THU0165

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

Maya Buch¹, Alvin F. Wells², Andrea Rubbert-Roth³, Manish Jain⁴, Casey Schlacher⁵, Heidi Camp⁵, Yihan Li⁵, Yanna Song⁵, Peter Nash⁶.

¹University of Leeds & NIHR Biomedical Research Centre, Leeds, United Kingdom; ²Rheumatology and Immunotherapy Center, Franklin, United States of America; ³Kantonsspital St Gallen, St Gallen, Switzerland; ⁴Rheumatology, Great Lakes Clinical Trials, Chicago, United States of America; ⁵AbbVie Inc., North Chicago, United States of America; ⁶University of Queensland, Brisbane, Australia

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.

REFERENCES:

- Smolen J, et al. Ann Rheum Dis 2018;77:678;
- Burmester GR, et al. Lancet 2018;391:2503-12

Acknowledgement: AbbVie, Inc was the study sponsor, contributed to the study design, data collection, analysis & interpretation, and to writing, reviewing, and approval of the final version. Medical writing support was provided by John Ewbank, PhD, of 2 the Nth.

Disclosure of Interests: Maya Buch Grant/research support from: Pfizer LTD, UCB, Consultant for: AbbVie, Eli Lilly, EMD Serono, Pfizer Ltd., Sanofi, Alvin F. Wells Consultant for: AbbVie, Andrea Rubbert-Roth Consultant for: Abbvie, Speakers bureau: AbbVie, Manish Jain Consultant for: Abbvie, Novartis, Celgene, Medac, and Takeda., Speakers bureau: Abbvie, Novartis, Celgene, Medac, and Takeda., Casey Schlacher Shareholder of: AbbVie, Employee of: AbbVie, Heidi Camp Shareholder of: AbbVie, Employee of: AbbVie, Yihan Li Shareholder of: AbbVie, Employee of: AbbVie, Yanna Song Shareholder of: AbbVie, Employee of: AbbVie, Peter Nash Grant/research support from: AbbVie, Bristol-Myers Squibb, Eli Lilly, Janssen, Novartis, Pfizer Inc, Roche, Sanofi, UCB, Consultant for: AbbVie, Bristol-Myers Squibb, Eli Lilly, Janssen, Novartis, Pfizer Inc, Roche, Sanofi, UCB, Speakers bureau: AbbVie, Bristol-Myers Squibb, Eli Lilly, Janssen, Novartis, Pfizer Inc, Roche, Sanofi, UCB
DOI: 10.1136/annrheumdis-2019-eular.2626

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

Christina Charles-Schoeman¹, Thierry Somasse², Jeremy Sokolove². ¹University of California Los Angeles, Los Angeles, United States of America; ²AbbVie Immunology Clinical Development, Redwood City, United States of America

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.