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 LF6, Yanna Song7, Peter Naehr8.

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

Background: Upadacitinib (UPA), a selective JAK1 inhibitor, has demonstrated efficacy and safety in patients with rheumatoid arthritis (RA) as monotherapy 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 as 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 669 were randomized in SELECT-MONOTHERAPY and 445 in SELECT-NEXT. The combination therapy group, 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-MONOTHERAPY and SELECT-NEXT, 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.

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:

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 Sommase3, Jeremy Sokolove2, University of California Los Angeles, Los Angeles, United States of America; 1. Abbvie 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 study and the Phase 3 SELECT-NEXT study 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 -3.22]). A demographically similar placebo (PBO) group without selection based on degree of response was also included (20 patients from each study). J74 macrophages labeled with [3H]-cholesterol (treated with cAMP to express ABCA1) or left untreated) were exposed to patient sera. The difference observed between patients demonstrating minimal response (PBO) and major responder (UPA) groups was 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.