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Achievement of Treatment Targets and Maintenance of Response With Upadacitinib in Patients With Moderate-to-Severe Rheumatoid Arthritis in a Real-World Setting: Final 2-Year Outcomes From the UPHOLD Study

Andrew Östör[1,2], Eugen Feist[3], Prodromos Sidiropoulos[4], Jérôme Avouac[5], Martin Rebella[6,7], Rajaie Namas[8], Erin McDearmon-Blondell[8], Ivan Lagunes-Galindo[9], Tianming Gao[9], Tim Shaw[9], Suzan Attar[10]

[1]Monash University & Emeritus Research, Melbourne, VIC, Australia; [2]Australian National University, ACT, Australia; [3]Helios Department of Rheumatology and Clinical Immunology, Vogelsang-Gommern, Germany; [4]Faculty of Medicine, University of Crete, Heraklion, Greece; [5]Service de Rhumatologie, Hôpital Cochin, AP-HP Centre – Université Paris Cité, Paris, France; [6]Departamento de Medicina, Facultad de Medicina, Universidad de la República, Montevideo, Uruguay; [7]Unidad de Enfermedades Autoinmunes Sistémicas, MUCAM, Montevideo, Uruguay; [8]Medical Subspecialties Institute, Division of Rheumatology, Cleveland Clinic Abu Dhabi, Abu Dhabi, UAE; [9]AbbVie Inc., North Chicago, IL, USA; [10]King Abdulaziz University, Jeddah, Saudi Arabia

OBJECTIVE

To evaluate the long-term achievement of treatment targets, sustained clinical response, and safety of upadacitinib over 2 years in patients with moderate-to-severe RA in real-world practice

CONCLUSIONS

Almost half (46.3%) of patients (55.3% if analysed as observed) achieved DAS28(CRP) remission at 6 months, of whom 79.2% maintained remission at 12 months and 62.9% at 2 years

The long-term benefit-risk profile of upadacitinib in this study in a real-world setting is consistent with data reported in phase 3 clinical trials

Upadacitinib is effective for the long-term treatment of moderate-to-severe RA in real-world practice, with most improvements observed by 3 months and maintained or further improved by 2 years

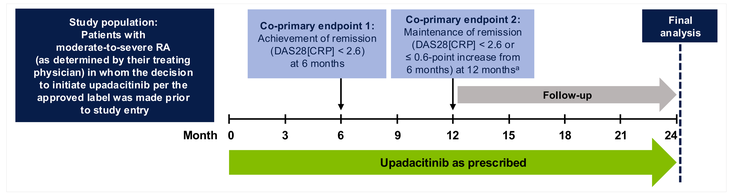
INTRODUCTION

- Upadacitinib, an oral selective JAK inhibitor,[1] has demonstrated efficacy with an acceptable safety profile in patients with moderate-to-severe RA in the SELECT clinical trials[2–7]
- However, real-world data on the long-term effectiveness and safety of upadacitinib in patients with RA are limited
  - Such data are important for clinical decision-making, as patient characteristics may differ between clinical trials and real-world practice, and clinical trial data may not exactly reflect outcomes in a real-world setting[8]
- The aim of the UPHOLD study (Upadacitinib Treatment Patterns, Achievement of Treatment Targets and Maintenance of Response in Moderate-to-Severe Rheumatoid Arthritis Patients in Real-World Practice) was to assess the achievement of treatment targets, sustained clinical response, and safety of upadacitinib in patients with moderate-to-severe RA over 2 years in a real-world setting

METHODS

- UPHOLD (NCT04497597) is an international, observational cohort study of upadacitinib-naïve adults with moderate-to-severe RA who received upadacitinib 15 mg, with the decision to initiate upadacitinib made by their treating physician prior to and independent of study enrolment
- Data are reported between October 16, 2020 (first patient enrolled) and May 15, 2024 (last patient last visit)

Figure 1. UPHOLD Study Design



[a]In patients who achieved DAS28(CRP) remission at 6 months.

- The co-primary endpoints were: i) proportion of patients receiving upadacitinib who achieved DAS28(CRP) remission (< 2.6) at 6 months and, of those, ii) proportion who maintained remission (or had a ≤ 0.6-point increase in DAS28[CRP]) at 12 months **(Figure 1)**
- The co-primary endpoints were analysed by modified nonresponder imputation (mNRI; discontinuations for any reason before prespecified timepoints were treated as nonresponders) and as observed (AO; in patients with nonmissing data) in modified full analysis set (mFAS)1 and mFAS2, respectively
  - mFAS1: all patients within the full analysis set (FAS; all patients receiving ≥ 1 upadacitinib dose) who completed 6 months of treatment and had DAS28(CRP) data available, and those who discontinued the study before 6 months
  - mFAS2: all patients achieving DAS28(CRP) remission within mFAS1, who completed 12 months of treatment and had DAS28(CRP) data available, and those who discontinued the study between 6 and 12 months
- Key secondary endpoints included: achievement and maintenance of DAS28(CRP) low disease activity (LDA; ≤ 3.2) through 24 months; maintenance of DAS28(CRP) remission/LDA by treatment strategy and prior therapy exposure through 24 months; mean DAS28(CRP) values by visit; proportion of patients in each DAS28(CRP), CDAI, and SDAI disease category by visit through 24 months; and change from baseline in patient-reported outcomes (PROs), including pain, morning stiffness, fatigue, HAQ-DI, and treatment burden, through 24 months
- All treatment-emergent adverse events (TEAEs) and selected TEAEs of interest in the FAS are reported as exposure-adjusted event rates (EAERs; events per 100 patient-years [E/100 PY])

RESULTS

Patients

- Of 1715 participants, 1713 were enrolled and 1699 received ≥ 1 upadacitinib dose, comprising the FAS
  - Of 1715 participants, 1029 (60.0%) completed the 24-month follow-up and 686 (40.0%) prematurely discontinued the study
  - Most frequent primary reasons for premature discontinuation were lack of efficacy (15.2%), adverse events (9.5%), and loss to follow-up (5.5%)
- Baseline demographics and disease characteristics are summarised in **Table 1**
  - Most patients (79.9%) were female; the mean age was 56.9 years; and the mean disease duration was 10.1 years
  - Almost half (48.3%) of FAS patients initiated upadacitinib as monotherapy, and 51.7% in combination with conventional synthetic DMARDs
  - Of 1524 patients who received prior RA therapy (not ongoing at the time of study initiation), 64.3% had received ≥ 1 biologic DMARD and 18.3% ≥ 1 prior targeted synthetic DMARD

Table 1. Baseline Demographics and Disease Characteristics

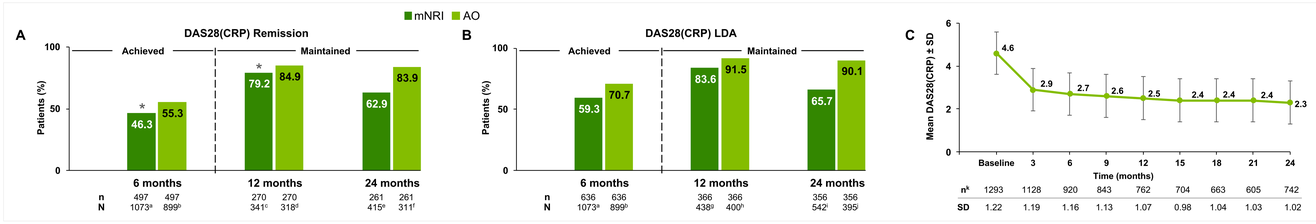
Parameter	FAS (N = 1699)
Age, years, mean (SD)	56.9 (12.4)
Sex, female, n (%)	1358 (79.9)
RA duration from diagnosis, years, mean (SD)	10.1 (9.1)
Erosions on X-ray, n (%)	710 (41.8)
Rheumatoid factor and/or ACPA positive, n (%)[a]	546 (77.8)
DAS28(CRP), mean (SD)	4.6 (1.2)
CDAI, mean (SD)	26.6 (12.6)
SDAI, mean (SD)	28.2 (14.0)
Swollen joint count, mean (SD)	5.7 (5.2)
Tender joint count, mean (SD)	8.2 (6.4)
Presence of ≥ 1 cardiovascular risk factor, n (%)[b]	1059 (62.3)
Initiated upadacitinib as monotherapy, n (%)	821 (48.3)
Initiated upadacitinib with conventional synthetic DMARDs, n (%)	878 (51.7)
Concomitant corticosteroids, n (%)[c]	735 (43.3)
Concomitant NSAIDs, n (%)[c]	355 (20.9)
Any prior therapies, n (%)[d]	
≥ *1 conventional synthetic DMARD*[e]	1209 (79.3)
≥ *1 biologic DMARD*[e]	980 (64.3)
≥ *1 targeted synthetic DMARD*[e]	279 (18.3)

ACPA, anti-citrullinated peptide antibody; FAS, full analysis set.
[a]Patients with ≥ 1 positive result for either rheumatoid factor or ACPA; n = 702. [b]History of hypertension, diabetes mellitus, high-density lipoprotein cholesterol ≤ 40 mg/dL in ≥ 1 measurement before enrolment, low-density lipoprotein cholesterol ≥ 130 mg/dL in ≥ 1 measurement before enrolment, and current/former tobacco/nicotine use. [c]N = 1312. [d]Not ongoing; N = 1524. [e]Patients may be counted multiple times between therapies.

Effectiveness

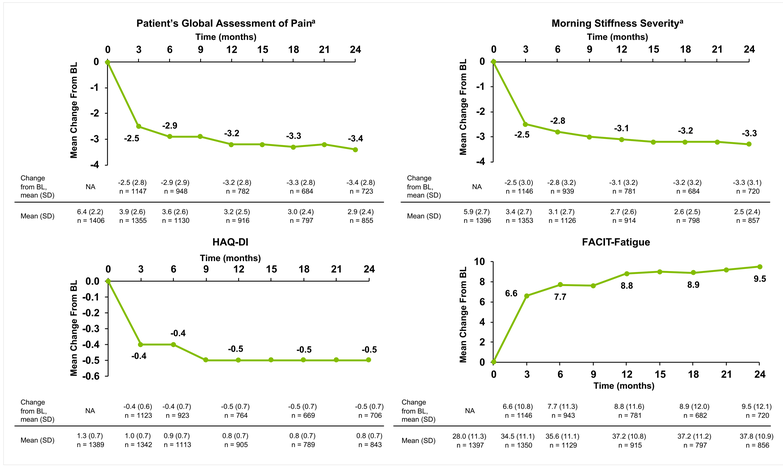
- Of the 1073 patients in the mFAS1, 46.3% (mNRI) and 55.3% (AO) achieved DAS28(CRP) remission at 6 months; of the 341 patients in the mFAS2, 79.2% (mNRI) and 84.9% (AO) maintained DAS28(CRP) remission at 12 months **(Figure 2A)**
  - A similar trend, with numerically higher rates, was observed for the achievement of DAS28(CRP) LDA at 6 months and maintenance of DAS28(CRP) LDA at 12 months **(Figure 2B)**
- Responses achieved at 6 months were maintained by most patients at 2 years; of those with a response at 6 months, 62.9% (mNRI) and 83.9% (AO) maintained DAS28(CRP) remission, and 65.7% (mNRI) and 90.1% (AO) maintained DAS28(CRP) LDA at 2 years **(Figure 2A** and **B)**
- The mean DAS28(CRP) value decreased from 4.6 at baseline to 2.9 at 3 months and 2.3 at 2 years **(Figure 2C)**
- The overall proportions of patients achieving DAS28(CRP), CDAI (≤ 2.8), and SDAI (≤ 3.3) remission at 2 years were 66.8%, 36.1%, and 36.7%, respectively (AO)
- Of patients who initiated upadacitinib as combination therapy, 13.4% (91/677) switched to upadacitinib monotherapy at 12 months and 22.6% (119/527) switched at 24 months
  - The proportion of patients maintaining remission at 24 months was consistent between those maintaining combination therapy (81.1% [90/111]) and monotherapy (87.4% [118/135]) (AO)
- Responses were similar across patient subgroups per prior therapy exposure (maintenance of DAS28(CRP) remission at 24 months: b/tsDMARD-naïve, 90.7%; prior exposure to targeted synthetic and/or biologic DMARDs, 69.2%–77.5%; and TNFi-only prior therapy, 80.6%) (AO)
- Improvements (reported as mean change from baseline) were observed in all assessed PROs at 3 months, which were maintained or further improved through 2 years **(Figure 3)**

Figure 2. (A, B) DAS28(CRP) Remission (< 2.6) and LDA (≤ 3.2), and (C) Mean DAS28(CRP) Value per Analysis Visit Through 2 Years (AO and mNRI)



AO, as observed; FAS, full analysis set; LDA, low disease activity; mFAS, modified FAS; mNRI, modified nonresponder imputation.
[a]Co-primary endpoints.
[b]mFAS1: FAS patients who completed 6 months of treatment and had DAS28(CRP) data available, or discontinued the study for any reason before 6 months. [c]mFAS2: mFAS1 patients who achieved REM at 6 months, completed 12 months of treatment and had DAS28(CRP) data available, or discontinued the study for any reason between 6 and 12 months. [d]mFAS2: mFAS1 patients with nonmissing DAS28(CRP) data. [e]FAS patients who achieved REM at 6 months, completed 24 months of treatment and had DAS28(CRP) data available at 6 and 24 months, or discontinued the study between 6 and 24 months. [f]FAS patients who achieved REM at 6 months, completed 12 months of treatment and had DAS28(CRP) data available at 6 and 24 months. [g]mFAS1 patients who achieved LDA at 6 months, completed 12 months of treatment and had DAS28(CRP) data available, or discontinued the study between 6 and 12 months. [h]mFAS1 patients who achieved LDA at 6 months, completed 12 months of treatment and had DAS28(CRP) data available. [i]FAS patients who achieved LDA at 6 months, had DAS28(CRP) data available at 6 and 24 months, and continued to receive upadacitinib at 24 months or discontinued the study between 6 and 24 months. [j]FAS patients who achieved LDA at 6 months, had DAS28(CRP) data available at 6 and 24 months, and continued to receive upadacitinib at 24 months. [k]Patients with nonmissing data.

Figure 3. Improvement in PROs Through 2 Years (AO)

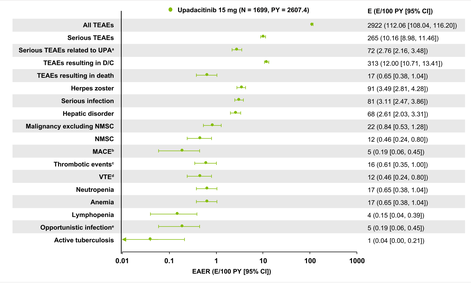


AO, as observed; BL, baseline; NA, not applicable; PRO, patient-reported outcome.
[a]Over the past 7 days using a 0–10 numeric rating scale.

Safety

- In total, 2922 TEAEs were reported, including 265 serious TEAEs **(Figure 4)**
  - Among selected TEAEs of interest, the most common were herpes zoster (3.5 E/100 PY), serious infection (3.1 E/100 PY), and hepatic disorder (2.6 E/100 PY)
- EAERs for malignancy excluding nonmelanoma skin cancer (NMSC) (0.8 E/100 PY), NMSC (0.5 E/100 PY), VTE (0.5 E/100 PY), and MACE (0.2 E/100 PY), were consistent with the upadacitinib safety data reported in previous phase 3 long-term clinical trials,[9] with no new safety signals

Figure 4. EAERs of TEAEs Through 2 Years



D/C, discontinuation; E, event; E/100 PY, events per 100 PY; EAER, exposure-adjusted event rate; FAS, full analysis set; NMSC, nonmelanoma skin cancer; PY, patient-years; TEAE, treatment-emergent adverse event.
Safety was evaluated by assessing all TEAEs (adverse events occurring after the first dose of study drug and up to 30 days after the last dose of study drug) occurring in the FAS up to the data cut-off date of May 15, 2024. There were no reported events of gastrointestinal perforation.
[a]Reasonable possibility. [b]Includes cardiovascular death, nonfatal myocardial infarction, and nonfatal stroke. [c]Includes VTE, other venous thrombosis, and arterial thromboembolic events. [d]Includes deep vein thrombosis, venous thromboembolism, and pulmonary embolism. [e]Excludes herpes zoster and active tuberculosis.

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