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Clinical and ultrasound remission at 48 weeks of upadacitinib in rheumatoid arthritis: real-world results from the Italian multicenter UPARAREMUS study

Andrea Picchianti Diamanti[1*], Valentino Paci[2], Michele Maria Luchetti Gentiloni[2], Simonetta Salemi[1], Giorgio Sesti[1], Ilaria Anna Bellofatto[1], Caterina Baldi[3], Paolo Falsetti[3], Maria Sole Chimenti[4], Arianna D'Antonio[4], Gloria Crepaldi[5], Alen Zabotti[6], Ivan Giovannini[6], Marco Canzoni[7], Donatella Fiore[7], Gian Domenico Sebastiani[8], Chiara Scirocco[8], Carlo Perricone[9], Bruno Laganà[1] and Annamaria Iagnocco[5]

Abstract

Background Achieving clinical remission is a key therapeutic goal in rheumatoid arthritis (RA). While pivotal trials and early real-world studies have demonstrated the efficacy of upadacitinib (UPA), data on its impact as assessed by imaging remain limited.
Here, we report the 48 weeks outcomes from the full cohort of the UPARAREMUS study.

Methods UPARAREMUS is a 12-month follow-up, observational study involving RA patients from 9 Italian rheumatology centers initiating UPA. The primary objective was to evaluate the proportion of patients achieving combined clinical and ultrasound (US) remission. Secondary endpoints included the proportion of patients achieving clinical or US remission alone at multiple time points.

Results A total of 115 patients were enrolled. Combined clinical and US remission was achieved in 35% of patients at week 12, increasing to 55% at week 24 and 72% at week 48. Younger age, lower baseline CDAI, and higher ESR were associated with higher remission rates, while baseline corticosteroid use was linked to a 65% lower likelihood of achieving remission. More than 60% of patients showed absence of power Doppler (PD) signal at week 24, rising to over 80% by week 48. The majority of patients in clinical remission also achieved US remission.

Conclusions After 12 months of UPA treatment, a substantial proportion of RA patients achieved combined clinical and US remission, independent of prior bDMARDs use or monotherapy. These findings highlight UPA's ability to induce and maintain deep disease control in real-world practice.

Keywords Clinical remission, Ultrasonographic remission, JAK inhibitors, Upadacitinib

Bruno Laganà was retired.

*Correspondence:
Andrea Picchianti Diamanti
andrea.picchiantidiamanti@uniroma1.it

Full list of author information is available at the end of the article

Significance and innovations

- This is the first study evaluating the effectiveness of UPA in patients with RA using both clinical and US remission as combined endpoints over a 12-month period.
- After 12 months of UPA treatment, 72% of patients achieved combined clinical and US remission, underscoring its effectiveness in controlling subclinical inflammation and achieving stringent remission in a real-world RA cohort.
- Clinical and US remission rates were comparable regardless of UPA monotherapy or prior exposure to bDMARDs. Younger age, lower CDAI, and higher ESR were positive predictors of combined remission, while corticosteroid use significantly reduced the odds of remission.

Introduction

Effective management of rheumatoid arthritis (RA) aims to achieve remission or maintain low disease activity in order to prevent long-term joint damage and preserve both functionality and quality of life [1]. To assess remission, both clinical research and routine practice rely on various measurement tools, including Boolean-based and index-based criteria such as the Simplified Disease Activity Index (SDAI) and the Clinical Disease Activity Index (CDAI). Additionally, the Disease Activity Score for 28 joints (DAS28), though less stringent, remains widely used in clinical settings [2–4].

The likelihood of achieving remission in RA varies depending on the disease-modifying antirheumatic drug (DMARD) used, the remission criteria applied, and patient-related factors such as comorbidities or disease duration, ranging around 20–40% of patients [5, 6].

Upadacitinib (UPA) is a selective and reversible oral JAK inhibitor currently approved for the treatment of RA, psoriatic arthritis, ankylosing spondylitis, non-radiographic axial spondyloarthritis, Crohn's disease, ulcerative colitis, and atopic dermatitis.

The SELECT RA clinical trial program demonstrated the rapid and sustained efficacy of UPA in reducing RA signs and symptoms, both in combination with methotrexate and as monotherapy. Furthermore, two head-to-head trials showed that patients treated with UPA achieved significantly higher remission rates at weeks 12 and 24 compared to those treated with adalimumab or abatacept, in methotrexate-inadequate responders. These findings were consistent across different remission criteria, including DAS28, CDAI, SDAI, and Boolean-based definitions [7–9].

More recently, real-world data have begun to confirm the clinical effectiveness of UPA in broader patient populations [10–14]. These findings are particularly important, as the efficacy observed in clinical trials conducted in controlled environments and with selected patient groups may not fully reflect the heterogeneity and complexity of real-world clinical practice.

However, evidence specifically addressing the impact of UPA on disease activity assessed by imaging is still limited. In fact, residual joint inflammation, detectable by ultrasonography (US) as active synovitis, can persist even in patients who fulfill clinical remission criteria [15–17]. This subclinical inflammation is a recognized predictor of disease flares and structural progression [18–23]. Baldi et al. recently demonstrated the effectiveness of UPA in 71 RA patients, showing significant improvements in both clinimetric and US parameters over 6 months [24].

In the preliminary data from the UPAdacitinib Rheumatoid Arthritis REMission UltraSonography (UPARAREMUS) study, we reported the efficacy of UPA in achieving both clinical and US remission up to 24 weeks in 60 RA patients [25].

Here, we present the 12-month outcomes from the full cohort of the UPARAREMUS study.

Methods

Patients and study design

This 12-month, longitudinal observational study was conducted across nine rheumatology centers in Italy. Consecutive patients with rheumatoid arthritis (RA), classified according to the 2010 EULAR/ACR criteria [1], were enrolled. Patients were categorized as either bDMARD-naïve (inadequate responders to conventional synthetic DMARDs [csDMARDs] with no prior bDMARD exposure) or bDMARD inadequate responders ("bio-failures"; insufficient response to both csDMARDs and bDMARDs).

Inclusion criteria

- Age 18–65 years.
- Moderate-to-severe disease activity (DAS28-CRP >3.2).
- bDMARD-naïve: inadequate response to ≥ 6 months of methotrexate (MTX) at standard doses, per EULAR response criteria [1].
- bDMARD-experienced: inadequate response to ≥ 6 months of MTX and bDMARD therapy, per EULAR response criteria [1].

Exclusion criteria

- Contraindications to upadacitinib (UPA), according to local prescribing information.
- Use of any bDMARDs or targeted synthetic DMARDs (tsDMARDs) other than UPA.
- Prior exposure to tsDMARDs or bDMARDs in bDMARD-naïve patients.

Ultrasonography

The US evaluation was carried out by rheumatologists all expert in musculoskeletal (MS) US, all of whom had demonstrated proficiency through an interobserver reliability test. This assessment, conducted using static images on an e-learning platform, required a weighted kappa score of ≥ 0.7 to ensure consistency and accuracy. Only those meeting this standard were approved to take part in the study. To maintain objectivity, sonographers had no access to clinical data.

To ensure high-quality imaging, only centers equipped with high-end US systems—such as MyLab X8 eXP, MyLab 70XVG, Logiq9, LogiqE9, or equivalent high-performance machines—were included. These devices were equipped with high-frequency probes (14–18 MHz) for optimal visualization. The severity of synovitis and PD synovitis detected via US was classified using a simplified semi-quantitative scale ranging from 0 to 3 (0 = absent, 1 = mild, 2 = moderate, 3 = severe) [26, 27].

For PD imaging, specific technical parameters were applied, including an 8.3–10 MHz frequency, a pulse repetition frequency of 600 Hz, and gain settings carefully adjusted to minimize noise artefacts. A low wall filter was also used. The primary focus for identifying active inflammation was PD-positive synovitis, as defined by the Outcome Measures in Rheumatology (OMERACT) criteria [26]. This lesion type is widely recognized as the most reliable marker of residual disease activity in RA and has been shown to have the highest predictive value for radiographic progression and clinical relapse compared to other US findings, such as tenosynovitis and erosions [17, 23].

Based on our previous research, bilateral assessments were performed on two key joints: the second MCP joint and the wrist [17]. Additionally, any joints identified as swollen during clinical examination were included in the US assessment. All evaluations followed international guidelines [28].

Endpoints and definitions

The primary endpoint of the study was to establish the proportion of enrolled patients with US and clinical remission at week 24 and 48 after starting UPA treatment.

Secondary endpoints were:

- Evaluating the percentage of patients with clinical remission according to CDAI, DAS28crp and SDAI score at weeks 12 (T1), 24 (T2), 36 (T3) and 48 (T4).
- Analyzing reduction in CDAI, DAS28crp and SDAI from baseline to each evaluation time (T1, T2, T3, T4).

Clinical remission was defined as CDAI, DAS28crp and SDAI < 2.6, ≤ 2.8 and ≤ 3.3 respectively [29–31].

In order to define US remission, no joint was allowed to show a PD signal ≥ 2, whereas a PD score of 1 was permitted in no more than one joint.

Ethical considerations

The study was conducted in accordance with the Declaration of Helsinki and approved by the ethics committee of the coordinating center (Lazio area 1, Approval numbers 6493_2021 on June 15, 2021) and by each center participating in the study; written informed consent was obtained from all the patients.

Study procedures

At five key time points—baseline (T0), 12 weeks (T1), 24 weeks (T2), 36 weeks (T3), 48 weeks (T4)—the following evaluations and procedures were conducted:

- Collection of medical history and health status;
- Comprehensive clinical examination, including assessment of disease activity using DAS28-CRP, CDAI, and SDAI scores;
- US evaluation of both wrists and second MCP joints bilaterally, as well as any swollen joints identified during the clinical examination.

UPA treatment was initiated independently of study participation, based on clinical judgment and in accordance with the European Medicines Agency (EMA)'s SmPC [30]. Patients received the approved RA dosage of 15 mg once daily.

Statistical analysis

All statistical analyses were performed using the R software (version 4.4.2). For descriptive analyses, categorical variables were reported as absolute numbers and frequencies, and continuous variables were expressed as median with interquartile range (IQR).

Subgroup comparisons were conducted using the Mann-Whitney U test for continuous variables and Pearson's chi-square test for categorical variables.

Due to non-normal distribution, differences from baseline for continuous variables were assessed using a linear mixed model (LMM) with Bonferroni correction, accounting for repeated measures and inter-subject variability.

The survival curves of the drug in each subgroup have been examined by the Kaplan-Meier method and compared statistically using a stratified log-rank test.

To identify baseline predictors of US plus clinical remission, a bidirectional stepwise logistic regression was employed. The model selection was guided by minimizing the Akaike Information Criterion (AIC), with each step evaluating the inclusion or exclusion of variables. Prior to the stepwise procedure, potential

multicollinearity was assessed using the Variance Inflation Factor (VIF), and variables exhibiting high multicollinearity were iteratively removed. Results were reported as Odds Ratios (ORs) with 95% confidence intervals (CI). A p-value less than 0.05 was considered significant.

Results

Demographic and clinical characteristics

A total of 115 patients affected by RA were enrolled, and 94 patients completed 48-week follow-up (T4) (Table 1). Among the more relevant baseline data, the median disease duration was 96 months (IQR 43.5–168), 39% of patients were bio-naïve, the great majority tested positive for anti-citrullinated protein antibodies (ACPA) (72.7%) and rheumatoid factor (RF) (73.9%). Disease activity scores reflected moderate-to-high activity, with a median DAS-28crp of 4.25 (IQR: 3.75–4.94), CDAI of 23.0 (IQR: 17.0–28.5), and SDAI of 24.2 (IQR: 18.0–29.2), about half of the patients were managed with UPA in monotherapy (45.2%).

Table 1 Demographic and clinical characteristics of the cohort at the baseline

Patients' characteristics	
Total, *n.*	115
Age, years median [IQR]	56 [50.5–61]
Gender (F/M), *n.* (%)	89 (77.4)/26 (22.6)
Comorbidities, yes *n.* (%)	74 (64.3)
BMI, median [IQR]	24.5 [21.5–28.0]
Smoke, active, *n.* (%)	32 (27.8)
Bio-naïve, *n.* (%)	45 (39.1)
Disease duration, months median [IQR]	96 [43.5–168]
Laboratory	
ACPA positive, *n* (%)	80 (72.7) missing values: 5
RF positive, *n* (%)	82 (73.9) missing values: 4
CRP (mg/dl), median [IQR]	0.9 [0.5–1.77]
ESR (mm/h), median [IQR]	30 [16–46]
Disease Activity	
Tender joints, *n.* (%)	5 [3–8]
Swollen joints, *n.* (%)	4 [1–5]
VAS pain (0–100), median [IQR]	70 [60–80]
VAS EGA (0–100), median [IQR]	60 [50–70]
VAS PGA (0–100), median [IQR]	70 [50–80]
DAS-28 CRP, median [IQR]	4.25 [3.75–4.94]
CDAI, median [IQR]	23.0 [17.0–28.5.0.5]
SDAI, median [IQR]	24.2 [18.0–29.2.0.2]
Treatment	
Monotherapy, *n* (%)	52 (45.2)
Combination therapy, *n.* (%)	63 (54.8)
CCS, yes, *n.* (%)	68 (61.3) missing values: 4
Ultrasound	
PD active joints, median [IQR]	2.0 [1.0–2.5.0.5]
PD grading, median [IQR]	3.0 [1.0–5.0]

Abbreviations: ACPA anti-citrullinated protein antibodies, *BMI* body mass index, *CRP* C-reactive protein, *DAS28-CRP* Disease Activity Score 28 joints —CRP, *RF* rheumatoid factor, *SD* standard deviation, *SDAI* Simplified Disease Activity Index, *CDAI* Clinical Disease Activity Index, *VAS* Visual Analogue Scale, *CCS* Corticosteroids, *PD* Power Doppler

Primary end-point

Clinical plus US remission was achieved in 35% of patients at week 12 with a progressive increase to 55.7% at week 24, 63.5% at week 36 and 72.3% at week 48 (Table 2; Fig. 1).

Patients who achieved the primary end point were significantly younger (56 vs. 61 years, $p = 0.015$), had a shorter disease duration (79 vs. 134 months, $p = 0.029$), lower baseline CDAI scores (23.0 vs. 26.0, $p = 0.045$) and were less likely to be on corticosteroids at baseline (79.2% vs. 52.2%, $p = 0.039$) (Table 3).

Factors associated with primary end point

To identify baseline predictors of US plus clinical remission, a bidirectional stepwise logistic regression was performed. Younger age, lower CDAI and higher ESR levels were associated with a higher likelihood of achieving the primary end point.

Specifically, each additional year in age was associated with a 5% decrease in the odds of remission (OR: 0.95, 95% CI: 0.91–0.99, $p = 0.015$), Each unit increase in CDAI was linked to a 6% reduction in the odds of remission (OR: 0.94, 95% CI: 0.89–0.99, $p = 0.025$). In contrast, each unit increase in ESR was associated with a 4% increase in the odds of remission (OR: 1.04, 95% CI: 1.01–1.06, $p = 0.0026$). Finally, patients receiving corticosteroids at baseline have 65% lower odds of achieving remission compared to those not on corticosteroids (OR: 0.35, 95% CI: 0.13–0.79, $p = 0.016$) (Table 4; Suppl. Materials).

The great majority of patients in clinical remission had concomitant US remission at both 24 and 48 weeks (92.2% and 90.7% respectively; Fig. 3).

Secondary end-points

Clinical remission steadily increased from 0% of patients at baseline to 42% at T1, 60% at T2, 68% at T3 and 80% at T4. 16% of patients were in US remission at baseline which progressively rose to 66% at T1, 79% at T2, 84% at T3, and 87% at T4 (Table 2).

Disease activity significantly reduced from baseline to each subsequent time point across all clinical indices, with the most substantial improvement decrease observed by week 12.

Specifically, the median DAS28-CRP decreased from 4.3 at baseline to 2.9 at T1, 2.3 at T2, 2.1 at T3, and 1.9 at T4. The median CDAI and SDAI followed a similar trend, with the CDAI dropped from 23.0 to 10.0 at T1, 7.0 at T2, 5.0 at T3, and 4.0 at T4, and the SDAI declined from 24.2

Table 2 Clinical and ultrasonographic disease parameters from baseline throughout the follow-up

	T0	T1	T2	T3	T4
Nr. of observations	115 (100)	114 (99.1)	106 (92.2)	96 (83.5)	94 (81.7)
DAS28-CRP	4.3 [3.8–4.9]	2.9 [2.1–3.6] ****	2.3 [1.7–3.2] ****	2.1 [1.4–2.8] ****	1.9 [1.3–2.6] ****
CDAI	23.0 [17.0–28.5.0.5]	10.0 [5.0–17.0]****	7.0 [3.0–12.8.0.8] ****	5.0 [2.0–9.0] ****	4.0 [1.0–8.0] ****
SDAI	24.2 [18.0–29.2.0.2]	10.2 [5.0–17.3.0.3] ****	7.7 [3.5–12.9] ****	5.1 [2.3–9.5] ****	4.3 [1.2–8.3] ****
VAS PAIN	70 [60–80]	40 [20–50] ****	20 [10–50] ****	20 [10–30] ****	20 [5–30] ****
CRP	0.9 [0.5–1.8]	0.3 [0.1–0.7] ****	0.2 [0.1–0.6] ****	0.2 [0.1–0.4] ****	0.1 [0.1–0.4] ****
PD active joints	2.0 [1.0–2.5.0.5]	0 [0.0–2.0] ****	0 [0.0–1.0] ****	0 [0.0–0.0] ****	0 [0.0–0.0] ****
PD grading	3.0 [1.0–5.0]	0 [0.0–2.0] ****	0 [0.0–1.0] ****	0 [0.0–0.0] ****	0 [0.0–0.0] ****
Clinical Remission	0 (0)	48 (42.1)	64 (60.4)	65 (67.7)	75 (79.8)
US Remission	19 (16)	76 (66.7)	84 (79.2)	81 (84.4)	82 (87.2)
Complete Remission	0 (0)	40 (35.1)	59 (55.7)	61 (63.5)	68 (72.3)

Differences from baseline for continuous variables were assessed using a linear mixed model (LMM) with Bonferroni correction. The *p*-values are evaluated from T0 to every timepoint: *<0.05; **<0.01; ***<0.001; ****<0.0001

Abbreviations: DAS28-CRP Disease Activity Score 28 joints —C-reactive protein, *SDAI* Simplified Disease Activity Index, *CDAI* Clinical Disease Activity Index, *VAS* Visual Analogue Scale, *PD* Power Doppler

at baseline to 10.2 at T1, 7.7 at T2, 5.1 at T3, and 4.3 at T4 (Fig. 2). Pain VAS scores showed a marked improvement, decreasing from 70 at baseline to 20 at T4, with a 50% reduction already achieved by T1. CRP levels significantly declined from 0.9 mg/dl at baseline to 0.1 mg/dl at T4, in line with the observed clinical improvements. Regarding ultrasound parameters, the median number of power-doppler-active joints significantly decreased from 2.0 at baseline to 0.0 from T1 to T4. Likewise, the median PD grade was reduced from 3.0 at baseline to 0.0 throughout follow-up. Overall, more than 60% of patients exhibited complete absence of PD signal at week 24 (T2), and this proportion further increased to over 80% by week 48 (T4) (Fig. 3).

Data collected at each follow up timing are summarised in Table 2.

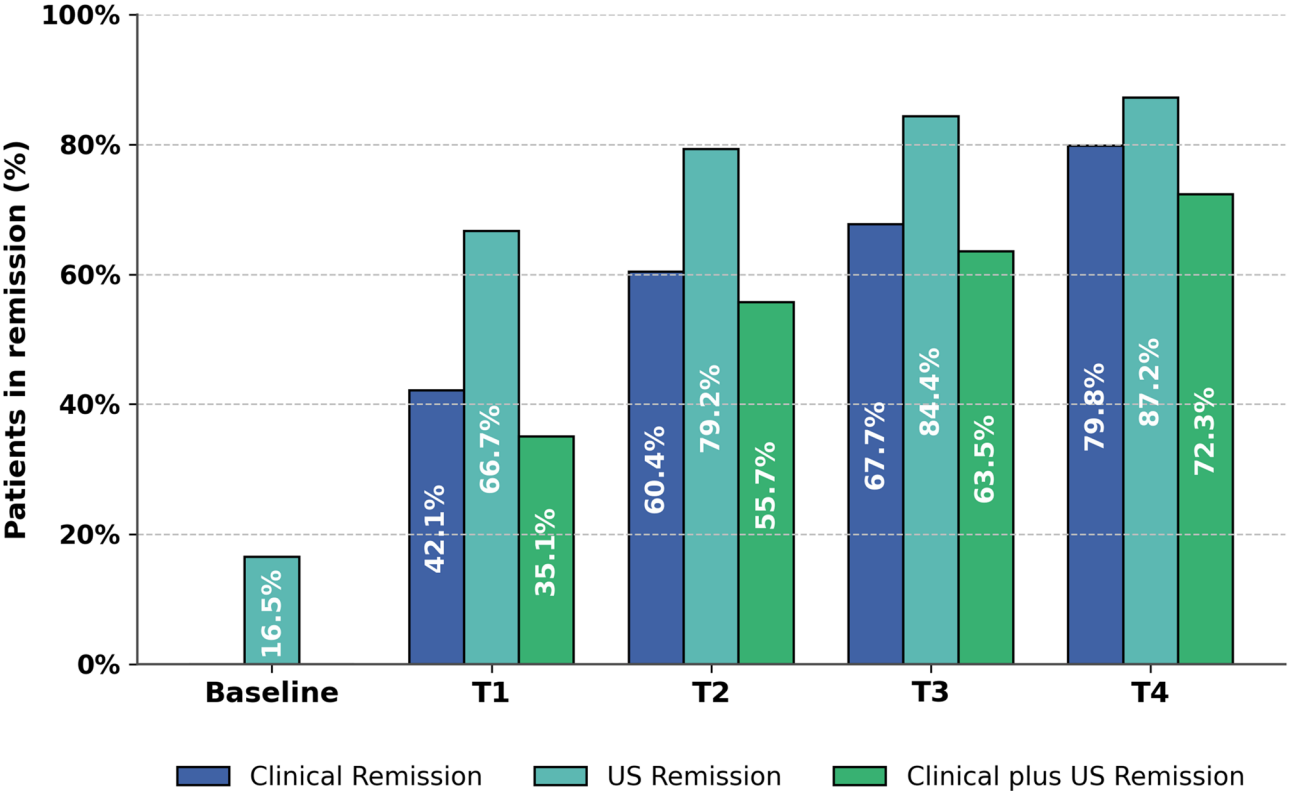


Fig. 1 Histograms representing the proportion of patients achieving the primary end-point, clinical and US remission alone, from baseline to 48 weeks. The asterisks denote the significance levels

Table 3 Baseline patients' characteristics associated with complete remission at 48 weeks

	Clinical and US remission after 48 weeks (T4)		*p* value
	Yes (*n* = 70) Baseline (T0)	No (*n* = 24) Baseline (T0)	
Age, years median [IQR]	56 [48.5–58.8]	61 [55.0–66.2.0.2]	***0.0148***
Gender (F/M), *n*. (%)	55 (78.6)/15 (21.4)	18 (75.0)/6 (25.0)	0.9374
Comorbidities, *n*. (%)	42 (60.0)	17 (70.8)	0.4822
BMI, median [IQR]	23.5 [21.1–27.5]	25.5 [21.5–29.6]	0.3323
Smoke, active, *n*. (%)	19 (27.1)	6 (25.0)	0.9500
Bio-naïve, *n*. (%)	32 (45.7)	7 (29.2)	0.2380
Disease duration, months median [IQR]	79 [31.5–166.0]	134 [105.0–171.0.0.0]	***0.0298***
Laboratory			
ACPA positive, *n* (%)	50 (74.6) missing values: 3	14 (60.9) missing values: 1	0.3225
RF positive, *n* (%)	53 (77.9) missing values: 2	13 (56.5) missing values: 1	0.0856
CRP (mg/dl), median [IQR]	1.1 [0.6–2.0.6.0]	0.6 [0.3–1.6]	0.1391
ESR (mm/h), median [IQR]	35 [17–52]	28 [16–37]	0.0866
Disease Activity			
Tender joints, *n*. (%)	5 [3–7]	6 [3.75–8.25]	0.5444
Swollen joints, *n*. (%)	4 [1–5]	5 [2.75–6.25]	0.0799
VAS pain (0–100), median [IQR]	60 [50–80]	80 [67–80]	0.0651
VAS EGA (0–100), median [IQR]	70 [50–80]	77 [70–80]	0.0806
VAS PGA (0–100), median [IQR]	60 [50–70]	70 [60–80]	0.0595
DAS-28 CRP, median [IQR]	4.12 [3.75–4.89]	4.62 [4.06–5.45]	0.0679
CDAI, median [IQR]	23.0 [17.2–26.0]	26.0 [21.9–31.5]	***0.0448***
SDAI, median [IQR]	24.2 [18.0–27.9.0.9]	27.0 [19.9–34.8]	0.1309
Treatment			
Monotherapy, *n* (%)	34 (48.6)	10 (41.7)	0.7279
Combination therapy, *n*. (%)	36 (51.4)	14 (58.3)	0.7279
CCS, yes, *n*. (%)	35 (52.2) missing values: 3	19 (79.2) missing values: 0	***0.0392***
Ultrasound			
PD active joints, median [IQR]	1 [1.0–2.0]	2 [1.0–2.75.0.75]	0.4511
PD grading, median [IQR]	2 [1.0–5.0]	3.5 [1.25–6.0.25.0]	0.2334

Comparison between patients who achieved clinical *and* US remission at 48 weeks and those who did not was assessed through Mann-Whitney U test and Pearson's chi-square test for continuous and categorical variables, respectively. The *p*-value was highlighted in bold if < 0.05

Abbreviations: ACPA anti-citrullinated protein antibodies, *BMI* body mass index, *CRP* C-reactive protein, *DAS 28-CRP* Disease Activity Score 28 joints —CRP, *RF* rheumatoid factor, *SD* standard deviation, *SDAI* Simplified Disease Activity Index, *CDAI* Clinical Disease Activity Index, *VAS* Visual Analogue Scale, *CCS* Corticosteroids, *PD* Power Doppler

Safety

Discontinuations due to treatment-emergent adverse events occurred in 6 out of 115 patients (5%) in the cohort (one case each of optic neuritis, respiratory infection, and neutropenia; and three cases of recurrent herpes zoster). Seven patients (6%) discontinued upadacitinib due to inefficacy, while eight patients were considered lost to follow-up.

The drug retention rate (DRR) at week 48 was 82%. Notably, main clinical and patient-related parameters—such as age, gender, BMI, disease duration, and previous exposure to bDMARDs—did not significantly influence the DRR (Fig. 4, Suppl. Materials).

Discussion

This study represents the first real-life investigation assessing the effectiveness of UPA in achieving both clinical and US remission in patients with RA during a 12-month follow-up.

A growing body of real-world evidence is increasingly supporting the efficacy and safety of UPA in patients with RA, as previously demonstrated in pivotal trials [7–14, 25].

However, data assessing the drug's ability to induce a deeper level of disease control, particularly when evaluated through musculoskeletal US is almost absent.

In this multicentric observational study, we investigated UPA effectiveness in achieving and maintaining

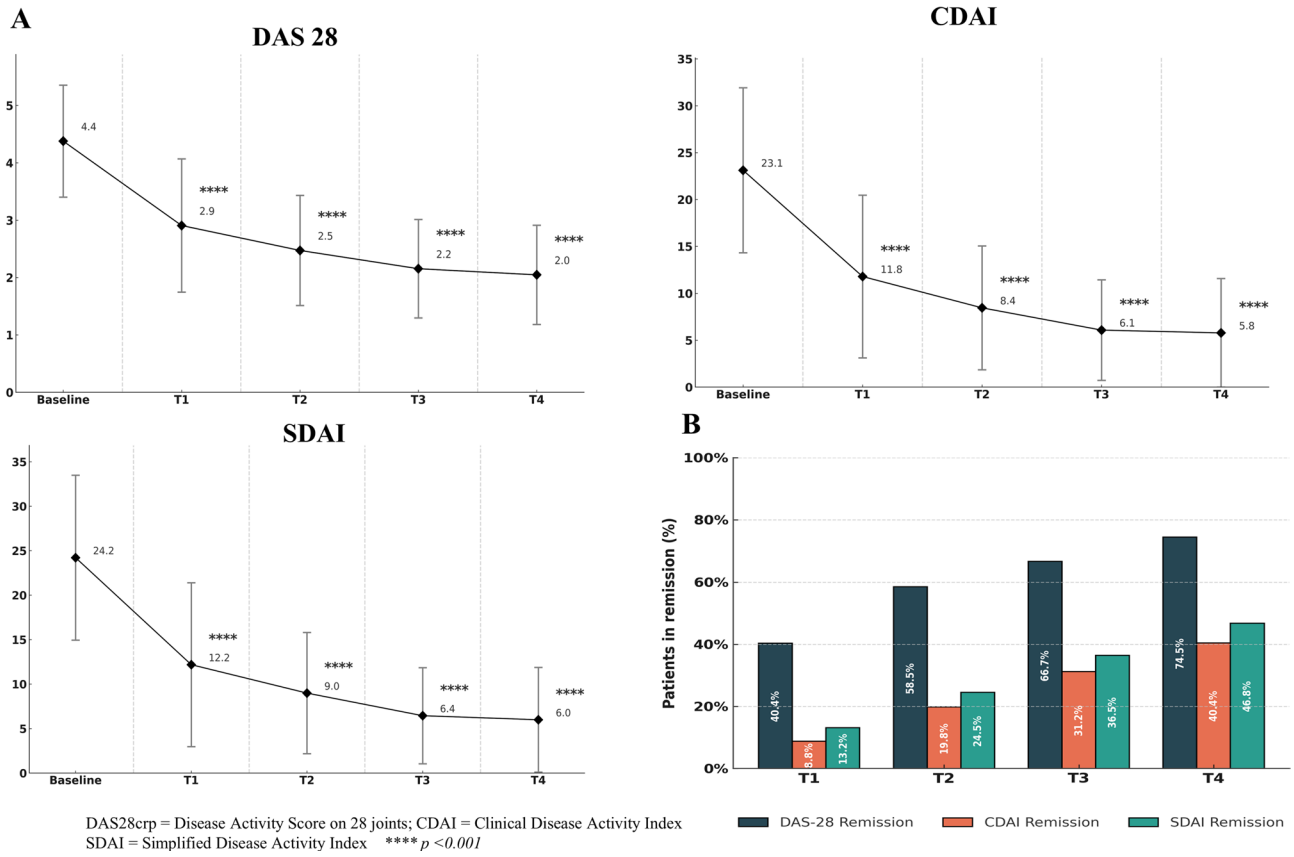


Fig. 2 **A**: Improvement in disease activity at baseline and different timepoints; **B**: Proportion of patients in clinical remission according to the different clinical indices The asterisks denote the significance levels

clinical and US remission over a 12-month period in a cohort of RA patients in a real-world setting.

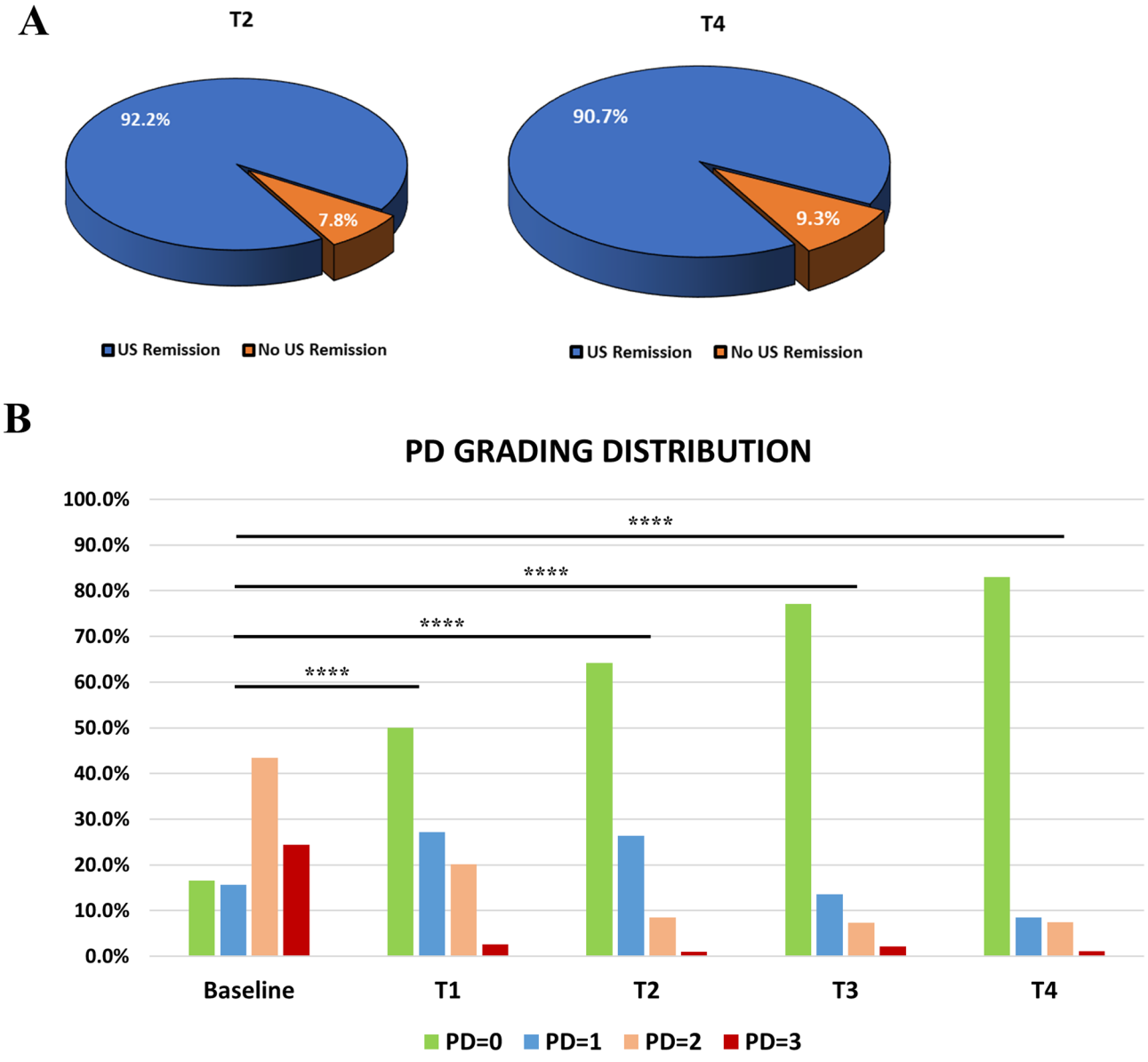
Our findings demonstrate that UPA, used either as monotherapy or in combination with methotrexate, in both bio-naive than bio-experienced patients, can lead to deep remission in a substantial proportion of patients. Specifically, combined clinical and US remission was observed in 35% of patients at week 12, and progressively increased to 55% by week 24 and 72% at week 48. Patients who achieved this composite outcome were significantly younger, had shorter disease duration, lower baseline CDAI scores, and were less likely to be on corticosteroids at baseline. A bidirectional stepwise logistic regression confirmed that younger age, lower CDAI, and higher ESR levels were associated with higher likelihood of achieving remission. Whereas, corticosteroid use at baseline was associated with a 65% lower probability of reaching clinical and US remission.

With regard to secondary outcomes, clinical remission alone was achieved in 42%, 60%, and 80% of patients at weeks 12, 24, and 48, respectively. Disease activity significantly declined from baseline across all clinical indices, with the greatest improvement observed by week 12.

Clinical efficacy was corroborated by a marked reduction in synovial power doppler signal over time, with more than 60% and 80% of patients showing complete absence of PD at T2 and T4, respectively. Accordingly, only a minority of patients in clinical remission failed to achieve concomitant US remission (7.8% and 9.3% at 24 and 48 weeks, respectively).

Finally, UPA demonstrated a favorable drug retention rate, with 82% of patients remaining on treatment at 48 weeks.

Notably, drug retention was not adversely influenced by key clinical or lifestyle factors such as elevated BMI, smoking status, or long-standing disease. These results suggest a stringent suppression of active synovitis over time, highlighting the effectiveness of UPA not only in achieving clinical remission but also in controlling subclinical inflammation, as assessed by US. The high rate of ultrasound remission observed in our study may in part reflect the relatively favorable characteristics of our population, in which 39% of patients were bio-naïve and the remainder had failed only one or two biologics. However, logistic regression analysis confirmed that prior biologic exposure did not negatively impact the likelihood of achieving remission, supporting its broad effectiveness in real-world clinical settings.



PD = Power Doppler; **** = $p<0.0001$

Fig. 3 A. Pie charts depicting the proportion of patients in ultrasound (US) remission versus no US remission at T2 and T4 among those achieving clinical remission **B.** Distribution of max PD grades (0–3) across the entire cohort from baseline through T4. Statistical analysis was conducted through the Friedman test followed by post-hoc comparisons between baseline and each subsequent timepoint using the Wilcoxon signed-rank test. The asterisks denote the significance levels

Only few previous studies have explored the effects of UPA on both clinical and US disease activity in patients with RA.

Specifically, Baldi et al. recently analyzed the efficacy and safety of UPA over a 6-month period, focusing on clinical and US parameters without assessing remission rates [24].

Significant improvements were observed in both clinimetric scores (DAS28-CRP, SDAI) and US scores (synovial hypertrophy and PD signal). Interestingly, concomitant csDMARDs therapy appeared to limit improvements in synovial hypertrophy, while higher baseline ESR or CRP levels were associated with better SDAI responses.

More recently, Boyadzhieva V et al. reported a significant decrease in both gray scale and power Doppler ultrasound scores in a cohort of 53 RA patients treated with tofacitinib or upadacitinib. Notably, patients receiving upadacitinib showed a rapid and marked improvement, with a mean reduction of 10 points in gray scale,

7.2 points in power Doppler, and 10.7 points in the OMERACT composite score from baseline [32].

Our interim analysis of the UPARAREMUS study, conducted on a subgroup of patients who completed 24 weeks of treatment, showed that 63% achieved complete remission and 65% clinical remission, along with a significant reduction in both clinical disease activity parameters and US activity scores [25].

Some observational studies have also evaluated UPA's performance in achieving clinical remission using different composite indices over 6 to 12 months of follow-up in RA patients.

The interim analysis of the CLOSE-UP study, conducted in a Canadian RA cohort, showed 63.5% clinical remission with DAS28-CRP, 29% with CDAI, and 26.4% with SDAI at 6 months [10].

The multicentre UPHOLD study by Ostor et al., involving a large international cohort of RA patients, reported 5% remission according to DAS28-CRP, 20% with CDAI, and 22% with SDAI at 6 months; these rates increased to 60%, and 28% at 12 months, respectively [11].

Notably, in line with our data, these studies demonstrated that remission rates were consistent regardless of UPA monotherapy or prior use of bDMARDs.

Some limitations of the present study should be acknowledged.

At first, approximately 15% of patients were already in US remission at baseline. This can be explained by the inclusion criteria, which required moderate to severe clinical disease activity, as in routine practice, but did not mandate US-confirmed synovitis. However, nearly 90% of patients in clinical remission also achieved US remission at follow-up, and we observed a consistent reduction in both the number of US-active joints and in the overall PD score, supporting the robustness of our findings. Another potential limitation is the reduced number of joints assessed by US. We evaluated the bilateral wrists, the bilateral 2nd MCP joints, and any clinically swollen joints. This previously published scoring system has been shown to provide high sensitivity while remaining practical and time-efficient in clinical practice [17]. While a more extensive joint assessment might have detected additional subclinical synovitis, literature evidence suggests that the number of joints evaluated does not strongly affect the proportion of patients classified as being in US remission [23]. Additional limitations include the 12-month follow-up period, which may not fully capture the long-term safety and efficacy of UPA in real-world clinical practice, and the potential for reporting or investigator bias inherent to observational study designs.

On the other hand, the study has several strengths, including its multicenter, prospective design, the use of a homogeneous cohort of RA patients, and its innovative and more comprehensive assessment of remission, which also incorporated US evaluation.

Conclusions

After 12-months of treatment with UPA, 72% of patients attained the primary end-point of combined clinical and US remission.

Clinical and US remission rates were comparable regardless of UPA monotherapy or prior exposure to bDMARDs. Younger age, lower baseline CDAI, and higher ESR emerged as positive predictors of remission, whereas baseline corticosteroid use, significantly reduced the likelihood of achieving the primary endpoint. These results support the effectiveness of UPA in promoting and sustaining deep disease control in patients with RA.

Supplementary Information

The online version contains supplementary material available at https://doi.org/10.1186/s13075-025-03671-z.

Supplementary Material 1: Figure 4. 48-month survival curve of upadacitinib in patients with rheumatoid arthritis.

Supplementary Material 2: Table 4. Baseline factors associated with Complete Remission at T2 in rheumatoid arthritis (RA) patients.

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Authors' contributions

Conceptualization, APD, BL, AI; methodology, APD, MC; formal analysis, VP; writing original draft, review and editing: APD, AI; IB; enrolling patients and collecting clinical data, AD, MSC, SS, GS, GMF, DF, GDS, AZ, IG, GC, MML, GF, VP, PF, CB, CS, CP.

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Data availability

The data that support the findings of this study are available from the authors databases upon reasonable request.

Declarations

Ethics approval and consent to participate

The study was conducted in accordance with the Declaration of Helsinki and approved by the Ethic Committee of the Coordinator Centre (Lazio area 1, Approval numbers 6493_2021 on June 15, 2021) and by each Centre participating in the study; a written informed consent was obtained from all the patients.

Consent for publication

All authors have read and agreed to the published version of the manuscript.

Competing interests

The authors declare no competing interests.

Author details

[1]Department of Clinical and Molecular Medicine, "Sapienza" University of Rome, S. Andrea University Hospital, Rome 00189, Italy
[2]Dipartimento di Scienze Cliniche e Molecolari, Clinica Medica, Università Politecnica delle Marche, Ancona, Italy
[3]Department of Medicine, Surgery and Neurosciences, Rheumatology Unit, University of Siena, Viale Mario Bracci, Siena 53100, Italy

[4]Department of System Medicine, Rheumatology, Allergology and Clinical Immunology, University of Rome Tor Vergata, Rome 00133, Italy
[5]Department of Clinical and Biological Science, Academic Rheumatology Centre, University of Turin, AO Mauriziano Torino, Turin 10128, Italy
[6]Department of Medicine, Rheumatology Clinic, University of Udine, Universitaria Friuli Centrale, c/o Azienda Sanitaria, Udine 33100, Italy
[7]ASL Roma 1 UOSD Reumatologia, Ospedale Nuovo Regina Margherita, Roma 00153, Italy
[8]U.O.C. Reumatologia, A.O. San Camillo-Forlanini, Roma, Italy
[9]Department of Medicine and Surgery, Rheumatology Unit, University of Perugia, Perugia, Italy

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