Efficacy and Safety of Upadacitinib Versus Adalimumab in Patients with Rheumatoid Arthritis Having Primary or Secondary Failure or Intolerance to a Tumor Necrosis Factor Inhibitor: Post Hoc Analysis of the SELECT-SWITCH Study

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OBJECTIVE

- To assess whether the 12-week therapeutic response after switching to upadacitinib or cycling to adalimumab differs when patients with rheumatoid arthritis are stratified by primary nonresponse, secondary nonresponse, or intolerance to a prior tumor necrosis factor inhibitor (TNFi)

INTRODUCTION

- For patients with rheumatoid arthritis (RA) who fail to achieve disease control with conventional synthetic disease-modifying antirheumatic drugs (csDMARDs), biologic DMARDs, including tumor necrosis factor inhibitors (TNFis), are recommended, with Janus kinase inhibitors (JAKis) considered for some patients[1,2,3]
- However, more than 50% of patients fail to achieve disease control with a TNFi within 2 to 4 years, some as primary nonresponse (lack of any meaningful clinical improvement to initial treatment) and some as secondary nonresponse (meaningful clinical improvement lost over time) or intolerance, each of which may be driven by different mechanisms[2,4,5]
- Despite growing evidence supporting switching to a drug with a different mechanism of action after an initial TNFi failure, approximately 46% to 64% of patients cycle to a second TNFi[2,6,7]
- In the ongoing phase 3b/4 SELECT-SWITCH study of patients who had an inadequate response to or intolerance of 1 non-adalimumab (ADA) TNFi, switching to upadacitinib (UPA), an oral JAKi, resulted in better disease control versus switching to ADA at week 12[8]
- The primary endpoint was met; a higher percentage of patients with active RA who switched to UPA versus cycling to ADA after the first TNFi failure achieved DAS28-CRP ≤ 3.2 at week 12[8]
- Further analysis is needed to identify the patients who benefit most from switching to UPA versus cycling based on the type of failure to the first TNFi

METHODS

PATIENTS, ELIGIBILITY, AND SUBGROUPS

- SELECT-SWITCH (NCT05814627) is an ongoing multicenter, randomized double-blind, head-to-head study comparing the efficacy of UPA and ADA[8]
- Patients with active RA on a stable background dose of methotrexate (MTX) (range: 15 to 25 mg/week) who had experienced an inadequate response or intolerance to a single non-ADA TNFi (intolerance cap set at ≤ 15% of total patients) were enrolled
- Patients were randomized 1:1 to UPA 15 mg once daily (QD) or ADA 40 mg every other week (EOW) for 12 weeks after which they were eligible for a blinded extension up to 48 weeks
- Patients were stratified into primary or secondary nonresponders, as assessed by the investigator, or those who were intolerant (discontinued due to intolerability or toxicity) to a TNFi

EFFICACY AND SAFETY

- Efficacy assessments included the proportion of patients who achieved DAS28-CRP ≤ 3.2 and <2.6, CDAI ≤ 10 and ≤ 2.8, SDAI ≤ 11 and ≤ 3.3, ACR20, ACR50, and ACR70
- Additionally, the mean change from baseline in DAS28-CRP, patient-reported pain (0 to 10 numerical rating scale [NRS]), FACIT-Fatigue, and HAQ-DI were reported
- Safety was monitored throughout the study and analyzed per subgroup
- Baseline characteristics and subgroup comparisons were summarized descriptively
- For binary endpoints, missing data and intercurrent events were handled with nonresponder imputation incorporating multiple imputation; for continuous endpoints, return-to-baseline multiple imputation was used to handle missing data

RESULTS

BASELINE DEMOGRAPHICS AND CLINICAL CHARACTERISTICS

- This analysis included 236 primary nonresponders (UPA, n=121; ADA, n=115), 194 secondary nonresponders (UPA, n=96; ADA, n=98), and 52 patients with drug intolerance to a single TNFi (UPA, n=25; ADA, n=27) **(Table 1)**
- Overall, the baseline demographics and clinical characteristics of patients treated with ADA and UPA were similar in each of the 3 subgroups analyzed; background MTX doses were similar for patients treated with UPA and ADA, regardless of subgroup

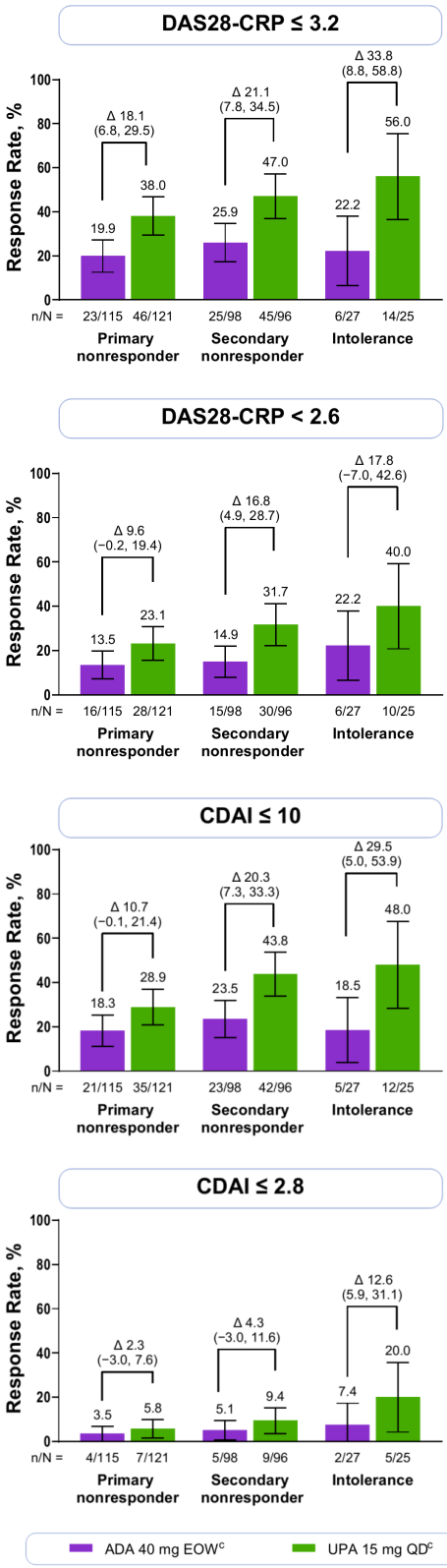
Table 1. Baseline Demographics and Clinical Characteristics

	Primary Nonresponders		Secondary Nonresponders		Intolerance	
	ADA[a] N = 115	UPA[a] N = 121	ADA[a] N = 98	UPA[a] N = 96	ADA[a] N = 27	UPA[a] N = 25
Sex (female), n (%)	82 (71.3)	91 (75.2)	83 (84.7)	75 (78.1)	20 (74.1)	20 (80.0)
Age, years, mean (SD)	55.2 (12.5)	56.0 (12.0)	56.1 (12.6)	54.0 (13.4)	56.6 (11.7)	57.0 (13.5)
Race						
American Indian / Alaska Native	4 (3.5)	7 (5.8)	15 (15.3)	14 (14.6)	1 (3.7)	1 (4.0)
Asian	19 (16.5)	19 (15.7)	7 (7.1)	9 (9.4)	6 (22.2)	4 (16.0)
Black	7 (6.1)	6 (5.0)	6 (6.1)	1 (1.0)	0	0
White	81 (70.4)	89 (73.6)	66 (67.3)	70 (72.9)	20 (74.1)	20 (80.0)
Multiple	4 (3.5)	0	4 (4.1)	2 (2.1)	0	0
BMI (kg/m^2), mean (SD)	28.8 (7.4)	29.4 (6.4)	28.7 (6.8)	29.8 (6.9)	27.5 (5.1)	28.1 (6.0)
Patients with at least 1 cardiovascular risk factor[b], n (%)	83 (72.2)	89 (73.6)	75 (76.5)	68 (70.8)	17 (63.0)	16 (64.0)
Duration of RA diagnosis, years, mean (SD)	9.9 (9.5)	8.2 (8.3)	10.8 (9.1)	13.1 (8.4)	9.3 (8.7)	7.7 (6.7)
MTX, dose at baseline (mg/week), median (IQR)	15.0 (15.0, 20.0)	15.0 (15.0, 20.0)	15.0 (15.0, 20.0)	15.0 (15.0, 20.0)	15.0 (15.0, 15.0)	15.0 (10.0, 20.0)
TNFi exposure, days, median (min, max)	219.0 (2, 7305)	244.0 (20, 9314)	587.5 (1, 7869)	641.0 (43, 7686)	65.5 (1, 3137)	59.0 (1, 3302)
DAS28-CRP, mean (SD)	5.7 (0.8)	5.8 (0.8)	5.8 (0.8)	5.7 (0.8)	5.5 (0.8)	5.6 (0.9)
CDAI, mean (SD)	39.2 (11.7)	39.6 (9.7)	39.3 (9.9)	37.7 (10.3)	36.3 (8.9)	38.9 (12.6)
SDAI, mean (SD)	40.4 (11.8)	41.3 (10.6)	41.0 (10.6)	39.6 (10.8)	37.4 (9.1)	39.8 (12.8)
Pain (0 to 10, NRS), mean (SD)	7.2 (1.8)	7.5 (1.8)	7.7 (1.8)	7.3 (2.0)	7.1 (2.1)	6.8 (2.4)
FACIT-Fatigue, mean (SD)	27.5 (10.5)	26.2 (11.5)	25.5 (10.8)	26.7 (11.4)	29.8 (8.4)	30.1 (10.5)
HAQ-DI, mean (SD)	1.6 (0.6)	1.6 (0.6)	1.6 (0.6)	1.6 (0.6)	1.4 (0.6)	1.3 (0.6)

[a] Patients treated with ADA and UPA were also treated with a stable dose of background MTX.
[b] Cardiovascular risk factors include history of a cardiovascular event, hypertension, diabetes mellitus, former/current smoker, elevated low-density lipoprotein cholesterol, and lowered high-density lipoprotein cholesterol.
ADA, adalimumab 40 mg every other week (EOW); BMI, body mass index; IQR, interquartile range; MTX, methotrexate; NRS, numeric rating scale; TNFi, tumor necrosis factor inhibitor; UPA, upadacitinib 15 mg once daily (QD).

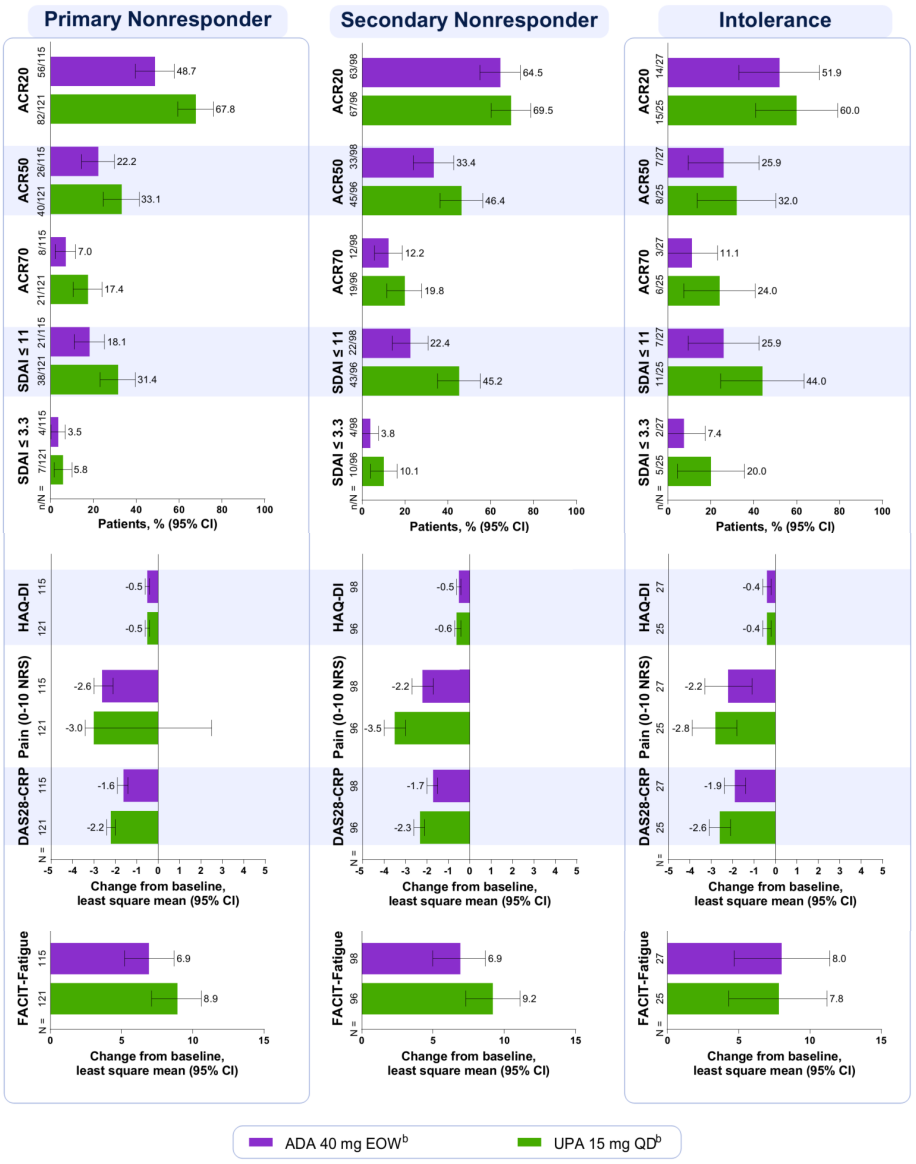
RESULTS

Figure 1. Disease Activity Response Rates Among Primary Nonresponders, Secondary Nonresponders, and Intolerance Subgroups at Week 12[a,b]



Δ, treatment difference (UPA minus ADA); ADA, adalimumab; EOW, every other week; MTX, methotrexate; QD, once daily; UPA, upadacitinib.
[a] Error bars and numbers in parentheses represent 95% confidence intervals.
[b] Binary endpoints were handled with nonresponder imputation incorporating multiple imputation.
[c] Patients treated with ADA and UPA also received a stable dose of background MTX.

Figure 2. Additional Efficacy Outcomes Among Primary Nonresponders, Secondary Nonresponders, and Intolerance Subgroups at Week 12[a]



ADA, adalimumab; CI, confidence interval; EOW, every other week; MTX, methotrexate; NRS, numeric rating scale; QD, once daily; UPA, upadacitinib.
[a] Binary endpoints were handled with nonresponder imputation incorporating multiple imputation; continuous endpoints were handled with return-to-baseline missing imputation.
[b] Patients treated with ADA and UPA also received a stable dose of background MTX.

DISEASE ACTIVITY AMONG PRIMARY NONRESPONDERS, SECONDARY NONRESPONDERS, AND INTOLERANCE SUBGROUPS

- By week 12, the proportion of patients treated with UPA who achieved DAS28-CRP ≤ 3.2/< 2.6 and CDAI ≤ 10/≤ 2.8 was higher than the proportion of patients treated with ADA who achieved these response rates, regardless of subgroup **(Figure 1)**
- Similarly, numerically higher proportions of patients treated with UPA achieved ACR20, ACR50, ACR70, and SDAI ≤ 11/≤ 3.3 versus ADA, irrespective of subgroup **(Figure 2)**
- UPA-treated patients had generally numerically greater mean changes from baseline in DAS28-CRP, pain, FACIT-Fatigue, and HAQ-DI, than ADA-treated patients regardless of subgroup

RESULTS (continued)

Table 2. Safety up to Week 12

n (%)	Primary Nonresponders		Secondary Nonresponders		Intolerance	
	ADA[a] N = 114	UPA[a] N = 121	ADA[a] N = 98	UPA[a] N = 96	ADA[a] N = 27	UPA[a] N = 25
Any TEAE	48 (42.1)	40 (33.1)	42 (42.9)	45 (46.9)	8 (29.6)	15 (60.0)
Serious TEAE	3 (2.6)	3 (2.5)	1 (1.0)	2 (2.1)	2 (7.4)	0
All deaths	0	0	0	0	0	0

ADA, adalimumab 40 mg every other week (EOW); MTX, methotrexate; TEAE, treatment-emergent adverse event; UPA, upadacitinib 15 mg once daily (QD).
[a] Patients treated with ADA or UPA also received a stable dose of background MTX.

SAFETY

- The observed treatment-emergent adverse events across subgroups were generally consistent with the known safety profile of UPA and ADA **(Table 2)**
- Additional safety data through week 12 have been previously reported[8]

CONCLUSIONS

- In patients with rheumatoid arthritis who have failed one TNFi, switching to upadacitinib compared with cycling to adalimumab provided a clinical benefit, regardless of the reason for previous failure
- These data support upadacitinib as a more efficacious option than adalimumab, with a favorable benefit-risk profile for all types of previous TNFi failure, which may help guide treatment decisions

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