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Evaluating the efficacy of upadacitinib in patients with moderate rheumatoid arthritis: a post-hoc analysis of the SELECT phase 3 trials

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Abstract

Objectives: Moderately active RA is associated with poor patient outcomes. Despite this, some health systems have restricted access to advanced therapies to those with severe RA. There is also limited evidence of the efficacy of advanced therapies in the moderately active RA population. This post-hoc analysis from four phase 3 trials explored the efficacy of upadacitinib (UPA) for moderately active RA.

Methods: Patients included in this analysis received UPA 15 mg once daily [monotherapy after switching from MTX or in combination with stable background conventional synthetic DMARDs (csDMARDs)] or placebo. Clinical, functional and radiographic outcomes were analysed separately for patients with moderate disease activity {28-joint count DAS using CRP [DAS28(CRP)] of >3.2 and ≤ 5.1} and severe disease activity [DAS28(CRP) >5.1].

Results: Patients with moderate disease activity who received UPA 15 mg (combination or monotherapy) after an inadequate response to biologic DMARDs and/or csDMARDs were significantly more likely to achieve a 20% improvement in the ACR response criteria, low disease activity status [DAS28(CRP) ≤ 3.2] or clinical remission [DAS28(CRP) < 2.6] by week 12/14 *vs* placebo. Statistically significant improvements in patient-reported functioning and pain from baseline were observed for UPA 15 mg *vs* placebo at week 12/14. Radiographic progression was also significantly reduced at week 26 compared with placebo. Similar improvements were observed for severe disease.

Conclusion: This analysis provides support for the use of UPA for the treatment of patients with moderate RA.

Trial registration: ClinicalTrials.gov: SELECT-NEXT: NCT02675426; SELECT-COMPARE: NCT02629159; SELECT-MONOTHERAPY: NCT02706951; SELECT-BEYOND: NCT02706847.

Lay Summary

What does this mean for patients?
Rheumatoid arthritis (RA) is a chronic disabling disease that is associated with joint pain and stiffness and poor quality of life. When left untreated, the inflammation in the joint lining destroys the joints. Modern treatment focuses on treating many aspects of the disease, such as reducing pain, fatigue and joint destruction. For cost reasons, some health systems have had to restrict access to certain drug treatments to people with severe RA only; however, people with moderate disease could also benefit from these treatments. It is therefore important to know whether a modern effective therapy works in people who have moderately active RA. In this study, we looked at four previously performed large clinical trials of an oral therapy called upadacitinib (UPA) and selected only the patients with moderately active RA receiving UPA or placebo (dummy treatment). These studies showed significant improvements in disease symptoms with UPA after 3 months when compared with placebo, with improved function and less pain in those receiving UPA. Joint destruction, measured by an X-ray, was also significantly reduced after 6 months compared with placebo. This study supports the use of modern therapies for treating people with moderate RA, in addition to severe RA.

Keywords: RA, moderate, moderate disease activity, upadacitinib, JAK inhibitors

Key messages

- Evidence is limited regarding the efficacy of advanced therapies for patients with moderately active RA.
- Clinical, functional and radiographic improvements were observed following upadacitinib initiation in patients with moderate RA.
- These results support the use of advanced therapies for the treatment of moderate RA.

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Introduction

Treatment decisions for RA are often based on disease activity, assessed using the 28-joint count (DAS28). Although patients with moderate disease activity (DAS28 >3.2 and ≤5.1) can experience poor outcomes [1, 2], some health systems have restricted the use of new advanced therapies, such as biologic and targeted synthetic DMARDs to patients with highly active disease (DAS28 >5.1). There is, however, limited evidence regarding the effectiveness of advanced treatments in moderate disease. Most randomized clinical trials for RA have inclusion criteria that encompass both moderate and severe disease, and only a small number of observational cohort studies have considered the efficacy of therapies for moderate disease activity [3–5].

Upadacitinib (UPA), an oral Janus kinase (JAK)1-selective inhibitor, has shown improvements in clinical and functional outcomes in patients with moderate-to-severe RA who have experienced a prior inadequate response (IR) to DMARD (DMARD-IR) across a series of phase 3 trials [6–9]. This post-hoc analysis aimed to explore the efficacy of UPA in patients with moderate RA using data from the large international SELECT phase 3 randomized clinical trial programme.

Methods

This was a post-hoc, subgroup analysis of data from the SELECT-NEXT, SELECT-COMPARE, SELECT-MONOTHERAPY and SELECT-BEYOND trials [6–9]. Included in this analysis were patients aged ≥18 years receiving UPA 15 mg once daily, either as monotherapy after switching from MTX (SELECT-MONOTHERAPY) or in combination with stable background conventional synthetic DMARD (csDMARD) therapy (SELECT-COMPARE, SELECT-NEXT and SELECT-BEYOND), or placebo [continued MTX (SELECT-MONOTHERAPY) or csDMARD therapy].

All patients receiving UPA had experienced a prior IR to csDMARDs (csDMARD-IR; treatment duration ≥3 months), whereas patients from SELECT-BEYOND had experienced a prior inadequate response to one or more biologic DMARDs (bDMARD-IR). Full information about the study design and eligibility criteria for the individual phase 3 trials is published elsewhere [6–9].

Data analysis

Data were evaluated separately for patients with moderate (DAS28 of >3.2 and ≤5.1) and severe (DAS28 of >5.1) baseline disease activity. Data from SELECT-COMPARE and SELECT-NEXT were integrated for this analysis [csDMARD-IR group (combination therapy)]; patients receiving monotherapy (SELECT-MONOTHERAPY) and those with bDMARD-IR (SELECT-BEYOND) were analysed separately.

The proportion of patients achieving a 20% improvement in the ACR criteria (ACR20) [10], and the proportion meeting the criteria for low disease activity {defined as a DAS28 using CRP [DAS28(CRP)] ≤ 3.2} and remission [DAS28(CRP) < 2.6] [11] were evaluated at week 12 (SELECT-COMPARE/SELECT-NEXT and SELECT-BEYOND) or week 14 (SELECT-MONOTHERAPY), in line with the trial primary endpoints. Patient-reported outcomes were also evaluated at baseline and week 12/14. The HAQ disability index (HAQ-DI) [12] score was used to assess perceived difficulty with functional tasks [scores ranged from zero (no disability) to three (very severe disability); a decrease from baseline indicated improvement]. Pain severity was measured on a visual analogue scale (VAS), with scores ranging from 0 (no pain) to 100 cm (worst possible pain) and with a decrease from baseline indicating improvement (note that these data were not available for SELECT-MONOTHERAPY).

In addition, the proportion of patients with radiographic progression at week 26 (SELECT-COMPARE only) was evaluated based on the van der Heijde modified total sharp score (mTSS). The mTSS measures joint damage from radiographs of the hands and feet (assessed by two independent assessors); total mTSS scores range from 0 to 280, with no radiographic progression defined as a change from baseline of mTSS ≤ 0.

Differences between the UPA 15 mg and placebo groups were evaluated for all endpoints. For binary endpoints, treatment groups were compared using the Cochran–Mantel–Haenszel test adjusted for prior IR [csDMARD-IR (combination therapy and monotherapy groups) or bDMARD-IR]. The 95% CIs for response rates were calculated based on normal approximation to the binomial distribution. For continuous variables, 95% CIs and differences between groups were evaluated using mixed-effect model repeated measurement analysis. An unstructured variance–covariance matrix was specified, whereby treatment, visit, treatment-by-visit interaction and prior DMARD-IR response group were included as fixed factors, with the baseline value specified as a covariate. Missing data were handled using non-responder imputation for binary endpoints and mixed-effect model repeat measurement for continuous variables. In addition, a separate logistic regression analysis was carried out, adjusting for baseline disease duration, DAS28 and HAQ-DI scores and prior biologic use to evaluate the likelihood of patients with moderate and severe disease achieving key endpoints at week 12. A mixed-effect model repeated measurement analysis was also conducted that adjusted for the same characteristics as the logistic regression analysis.

The SELECT phase 3 trials were conducted in accordance with the International Conference on Harmonization (ICH) Good Clinical Practice (GCP) guidelines, the Declaration of Helsinki and other applicable regulations. Study-related documents were approved by institutional ethics committees and review boards in each country. The UPA phase 3 trials included in this study were approved by the South Central–Oxford B Research Ethics Committee. All patients provided written informed consent.

Results

Table 1 summarizes baseline characteristics and efficacy outcomes for UPA 15 mg (in combination with csDMARD) *vs* placebo for patients with prior csDMARD-IR (based on integrated analysis of SELECT-COMPARE and SELECT-NEXT); corresponding analyses for SELECT-MONOTHERAPY (UPA 15 mg monotherapy *vs* placebo) are shown in Table 2. Significantly greater proportions of csDMARD-IR patients with moderate disease activity who received UPA 15 mg (as either combination or monotherapy) achieved the ACR20 [combination: $P \leq 0.001$ (Table 1); monotherapy: $P \leq 0.01$ (Table 2)], low disease activity [DAS28(CRP) ≤ 3.2; combination: $P \leq 0.001$ (Table 1); monotherapy: $P \leq 0.01$ (Table 2)] and remission criteria [DAS28(CRP) < 2.6; $P \leq 0.001$ for both combination and monotherapy (Tables 1 and 2)] compared with the placebo group at week 12/14;

Table 1. Baseline characteristics and efficacy endpoints (SELECT-COMPARE/SELECT-NEXT)

Time point	Key endpoints	csDMARD-IR (SELECT-COMPARE and SELECT-NEXT integrated analysis)			
		Moderate		Severe	
		UPA 15mg ($n = 209$)	Placebo ($n = 195$)	UPA 15 mg ($n = 649$)	Placebo ($n = 671$)
Baseline	Age, mean (S.D.), years	53.7 (12.6)	54.5 (12.4)	54.9 (11.6)	54.1 (12.3)
	Female, *n* (%)	161 (77.0)	157 (80.5)	529 (81.5)	517 (77.0)
	Duration since diagnosis, mean (S.D.), years	7.5 (7.4)	7.3 (6.7)	8.0 (7.9)	8.2 (8.2)
	DAS28(CRP), mean (S.D.)	4.6 (0.4)	4.6 (0.4)	6.2 (0.7)	6.1 (0.7)
	HAQ-DI, mean (S.D.)	1.2 (0.6)	1.2 (0.6)	1.7 (0.6)	1.7 (0.6)
	Pain VAS (0–100), mean (S.D.)	52.5 (21.4)	48.4 (21.6)	69.8 (18.2)	68.9 (17.9)
	mTSS, mean (S.D.)	34.295 (48.662) ($n = 144$)	29.952 (45.085) ($n = 125$)	34.369 (50.805) ($n = 492$)	37.431 (53.254) ($n = 518$)
Week 12	ACR20, % response (95% CI)	63.6 (57.1, 70.2)***	33.8 (27.2, 40.5)	71.2 (67.7, 74.7)***	37.0 (33.3, 40.6)
	ACR50, % response (95% CI)	41.6 (34.9, 48.3)***	14.4 (9.4,19.3)	44.1 (40.2, 47.9)***	15.1 (12.3, 17.8)
	ACR70, % response (95% CI)	21.5 (16.0, 27.1)***	4.1 (1.3, 6.9)	24.7 (21.3, 28.0)***	5.5 (3.8, 7.2)
	DAS28(CRP) ≤ 3.2, % response (95% CI)	61.7 (55.1, 68.3)***	28.7 (22.4, 35.1)	40.7 (36.9, 44.5)***	10.3 (8.0, 12.6)
	DAS28(CRP) < 2.6, % response (95% CI)	41.1 (34.5, 47.8)***	14.9 (9.9, 19.9)	25.1 (21.8, 28.5)***	4.6 (3.0, 6.2)
	ΔDAS28(CRP), mean (95% CI)	−1.817 (−2.000, −1.634)***	−0.779 (−0.966, −0.592)	−2.546 (−2.671, −2.422)***	−1.175 (−1.296, −1.054)
	ΔHAQ-DI, mean (95% CI)	−0.43 (−0.51, −0.35 [$n = 191$])***	−0.23 (−0.32, −0.15 [$n = 183$])	−0.67 (−0.72, −0.61 [$n = 622$])***	−0.31 (−0.36, −0.25 [$n = 635$])
	ΔPain VAS (0–100), mean (95% CI)	−25.0 (−28.6, −21.4 [$n = 191$])***	−6.9 (−10.6, −3.2 [$n = 183$])	−32.8 (−35.1, −30.5 [$n = 624$])***	−16.1 (−18.4, −13.8 [$n = 635$])
Week 26 (SELECT-COMPARE only)	ΔmTSS ≤ 0, % response (95% CI)]	89.8 (84.6, 95.1 [$n = 128$])	83.3 (76.5, 90.2 [$n = 114$])	81.6 (78.1, 85.2 [$n = 457$])**	73.9 (70.0, 77.8 [$n = 479$])
	Δ mTSS [mean (95% CI)	−0.166 (−0.394, 0.061 [$n = 128$])*	0.128 (−0.099, 0.354 [$n = 114$])	0.362 (0.001, 0.722 [$n = 457$])***	1.130 (0.778, 1.482 [$n = 479$])

Where scores were not available for all patients in that group, the total number of patients included in the analysis [*n*] is specified.
* Nominal $P < 0.05$,
** nominal $P < 0.01$ and
*** nominal $P < 0.001$ for comparison of UPA *vs* placebo (continued conventional synthetic DMARD).
Δ: change from baseline; ACR20: ACR response criteria; csDMARD-IR: inadequate response to prior conventional synthetic DMARD; DAS28: 28-joint count DAS; HAQ-DI: HAQ disability index; mTSS: modified total sharp score; UPA: upadacitinib.

Table 2. Baseline characteristics and efficacy endpoints (SELECT-MONOTHERAPY)

Time point	Key endpoints	csDMARD-IR (SELECT-MONOTHERAPY)			
		Moderate		Severe	
		UPA 15mg ($n = 72$)	Placebo ($n = 73$)	UPA 15 mg ($n = 144$)	Placebo ($n = 143$)
Baseline	Age, mean (s.d.), years	52.7 (14.1)	54.3 (11.5)	55.4 (11.1)	55.8 (10.9)
	Female, *n* (%)	53 (73.6)	59 (80.8)	120 (83.3)	120 (83.9)
	Duration since diagnosis, mean (s.d.), years	5.1 (5.0)	5.9 (7.1)	8.6 (10.1)	5.8 (6.4)
	DAS28(CRP), mean (s.d.)	4.6 (0.4)	4.5 (0.5)	6.1 (0.7)	6.2 (0.7)
	HAQ-DI, mean (s.d.)	1.1 (0.6)	1.1 (0.6)	1.7 (0.6)	1.7 (0.6)
Week 14	ACR20, % response (95% CI)	59.7 (48.4, 71.1)**	37.0 (25.9, 48.1)	72.2 (64.9, 79.5)***	43.4 (35.2, 51.5)
	DAS28(CRP) $\leq$ 3.2, % response (95% CI)	59.7 (48.4, 71.1)**	32.9 (22.1, 43.7)	36.8 (28.9, 44.7)***	12.6 (7.2, 18.0)
	DAS28(CRP) $<$ 2.6, % response (95% CI)	40.3 (28.9, 51.6)***	15.1 (6.9, 23.3)	22.2 (15.4, 29.0)***	4.9 (1.4, 8.4)
	ΔDAS28(CRP), mean (95% CI)	−1.79 (−2.09, −1.49 [$n = 65$])***	−0.78 (−1.09, −0.47 [$n = 64$])	−2.55 (−2.80, −2.31 [$n = 131$])***	−1.46 (−1.70, −1.22 [$n = 130$])
	ΔHAQ-DI, mean (95% CI)	−0.47 (−0.59, −0.36 [$n = 65$])**	−0.22 (−0.34, −0.11 [$n = 65$])	−0.74 (−0.85, −0.63 [$n = 133$])***	−0.37 (−0.48, −0.25 [$n = 130$])

Where scores were not available for all patients in that group, the total number of patients included in the analysis [*n*] is specified. Pain VAS scores were not available for SELECT-MONOTHERAPY.

* Nominal $P < 0.05$,

** nominal $P < 0.01$ and

*** nominal $P < 0.001$ for comparison of UPA *vs* placebo (continued MTX).

Δ: change from baseline; ACR20: ACR response criteria; csDMARD-IR, inadequate response to prior conventional synthetic DMARD; DAS28: 28-joint count DAS; HAQ-DI: HAQ disability index; UPA: upadacitinib.

similar results were observed for patients with severe disease activity at baseline (see Tables 1 and 2). Significantly greater improvements in patient-reported physical function were also observed at week 12/14 for UPA 15 mg *vs* placebo in both the moderate and severe disease groups (Tables 1 and 2).

Results from SELECT-COMPARE (Table 1) indicated that radiographic progression (as measured by mean change in mTSS) at week 26 was reduced for UPA 15 mg compared with placebo for patients with moderate disease activity (mean change: −0.166 *vs* 0.128; $P < 0.05$) and severe disease activity (mean change: 0.362 *vs* 1.130; $P < 0.001$).

Supplementary Table S1, available at *Rheumatology Advances in Practice* online, summarizes the efficacy of UPA 15 mg *vs* placebo in patients with prior bDMARD-IR (from SELECT-BEYOND). At week 12, statistically higher proportions of patients who received UPA 15 mg achieved the ACR20 [$P < 0.05$ (moderate); $P < 0.001$ (severe)], low disease activity [$P < 0.001$ (moderate and severe)] and remission [$P < 0.05$ (moderate); $P < 0.001$ (severe)] criteria compared with placebo for both moderate and severe disease activity.

Patients with prior bDMARD-IR and severe disease activity who received UPA 15 mg reported significantly greater improvements in HAQ-DI and pain VAS scores from baseline at week 12 compared with the placebo group ($P < 0.0001$; Supplementary Table S1, available at *Rheumatology Advances in Practice* online). Although improvements in HAQ-DI and pain VAS scores from baseline were also observed at week 12 in patients with moderate disease, there were no statistically significant differences observed between the UPA 15 mg and placebo groups, although this is confounded by low patient numbers in these groups.

Supplementary Table S2, available at *Rheumatology Advances in Practice* online, shows the result of a logistic regression analysis adjusting for disease duration, initial DAS28, HAQ-DI and prior biologic use, and Supplementary Table S3, available at *Rheumatology Advances in Practice* online, shows the result of a mixed-effect model repeated measurement analysis adjusting for the same variables. All supplementary material is available at *Rheumatology Advances in Practice* online. At week 12, patients from the csDMARD-IR cohort with both moderate and severe disease activity were statistically more likely to achieve low disease activity [$P < 0.001$ (moderate and severe) for DAS28(CRP) ≤ 3.2], remission [$P < 0.001$ (moderate and severe) for DAS28(CRP) ≤ 2.6], improvements in physical function [$P < 0.001$ (moderate and severe) for HAQ-DI] and pain [$P < 0.001$ (moderate and severe) for pain VAS] when treated with UPA 15 mg compared with placebo (Supplementary Tables S2 and S3, available at *Rheumatology Advances in Practice* online). For the bDMARD-IR cohort at week 12, when adjusting for disease duration, initial DAS28, HAQ-DI and prior biologic use, patients with moderate disease activity were statistically more likely to achieve low disease activity ($P < 0.01$) and remission ($P < 0.05$) criteria when treated with UPA 15 mg compared with placebo (Supplementary Tables S2 and S3, available at *Rheumatology Advances in Practice* online).

Discussion

Despite the known burden associated with moderate RA [1, 2], only a small number of studies have considered the efficacy of advanced therapy for the treatment of moderate disease [3–5]. The present results showed that patients with moderate disease activity who received a once daily dose of UPA 15 mg, either in combination with csDMARDs or as monotherapy, experienced significantly greater improvements (by week 12/14) in clinical and patient-reported outcomes compared with the control groups. Notably, these improvements were observed for patients who had an inadequate response to bDMARDs and to conventional DMARD treatment. Furthermore, the significant improvement in pain within the csDMARD-IR cohort within a short time frame (12 weeks) is a key finding, because a meaningful improvement in reported pain has the potential to improve quality of life in this population, which has traditionally been associated with inadequate responses to other therapies.

These findings are significant given that some health technology assessment bodies, such as the National Institute for Health and Care Excellence (NICE) in the UK, until recently allowed access to advanced therapies only for patients with highly active disease (DAS28 ≥ 5.1), partly owing to their high expense relative to conventional treatments [13]. Other countries have also applied stringent reimbursement criteria for accessing advanced therapies, such as bDMARDs, despite wider guidance supporting the use of these treatments for moderately active disease [14]. Consequently, disparities have emerged in terms of access to advanced therapies across countries with similar population sizes of eligible patients, leaving a sizeable proportion of patients with uncontrolled disease and no other treatment options [15]. Patients with inadequately controlled RA are likely to experience a wide array of physical and emotional difficulties during their everyday lives, which might impact their wider mental health and work productivity [16–19]. Furthermore, qualitative research involving patients with moderate RA suggests that patients would be receptive to trying more intense management regimes [20].

In order to evaluate fully the clinical and cost-effectiveness of enabling wider-reaching access to innovative treatments, it will be important to continue to build evidence bases demonstrating the impact of advanced treatments in patients with moderate disease.

Although these data are derived from randomized clinical trials, there are limitations to this post-hoc analysis. The short follow-up duration of 12/14 weeks (except for mTSS, considered at 26 weeks) means the longer-term outcomes of UPA 15 mg for patients with moderate RA are unclear. Radiographic data were available only from SELECT-COMPARE; therefore, limited inferences can be drawn about structural outcomes for patients with moderate disease treated with UPA 15 mg as monotherapy or after prior inadequate response to other DMARDs. Additionally, the relatively low number of participants for the bDMARD-IR analysis might have impacted the ability to detect a statistically significant difference for the HAQ-DI and pain VAS scores compared with baseline in this group.

In conclusion, based on data from four large phase 3 trials, the results of the present study demonstrated that a once-daily dose of UPA 15 mg was effective in improving clinical and patient-reported outcomes in patients with moderate and severe RA disease activity with prior inadequate responses to DMARD therapy, when administered either as monotherapy or in combination with csDMARDs. These findings provide new evidence in support of the use of advanced therapies, such as UPA, for the treatment of patients with RA with

moderate disease activity, in addition to those with more severe disease.

Supplementary material

Supplementary material is available at *Rheumatology Advances in Practice* online.

Data availability

AbbVie is committed to responsible data sharing regarding the clinical trials we sponsor. This includes access to anonymized, individual and trial-level data (analysis data sets), as well as other information (e.g. protocols and Clinical Study Reports), as long as the trials are not part of an ongoing or planned regulatory submission. This includes requests for clinical trial data for unlicensed products and indications.

These clinical trial data can be requested by any qualified researchers who engage in rigorous, independent scientific research and will be provided following review and approval of a research proposal and Statistical Analysis Plan (SAP) and execution of a Data Sharing Agreement (DSA). Data requests can be submitted at any time, and the data will be accessible for 12 months, with possible extensions considered. For more information on the process, or to submit a request, visit the following link: https://www.abbvie.com/our-science/clinical-trials/clinical-trials-data-and-information-sharing/data-and-information-sharing-with-qualified-researchers.html.

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