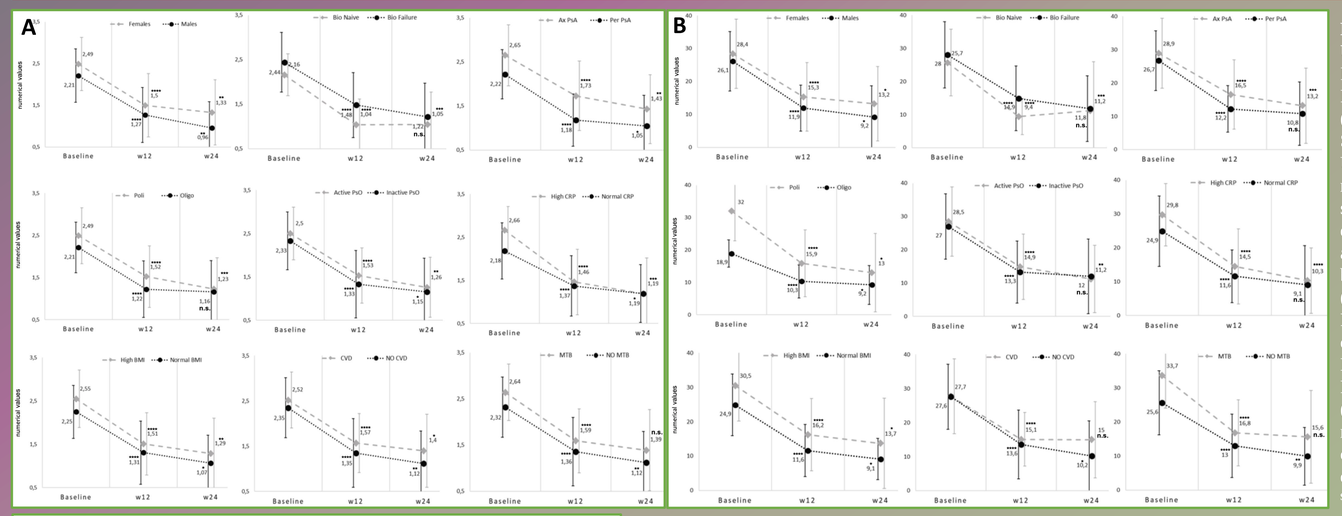

Figure 2. Clinical responses to Upadacitinib in the UPREAL-PsA study. In A is shown DAPSA (Disease Activity in Psoriatic Arthritis) and in B ASDAS-CRP (Ankylosis Spondylitis Disease Activity Score with C-reactive protein) values in the UPREAL-PsA (Upadacitinib therapy in the real-life in patients with psoriatic arthritis) study at week 12(w12) and 24(w24) in different patients' subgroups: Bio-Naïve and Bio-Failure: naïve to or treated with biological drugs; AxPsA and PerPsA: axial (prevalent) or peripheral inflammation; Poli and Oligo: polyarticular or oligoarticular involvement; PsO: Psoriasis; Norm-CRP vs High-CRP: C-Reactive Protein normal or upper the normal limit (0.05 mg/dl); High- vs normal-BMI: body mass index>30 o <30, respectively; CVD: cardiovascular diseases; MTB: metabolic diseases. Statistical analysis: P-significance: n.s.: not significant; p: <0.05*, <0.01**, <0.001***, <0.0001****.

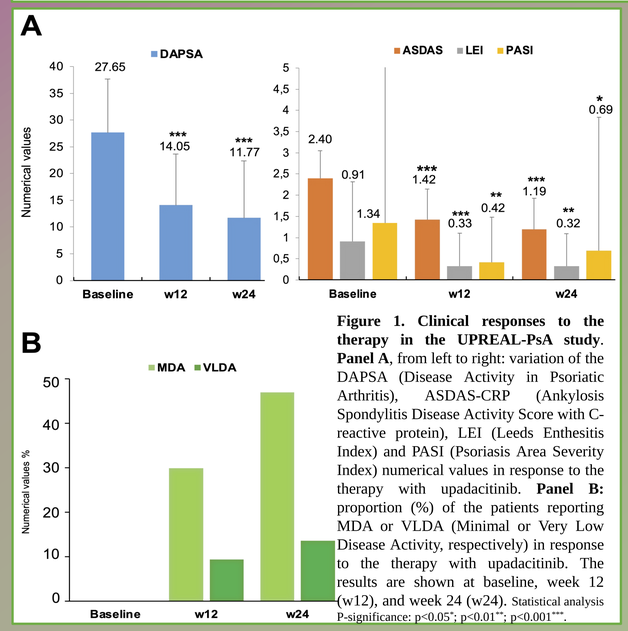

Figure 1. Clinical responses to the therapy in the UPREAL-PsA study. **Panel A**, from left to right: variation of the DAPSA (Disease Activity in Psoriatic Arthritis), ASDAS-CRP (Ankylosis Spondylitis Disease Activity Score with C-reactive protein), LEI (Leeds Enthesitis Index) and PASI (Psoriasis Area Severity Index) numerical values in response to the therapy with upadacitinib. **Panel B:** proportion (%) of the patients reporting MDA or VLDA (Minimal or Very Low Disease Activity, respectively) in response to the therapy with upadacitinib. The results are shown at baseline, week 12 (w12), and week 24 (w24). Statistical analysis P-significance: p<0.05*; p<0.01**; p<0.001***.

	Baseline	Week 12	p[a]	Week 24	p[b]
Nr. of patients (%)	126 (100.0)	97 (77.0)	/	66 (52.4)	/
Disease-Clinimetric Parameters					
Tender Joint Count, mean ± SD	9.36 ± 6.76	4.05 ± 4.70	**<0.001**	3.59 ± 6.35	**<0.001**
Swollen Joint Count, mean ± SD	3.02 ± 3.06	1.09 ± 2.53	**<0.001**	0.86 ± 2.19	**<0.001**
Leeds Enthesitis Index, mean ± SD	0.91 ± 1.41	0.33 ± 0.78	**<0.001**	0.32 ± 0.77	**0.0033**
PASI, mean ± SD	1.34 ± 4.17	0.42 ± 1.06	**0.0094**	0.69 ± 3.15	**0.0373**
PtGA (scale 0-100) mean ± SD	71.99 ± 16.6	43.42 ± 20.9	**<0.001**	36.06 ± 21.6	**<0.001**
PGA (scale 0-100) mean ± SD	63.11 ± 16.2	31.92 ± 21.1	**<0.001**	28.56 ± 23.8	**<0.001**
VAS (scale 0-100) mean ± SD	71.21 ± 18.0	42.50 ± 24.7	**<0.001**	33.11 ± 23.0	**<0.001**
HAQ, mean ± SD	1.24 ± 0.90	0.66 ± 0.78	0.0709	0.44 ± 0.56	**0.0075**
C-Reactive Protein, mg/dl	0.99 ± 1.80	0.40 ± 0.75	**<0.001**	0.35 ± 0.83	**<0.001**
DAPSA, mean ± SD	27.65 ± 10.0	14.05 ± 9.48	**<0.001**	11.77 ± 10.7	**<0.001**
ASDAS-CRP, mean ± SD	2.40 ± 0.65	1.42 ± 0.73	**<0.001**	1.19 ± 0.74	**<0.001**
Clinical Activity					
MDA nr. (%)	0 (0.0)	29 (30.9)	/	31 (47.0)	/
VLDA nr. (%)	0 (0.0)	9 (9.6)	/	9 (13.6)	/

Table 2. Clinical parameters, clinimetric test, and clinical response to the therapy in UPREAL-PsA study patients. Variation of clinical parameters and clinimetrics test in response to the therapy in UPREAL-PsA (Upadacitinib therapy in the real-life in patients with psoriatic arthritis) study at week 12(w12) and 24(w24). PASI: Psoriasis Area Severity Index; PtGA: Patient Global Assessment; PGA: Physician Global Assessment; VAS pain: Visual Analogue Scale for pain; HAQ: Health Assessment Questionnaire; DAPSA: Disease Activity in Psoriatic Arthritis; ASDAS-CRP: Ankylosing Spondylitis Disease Activity Score/C-reactive protein; MDA or VLDA: Minimal or Very Low Disease Activity, respectively. Statistical analysis. P significant (in bold) if <0.05; p[a] between baseline and w12 and p[b] between w12 vs w24.

	Odds Ratio	Std Error	z	p>|z|	95% Confidence Interval
Gender Male vs Female	2.537	1.166	2.02	***0.043***	1.030- 6.247
CRP High vs Normal	2.493	1.141	2.00	***0.046***	1.016- 6.115
Bio-DMARD Naive vs Failure	4.128	2.368	2.47	***0.013***	1.340-12.708
Psoriasis Active vs Inactive	0.462	0.211	-1.69	0.092	0.188-1.133

Table 3. Multivariate logistic regression. Results of the multivariate logistic regression analysis between the subgroups of the patients of the UPREAL-PsA (Upadacitinib therapy in the real-life in patients with psoriatic arthritis) study. Std Error, standard error, CRP, C Reactive Protein normal or upper (High) the normal limit (0.05 mg/dl); Bio-DMARD, biological Disease Modifying Anti-Rheumatic Drug naïve or refractory (Failure) to at least one biologic DMARDs. Statistical analysis was conducted using "Stata" software. P significant if <0.05 (shown in bold).