SCUOLA DERMATOLOGICA
SERGIO CHIMENTI
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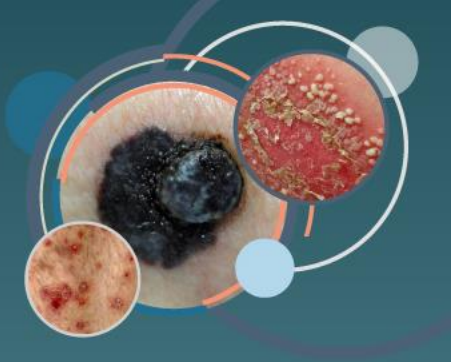
1° INCONTRO 2024
YES or NO CONTEST
Dermatology Update



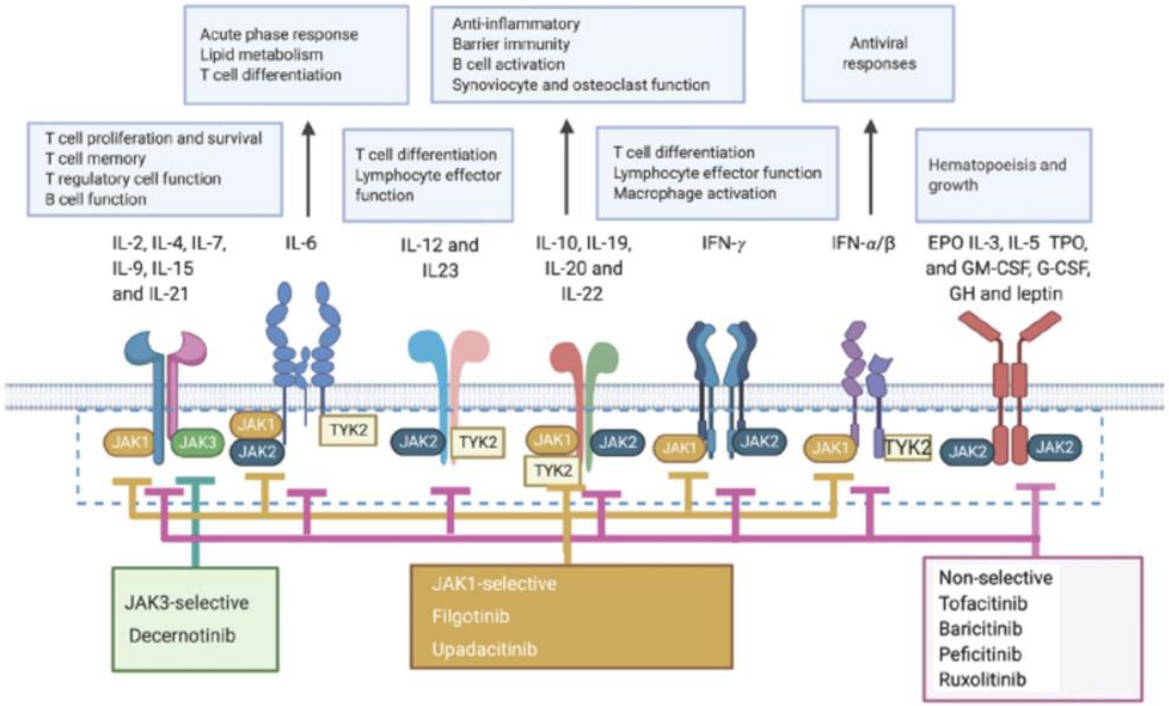
Enrico Matteini

Place-in-therapy delle small molecules nella psoriasi: Upadacitinib

1. Upadacitinib è un inibitore selettivo per JAK1 e JAK2?

1. **Sì**
2. **No**

Upadacitinib in PsA



Type I and II cytokine receptors (bound by over 50 cytokines, IL, IFNs, CSFs and hormones) - share a distinct intracellular signaling pathway mediated by JAKs

JAK-STAT signaling pathways are activated by more than 60 extracellular stimuli and phosphorylate downstream STAT proteins, which translocate to the nucleus and activate target genes

UPA is used for the treatment of RA, PsA, UC, CD and for nrSpA, AS

1. Akkoc N, et al. Curr Rheumatol Rep. 2021.

Upadacitinib in PsA: the **PTV experience**

	N	Mean	Range	σ
Patients, n	7			
Males, n	2			
Females, n	5			
Age, yrs		50,97	34,40-66,	±11,03
BMI, n		28,09	18,69-36,4	±6,34
Pso duration, yrs		13,49	3,48-28,3	±8,67
PsA duration, yrs		13,77	3,12-25,38	±8,03
Comorbidities, n				
HTN	4			
T2DM	1			
HCL	3			
HTG	3			
MOD	1			
IBD	1			
Other	4			

Table I. Patients' demographic and clinical characteristics, We treated **16 patients**, all affected by PsA according to CASPAR criteria. [2] In table I are reported all patients treated for at least 12 weeks. Concerning PsA clinical subtypes, 6/7 patients suffered from polyarthritis while 1 patient had an oligoarthritis with axial involvement (SpA). 1/7 patient suffered from Ulcerative Colitis and Hidradenitis Suppurativa. 2/7 patients had a diagnosis of Fibromyalgia Syndrome

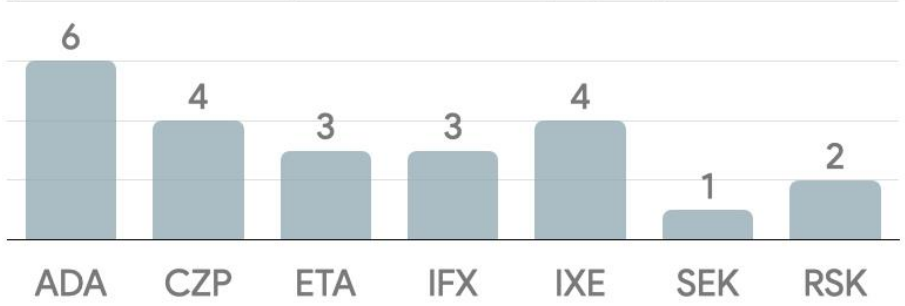


Figure 1. Patients' previous treatments. All patients were unresponsive to cDMARDs and to at least 2 bDMARD

1. Personal experience, for educational purpose only
2. Taylor W, Gladman D, et al. Classification criteria for psoriatic arthritis: development of new criteria from a large international study. Arthritis Rheum. 2006;54:2665-73

Diagnosis of PsA: the **CASPAR criteria**

CASPAR criteria were developed to standardize cohorts in PsA clinical trials, are useful to identify patients with PsA, but are not required for diagnosis, CASPAR classifies an individual as having PsA if they score 3 or more. Features within CASPAR include: a) the different structures that can be affected by inflammation b) a number of features typical of PsA such as psoriasis, nail disease, dactylitis and negative rheumatoid factor

ClASsification criteria for Psoriatic ARthritis criteria do not include early morning/post rest joint stiffness, ultrasound findings of synovitis/ tendonitis or radiological erosive damage, all of which can be an additional useful diagnostic indicators for PsA

	Clinical features	Score
1	Evidence of psoriasis	1 or 2
	Current psoriasis (skin/scalp disease) present today as judged by a dermatologist or rheumatologist	2
	Personal history of psoriasis obtained from patient, family doctor, dermatologist, rheumatologist or other qualified healthcare provide	1
	Family history of psoriasis in a first- or second-degree relative according to patient report	1
2	Psoriatic nail dystrophy *Typical psoriatic nail dystrophy including onycholysis, pitting and hyperkeratosis*	1
3	A negative test for rheumatoid factor	1
4	Dactylitis (swelling of an entire digit) [a] recorded by a rheumatologist	1
5	5. Radiological evidence of juxta-articular new bone formation [b]	1

(a) Current or previous history; (b) Ill-defined ossification near joint margins (but excluding osteophyte formation) on plain radiographs of hand or foot

1. Taylor W, et al. Classification criteria for psoriatic arthritis: development of new criteria from a large international study. Arthritis Rheum. 2006;54:2665-73

Pain differentiation: clinical **PsA mimickers**

Fibromyalgia (FM) and osteoarthritis are relevant PsA mimickers, particularly at the early stages of PsA, when signs of articular inflammation are less easily detectable by clinicians [1,2]

FM syndrome (FMS) is a complex chronic widespread pain (CWP) disorder of unknown origin, classified as primary or concomitant to other conditions (e.g. several rheumatic diseases, thyroid disorders)

In psoriasis, the prevalence of FMS has been reported to range between 5.4 and 8.3%, which is higher than that found in the general population

1. Marchesoni A, et al. The problem in differentiation between Psoriatic-related Polyenthesitis and Fibromyalgia. Rheumatology 2018;57:32–40
2. McGonagle D, et al. Differentiation between osteoarthritis and Psoriatic arthritis: implications for pathogenesis and treatment in the biologic therapy era. Rheumatology. 2015;54:29–38

Fibromyalgia **rapid screening tool** (FIRST)

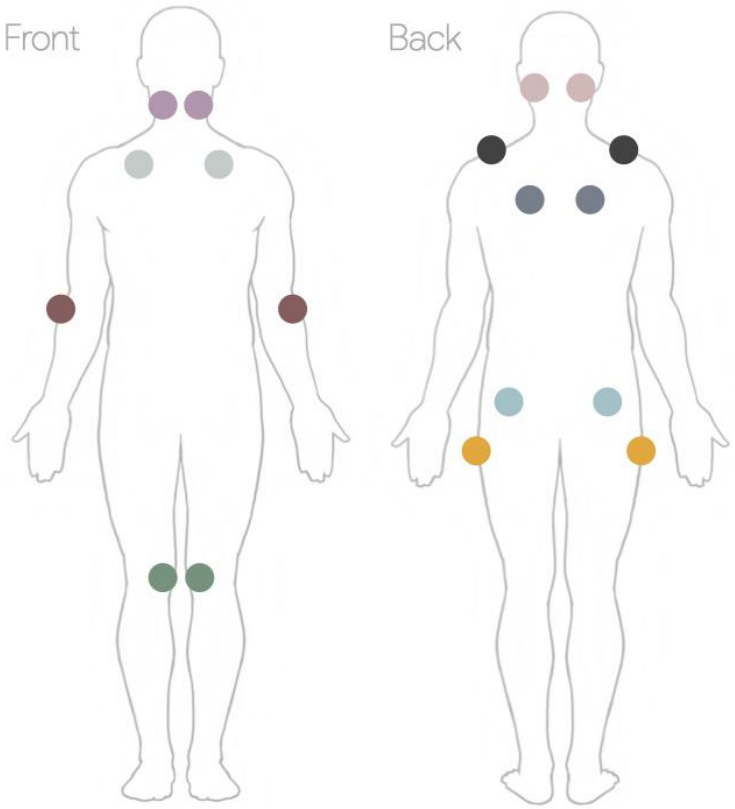
Items	
1	I have pain all over my body
2	My pain is accompanied by a continuous and very unpleasant general fatigue
3	My pain feels like burns, electric shocks or cramps
4	My pain is accompanied by other unusual sensations throughout my body, such as pins and needles, tingling or numbness
5	My pain is accompanied by other health problems such as digestive problems, urinary problems, headaches or restless legs
6	My pain has a significant impact on my life, particularly on my sleep and my ability to concentrate, making me feel slower generally

You have been suffering from joint, muscle or tendon pain for the past 3 months at least. Please answer this questionnaire in order to help your doctor evaluate your pain and symptoms more effectively

Please fill in this questionnaire by answering either yes or no (only 1 answer: YES or NO) to each of the following statements. Put a cross in the box that corresponds to your answer

1. Perrot S, et al. Development and validation of the Fibromyalgia Rapid Screening Tool (FiRST). Pain. 2010;150:250-256

Clinical diagnosis of Fibromyalgia



According to the ACR, the diagnosis of FM includes two variables: 1) bilateral pain above and below the waist, characterized by centralized pain and 2) chronic generalized pain that last for at least three months, characterized by pain on palpation in at least 11 of 18 specific body sites

18 tenderness points for the diagnosis of FM	
Occiput	At the sub occipital muscle insertions
Low cervical	At the anterior aspects of the inter transverse spaces at
Trapezium	At the midpoint of the upper border
Supraspinatus	At origins, above the scapula spine near the medial border
Second rib	Upper lateral to the second costochondral junction
Lateral epicondyle	2 cm distal to the epicondyles
Gluteal	In upper outer quadrants of buttocks in anterior fold of
Greater trochanter	Posterior to the trochanteric prominence
Knee	At the medial fat pad proximal to the joint line

1. Perrot S, et al. Development and validation of the Fibromyalgia Rapid Screening Tool (FiRST). Pain. 2010;150:250-256

Upadacitinib in PsA: the **PTV experience**

Ongoing clinical trial to evaluate the RW incidence of FM in psoriatic patients. At Apr, the 9th 2024 we evaluated 26 patients (18 M and 7 F, mean age 55.69 years) by the FIRST questionnaire and clinical elicitation of the 18 specific trigger points. The FIRST questionnaire was positive in 5 patients (19.23%). 3 patients (11.54%) pain on palpation in at least 11 of 18 specific body sites

AGE	F	M	Pso	PsA	Tx	FIRST	TP	PASI	DLQI	TJC	SJC	VES	PCR	EGA	PGA	pVAS	DAPSA
58,23	1	0	1	1	UPA	+	15	0	7	0	0	2	0,6	0	5	7	12,6
62,35	1	0	1	1	RSK	+	11	0	0	0	0	4	0,5	0	0	10	10,5
38,74	1	0	1	1	RSK	+	12	5	24	3	0	17	1,1	5	9	10	23,1
70,24	1	0	1	1	IXE	+	8	0	0	0	0	3	1,5	0	0	7	8
51,48	1	0	1	0	IXE	+	2	0	0	0	0	2	0,5	0	5	4	9,5

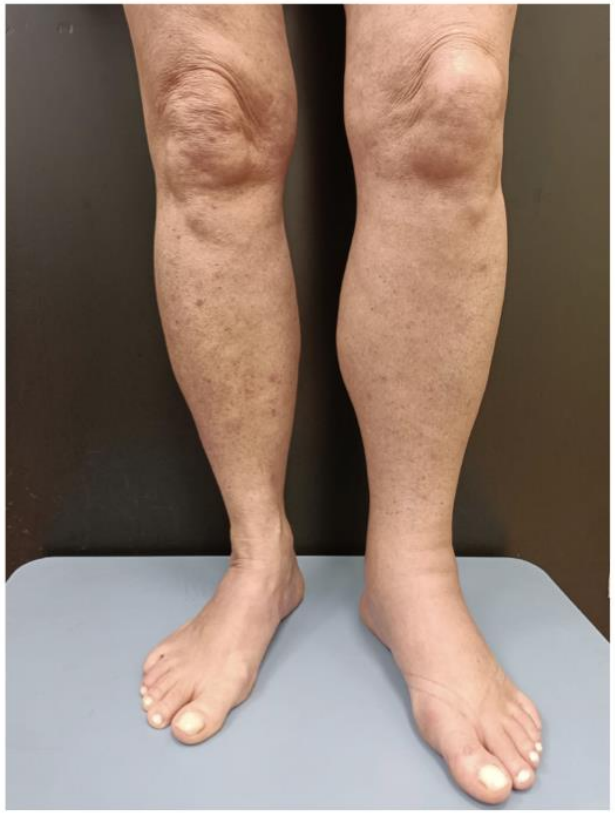
1. Personal experience, for educational purpose only

UPA personal experience: **skin domain**

	Baseline	Wk 4	Wk 12
mPASI	1,86	0,14	0
mDLQI	2,57	0,29	0

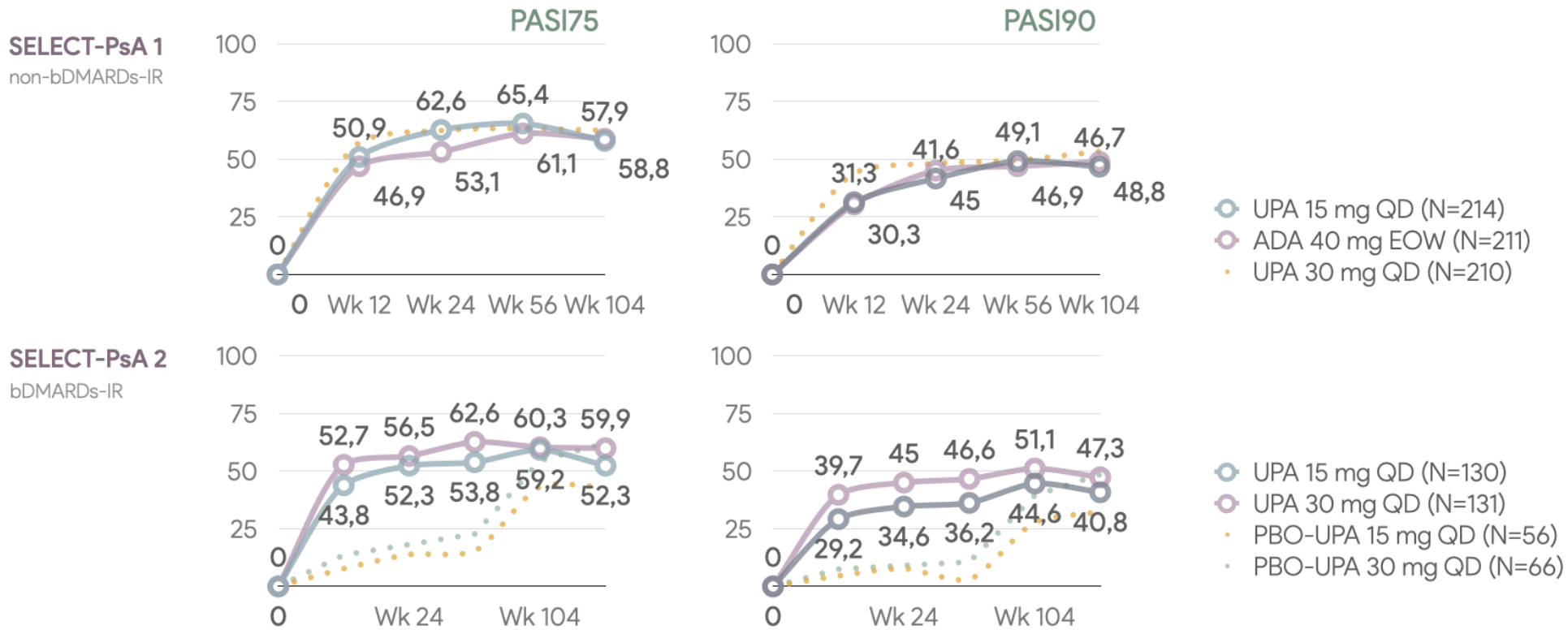
Table I. Mean PASi and DLQI scores improvement from baseline to week 12

Despite all patients achieved PASI100 at week 12, the low PASI scores at baseline (mPASI at baseline was 1,86) make this result not significant when compared to the effectiveness on the joint domain



1. Personal experience, for educational purpose only

Upadacitinib in PsA: the **literature**



1. McInnes IB, et al. Efficacy and Safety of Upadacitinib in Patients with Psoriatic Arthritis: 2-Year Results from the Phase 3 SELECT-PsA 1 Study. Rheumatol Ther. 2023;10:275-292

UPA personal experience: **joint domain**

The **Disease Activity index for PSoriatic Arthritis (DAPSA)** index is a composite measure, which comprises swollen and tender joint counts, patient global and pain assessment and an acute phase reactant. Indeed, composite measures to evaluate activity of systemic arthritis have been shown to be more reliable than their individual components

DAPSA = TJC + SJC + pain VAS + PGA + CRP

While it is sensitive to change using clinical trial and observational data and can be used to determine the traditional disease activity states including REM, it is also highly relevant to gather evidence regarding the validity of these states with regard to important outcomes that are linked to disease activity

Importantly, also with respect to joint damage the DAPSA was significantly correlated with progression of structural changes, since the probability of progression increased with increasing DAPSA states

One important advantage of DAPSA over other indices is that it provides a continuous **measure and thresholds for high, moderate or low activity and remission** based on a score. Higher DAPSA scores are **significantly associated with higher probability of structural progression**. In addition, it has been validated in clinical trials. Limitations of DAPSA are that it does not contain domains for skin, enthesitis, dactylitis, or axial disease assessments

DAPSA	Psoriatic arthritis
0-4	Remission
5-14	Low disease activity
15-28	Moderate disease activity
>28	High disease activity

Table II. Cut-off values to evaluate psoriatic arthritis activity by DAPSA

Abbreviation: TJC, tender joint count; SJC, swollen joint count; VAS, visual anagogic scale; PGA, patient global assessment; CRP, C-reactive protein

1. Aletaha D, et al. Disease activity states of the DAPSA, a psoriatic arthritis specific instrument, are valid against functional status and structural progression. Ann Rheum Dis. 2017;76:418-421

UPA personal experience: **joint domain**

	Mean	Range	σ
Baseline	32,69	24,4-49,8	±9,83
Week 4	17,01	0,9-41,1	±14,21
Week 12	10,63	0,6-18,4	±7,66

Table III. Mean DAPSA improvement from baseline to week 12

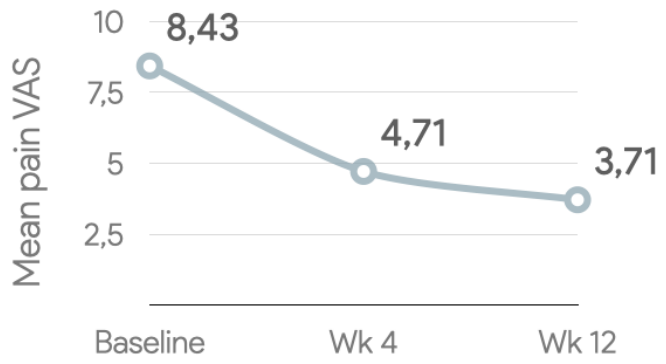


Figure 2. Mean pain VAS improvement from baseline to week 12

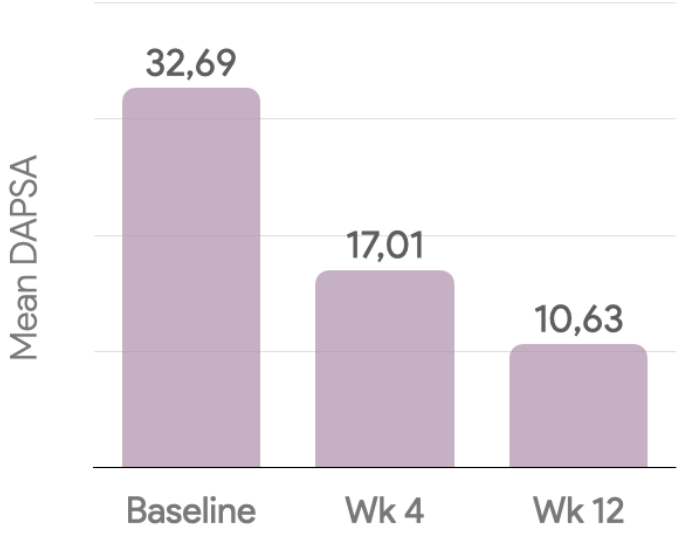
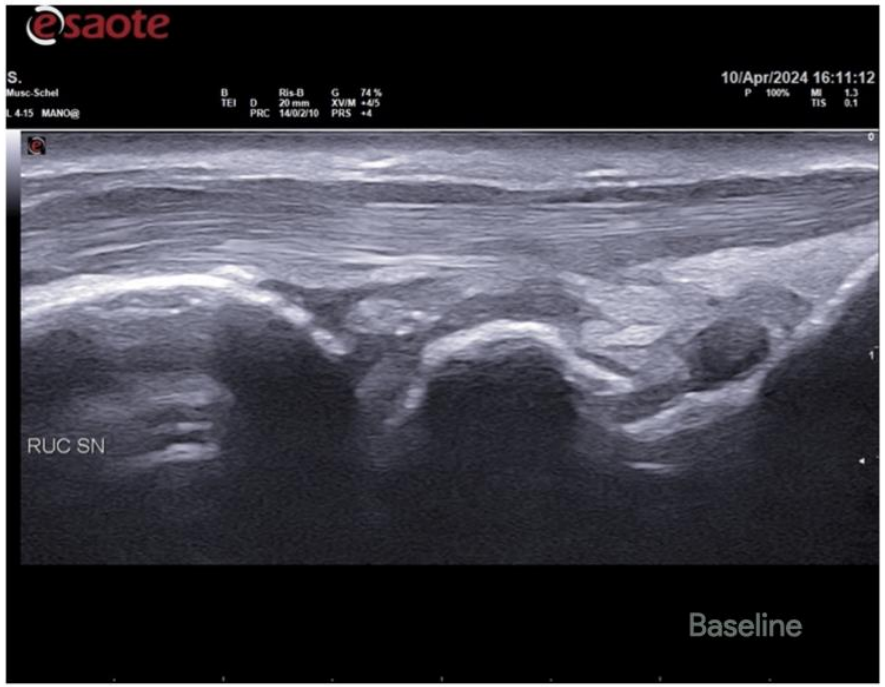
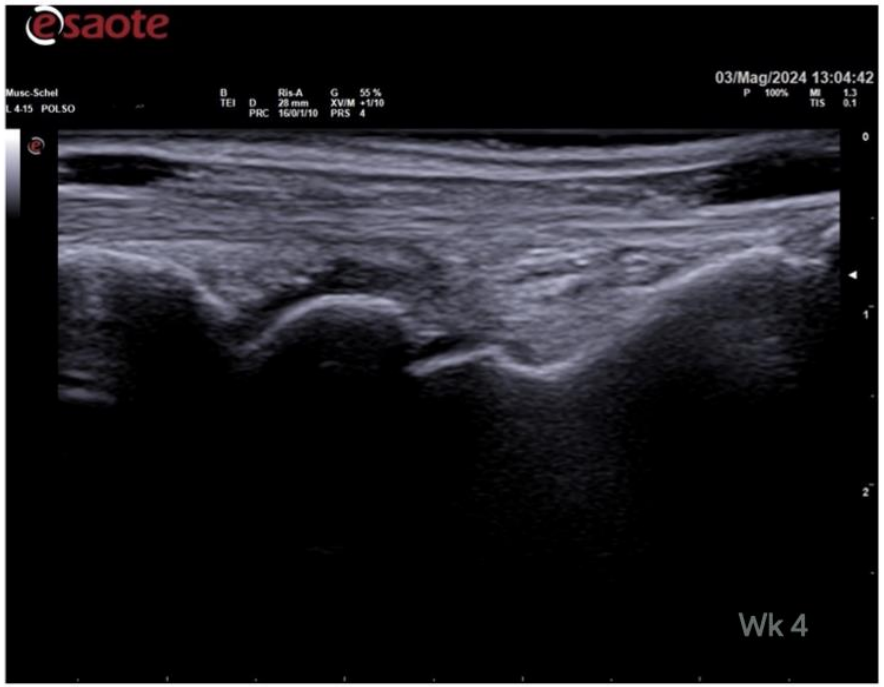


Figure 3. Mean DAPSA improvement from baseline to week 12. Patients improved from an High or Moderate disease activity to a Low disease activity. 2 patients achieved remission as soon as week 4

1. Personal experience, for educational purpose only

UPA personal experience: **joint domain**





1. Personal experience, for educational purpose only. Images: courtesy of Arianna D'Antonio, MD

2. Una compromissione epatica severa rappresenta una controindicazione assoluta per la terapia con Upadacitinib?

1. **Sì**
2. **No**

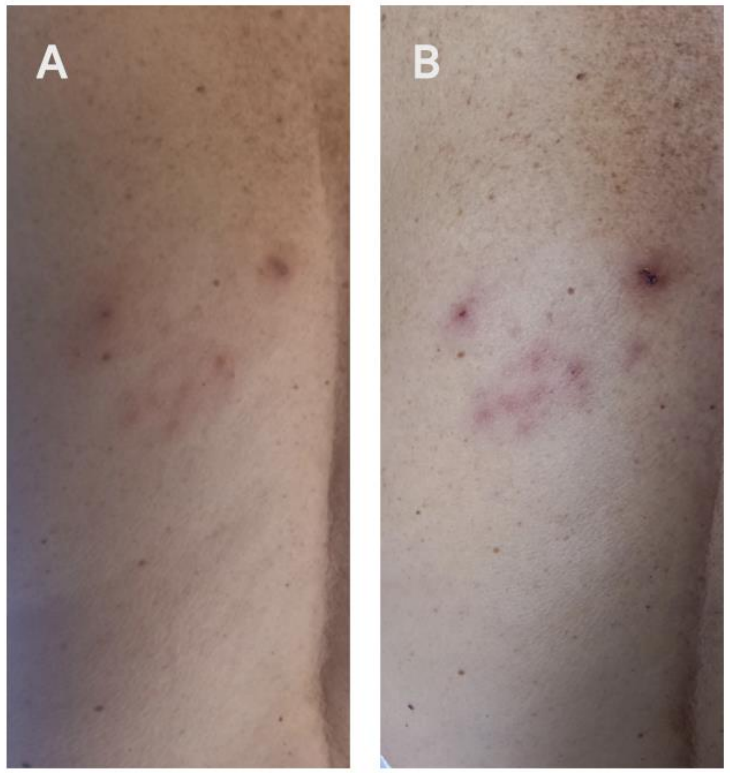
Upadacitinib in PsA: **adverse events**

- Upper respiratory tract infections
- Herpes zoster
- Higher rates of Non-melanoma skin cancer (NMSC)
- Alteration of the lipid profile
- Elevated creatine phosphokinase (CPK)
- Anemia, neutropenia, lymphopenia
- Hepatic disorder

The majority of the adverse events were generally non-serious and did not lead to treatment discontinuation.

1. Burmester GR. et al. Safety profile of upadacitinib over 15 000 patient-years across rheumatoid arthritis, psoriatic arthritis, ankylosing spondylitis and atopic dermatitis. RMD Open. 2023;9(1):e002735.

UPA personal experience: **safety**



In the UPA phase III RA clinical program, Herpes Zoster (HZ) incidence and event rates were higher with UPA versus ADA + MTX or MTX monotherapy, and higher with the 30 mg versus 15 mg dose. Patients from Asia and those with a history of HZ may be at increased risk of HZ while receiving UPA [2]

Figure 4. Personal experience. HZ in a patient (G.D.B. non included in the analysis) treated with upadacitinib. The VZV reactivation occurred after 4 weeks of UPA treatment (A) and resolved after 7 days of treatment with Brivudin 125 mg daily (B) [1]

1. Personal experience, for educational purpose only
2. Winthrop KL, et al. Incidence and risk factors for herpes zoster in patients with rheumatoid arthritis receiving upadacitinib: a pooled analysis of six phase III clinical trials. Ann Rheum Dis. 2022;81:206-213

3. E’ possibile ricorrere ad una dose di 30 mg/dì in pazienti con artrite psoriasica scarsamente responsivi al dosaggio standard di 15 mg/dì in assenza di eventi avversi?

1. **Sì**
2. **No**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