THU0165

A COMPARATIVE ANALYSIS OF UPADACITINIB MONOTHERAPY AND UPADACITINIB COMBINATION THERAPY FOR THE TREATMENT OF RHEUMATOID ARTHRITIS FROM TWO PHASE 3 TRIALS

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Background: Upadacitinib (UPA), a selective JAK1 inhibitor, has demonstrated efficacy and safety in patients with rheumatoid arthritis (RA) as monotherapy and in combination with conventional synthetic disease-modifying anti-rheumatic drugs (csDMARDs) such as methotrexate (MTX).^{1,2} However, UPA monotherapy has not been compared directly with UPA combination therapy in the Phase 3 program.

Objectives: To compare the efficacy of UPA monotherapy and UPA in combination with MTX using data from two Phase 3 trials of RA patients with an inadequate response (IR) to prior MTX therapy.

Methods: In SELECT-MONOTHERAPY, 648 MTX-IR patients were randomized to receive UPA 15 mg or 30 mg monotherapy once daily (QD), or continue with MTX monotherapy (cMTX; given as a blinded study drug), for 14 weeks. In SELECT-NEXT, 661 csDMARD-IR patients were randomized to receive UPA 15 mg or 30 mg QD or placebo (PBO) for 12 weeks on a background of csDMARDs. Only patients receiving concomitant MTX (with or without additional csDMARDs) at baseline in SELECT-NEXT were included in this analysis. The primary endpoints of both studies were the proportion of patients achieving ACR20 and DAS28(CRP) ≤ 3.2 . Additional endpoints included ACR50/70, DAS28(CRP) < 2.6 , CDAI remission (≤ 2.8), CDAI low disease activity (LDA; ≤ 10), and change from baseline in HAQ-DI. Logistic regression or ordinary least squares analyses were used to compare outcomes with monotherapy versus combination therapy, adjusting for demographics and baseline disease characteristics.

Results: A total of 1114 patients were included in the analysis, of whom 648 received monotherapy in SELECT-MONOTHERAPY and 466 received combination therapy in SELECT-NEXT. Of the patients receiving combination therapy, 338 (72.5%) were receiving MTX background therapy only and 128 (27.5%) were receiving MTX plus other csDMARDs. Baseline characteristics were generally similar between the study cohorts; the majority of patients in both studies were female and of white ethnicity, with a mean age of approximately 55 years and a mean MTX dose of approximately 17 mg/week. Consistent with previously reported results from SELECT-MONOTHERAPY¹ and SELECT-NEXT,² both UPA monotherapy and UPA combination therapy led to significant improvements in efficacy outcomes versus cMTX/PBO+MTX (Table). No significant differences were observed between UPA monotherapy and UPA combination therapy across a range of clinical endpoints, including ACR20/50/70 responses and measures of LDA and remission. In addition, improvements in quality of life as measured by HAQ-DI were similar with UPA monotherapy and combination therapy. Efficacy was comparable between the two UPA doses in the combination therapy group, whereas in the monotherapy group numerically higher responses were observed with UPA 30 mg versus UPA 15 mg.

Table. Week 12/14 efficacy outcomes in patients receiving monotherapy and combination therapy.

Endpoint	Monotherapy (Week 14) (SELECT-MONOTHERAPY)			Combination therapy with MTX (Week 12) (SELECT-NEXT)			p-value (mono vs combo) ^a	
	cMTX (n=216)	UPA 15 mg QD (n=217)	UPA 30 mg QD (n=215)	PBO+MTX (n=165)	UPA 15 mg QD+MTX (n=148)	UPA 30 mg QD+MTX (n=153)	UPA 15 mg QD	UPA 30 mg QD
ACR20, %	41.2	67.7	71.2	38.2	66.2	65.4	0.962	0.561
DAS28(CRP) ≤ 3.2 , %	19.4	44.7	53.5	18.2	48.6	49.7	0.564	0.878
ACR50, %	15.3	41.9	52.1	16.4	41.2	43.1	0.578	0.217
ACR70, %	2.8	22.6	33.0	4.8	20.9	26.1	0.172	0.134
DAS28(CRP) < 2.6 , %	8.3	28.1	40.9	9.7	28.4	30.7	0.594	0.142
CDAI ≤ 2.8 , %	0.9	12.9	19.5	3.0	9.5	13.7	0.063	0.069
CDAI ≤ 10 , %	24.5	34.6	46.5	20.6	41.2	43.8	0.164	0.661
HAQ-DI change from baseline	-0.22	-0.56	-0.63	-0.32	-0.61	-0.60	0.593	0.108

^aBased on logistic regression (binary outcomes) or ordinary least squares (continuous outcome) analyses for the comparison of monotherapy versus combination therapy, with treatment group as the fixed factor and various demographic (age, sex, race, region, weight, and smoking status) and baseline characteristics (CRP, DAS28(CRP), HAQ-DI, RA duration, and RF and anti-CCP positivity) as covariates.

Conclusion: In MTX-IR patients with RA, the efficacy of UPA appears comparable when administered as monotherapy or when given in combination with MTX.

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THU0166

TREATMENT WITH UPADACITINIB IS ASSOCIATED WITH IMPROVEMENTS IN REVERSE CHOLESTEROL TRANSPORT IN PATIENTS WITH RHEUMATOID ARTHRITIS: CORRELATION WITH CHANGES IN INFLAMMATION AND HDL LEVELS

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Background: Rheumatoid arthritis (RA) is a systemic inflammatory condition associated with increased rates of atherosclerotic morbidity and mortality. One mechanism by which inflammation may increase atherosclerotic progression is via pathogenic remodeling of high-density lipoprotein (HDL)-associated proteins with resultant reduction in HDL function.¹ Upadacitinib (UPA), a selective JAK1 inhibitor, has demonstrated efficacy in patients with moderate-to-severe RA.

Objectives: To assess the effect of UPA treatment on cholesterol efflux capacity (CEC) and evaluate the association of CEC with changes in inflammation and serum lipids.

Methods: A subset of patients from the Phase 2 BALANCE II study² and the Phase 3 SELECT-NEXT study³ were selected from the pool of patients with serum samples available at baseline and Week 12. Patients were matched for age and sex, and selected based on level of response to UPA therapy (BALANCE II, UPA 6 mg BID: 39 responders [mean change in DAS28-CRP at Week 12 -3.22] and 30 non-responders [mean change in DAS28-CRP -0.33]; SELECT-NEXT, UPA 15 mg QD: 20 responders [mean change in DAS28-CRP -3.78] and 20 non-responders [mean change in DAS28-CRP -0.67]). A demographically similar placebo (PBO) group without selection based on degree of response was also included (20 patients from each study). J774 macrophages labeled with [³H]-cholesterol (treated with cAMP to express ABCA1 or left untreated) were exposed to patient sera. The difference between cholesterol efflux from serum-exposed and unexposed cells provided a measurement of CEC. Results were compared between the responder, non-responder, and PBO groups using Tukey's mean comparison method; correlations were calculated using the Pearson method; and all statistical analyses were performed in JMP 13.10 (SAS Institute).

Results: In both studies, changes in global and ABCA1-dependent CEC, and to a lesser extent non-ABCA1-dependent CEC, were significantly higher in the UPA-treated group compared with the PBO group (Figure). In the BALANCE II study, there was a significant increase in CEC among UPA responders relative to PBO and a numerically apparent difference observed between UPA non-responders and PBO. Notably, in the SELECT-NEXT study, a similar and highly significant improvement in CEC was observed for both UPA-treated groups relative to PBO (without a significant difference between the responder and non-responder groups). Despite the lack of a consistent association between change in CEC and change in clinical disease activity, observed increases in CEC correlated significantly with reductions in CRP levels in all groups across all active treatment groups. Additionally, increases in CEC at Week 12 correlated well with changes in total blood cholesterol and HDL levels, but weakly with changes in blood low-density lipoprotein (LDL) levels.

Conclusion: UPA treatment is associated with significant improvement in CEC. This effect was observed even among those demonstrating minimal clinical response (but not in those treated with PBO). The effect seems to be primarily driven by ABCA1-dependent cholesterol efflux and is strongly correlated with a rise in HDL cholesterol as well as reduction in systemic inflammation as measured by change in CRP.

Figure: Changes in ABCA1-dependent cholesterol efflux are significantly elevated in UPA-treated patients at Week 12

Abstract THU0166 – Figure 1

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THU0167

SAFETY PROFILE OF UPADACITINIB IN RHEUMATOID ARTHRITIS: INTEGRATED ANALYSIS FROM THE SELECT PHASE 3 CLINICAL PROGRAM

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Background: Upadacitinib (UPA), a JAK1-selective inhibitor, significantly improved clinical signs and symptoms of rheumatoid arthritis (RA) in patients (pts) naïve to methotrexate (MTX) and with an inadequate response to conventional synthetic DMARDs (csDMARD-IR) or biologic DMARDs (bDMARD-IR)^{1,2,3}.

Objectives: Assess the safety of UPA as monotherapy (mono) and as combination therapy with background csDMARDs in pts with moderately to severely active RA from the safety database of the Phase 3 clinical program.

Methods: Treatment-emergent adverse events (TEAEs) from 5 pivotal, randomized, double-blind, controlled Phase 3 trials of UPA 15 mg [included in all 5 trials] or 30 mg QD [included in 4 trials] in RA pts were analyzed using integrated short-term (ST, 12/14 week, placebo [PBO]-controlled; n [%]), individual studies with long-term [LT] active comparator (UPA mono vs MTX; UPA 15 mg with background MTX vs originator adalimumab, ADA, events/100 patient-years [E/100PY]) and integrated LT (all Phase 3 exposure; E/100PY) analyses sets.

Results: Across the Phase 3 trials, 3834 pts received ≥1 dose of UPA 15 mg (n=2630) or 30 mg QD (n=1204) =4020.1 PY of UPA exposure with no option to switch doses. The ST frequencies of overall SAEs and AEs leading to discontinuation were low, but higher on both UPA doses vs PBO. LT event rates were similar on UPA 15 mg vs ADA and slightly higher on UPA vs MTX mono. Deaths occurred in all treatment groups. Serious infection (SIEs) frequencies were higher on both UPA doses vs PBO. SIE rates on both UPA doses were higher vs MTX, but similar on UPA 15 mg vs ADA. Herpes zoster (HZ) frequencies and

rates were higher on both UPA doses vs PBO, and vs MTX, ADA, respectively. The rates of SIE and HZ were higher on UPA 30 vs 15 mg. Adjudicated MACE were reported in all treatment groups including PBO. LT MACE rates were similar on UPA 15 mg and ADA and on UPA 15 mg and MTX mono, but higher on UPA 30 mg mono (low number of events, 2-4 per set). Adjudicated VTEs occurred at comparable frequencies on UPA vs PBO and at comparable rates on UPA vs active comparators. Malignancy (excluding non-melanoma skin cancer [NMSC]) rates were similar on UPA vs MTX, UPA 15 mg vs ADA, and 15 vs 30 mg. The NMSC rates on UPA 15 mg and ADA were similar; the rate on 30 mg was higher than 15 mg, but both UPA NMSC rates were in the range reported for RA patients treated with DMARDs⁴. The standardized incidence ratio (95% CI) for malignancy (15 mg: 0.98 [0.61, 1.49], 30 mg: 1.49 [0.85, 2.42]) was not elevated vs the general population.

Conclusion: Treatment with UPA increased the risk of SIE and HZ, but not those of VTE, MACE, and malignancy vs comparators. These data support that UPA has an acceptable safety profile in the treatment of moderately to severely active RA.

Abstract THU0167 – Table 1.

Table: Overall TEAEs and AEs in pts treated with UPA compared to PBO and active control

	PBO-Controlled Short-term Exposure			Long-term MTX-controlled Analysis			Long-term Adalimumab-Controlled Analysis ¹			All Phase 3 Long-term	
	UPA 15 mg QD (N=1035)	PBO (N=1042)	UPA 30 mg QD (N=384)	UPA 15 mg QD Mono (N=317)	UPA 30 mg QD Mono (N=314)	MTX Mono (N=319)	Any UPA 15 mg QD (N=1417)	Any ADA 40 mg QD (N=579)	Any UPA 15 mg QD (N=3039)	Any UPA 30 mg QD (N=1204)	Any UPA 30 mg QD (N=1204)
Any AE	56.0	48.4	59.9	34.4	38.2	30.1	26.4	29.8	26.7	36.7	36.7
Any SAE	3.4	1.8	4.9	14.3	15.4	11.9	12.9	15.6	15.0	21.3	21.3
Any AE leading to discontinuation	2.8	2.0	7.3	11.4	10.7	8.9	7.4	11.1	8.4	13.3	13.3
Deaths ²	0	0.2	0.3	1.2	1.8	0.3	0.4	0.9	0.5	1.0	1.0
AEs											
Serious Infections	1.2	0.6	1.8	4.1	5.0	2.9	4.1	4.3	3.8	6.2	6.2
Herpes Zoster	0.7	0.3	1.6	4.4	4.8	1.3	3.1	1.3	3.7	7.0	7.0
MACE (adjudicated)	<0.1	0.3	0.3	0.9	1.2	0.6	0.4	0.4	0.6	1.0	1.0
VTE (adjudicated)	0.2	<0.1	0	0	0.3	0.6	0.3	1.1	0.6	0.3	0.3
Any non-melanoma skin cancer (NMSC)	0	<0.1	0.5	0.3	0.3	0	0.2	0.2	0.3	1.1	1.1
Any malignancy other than NMSC	<0.1	<0.1	0.8	1.2	0.6	1.0	0.4	0.6	0.9	1.4	1.4

ADA, adalimumab; AE, adverse event; CV, cardiovascular; E, event; MACE, major adverse cardiovascular events; MI, myocardial infarction; Mono, monotherapy; MTX, methotrexate; PBO, placebo; PY, patient-years; QD, once-daily; RTI, respiratory tract infection; SAE, serious adverse event; TEAE, treatment-emergent adverse event; UPA, upadacitinib; VTE, venous thromboembolic event.

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