Rheumatoid arthritis - non biologic treatment and small molecules - PART 1

POS0086

ANALYSIS OF DISEASE ACTIVITY MEASURES IN THE CONTEXT OF A METHOTREXATE WITHDRAWAL STUDY AMONG PATIENTS WITH RHEUMATOID ARTHRITIS TREATED WITH TOFACITINIB 11 MG ONCE DAILY + METHOTREXATE: POST HOC ANALYSIS OF DATA FROM ORAL SHIFT

R. Fleischmann¹, B. Haraoui², M. H. Buch^{3,4}, D. Gold⁵, G. Sawyerr⁶, H. Shi⁷, A. Diehl⁷, K. Lee⁸. ¹Metroplex Clinical Research Center and University of Texas Southwestern Medical Center, Department of Medicine, Dallas, TX, United States of America; ²Institut de Rhumatologie de Montréal, Montréal, QC, Canada; ³School of Biological Sciences, Faculty of Biology, Medicine & Health, University of Manchester, Centre for Musculoskeletal Research, Manchester, United Kingdom; ⁴NIHR Manchester Biomedical Research Centre, Manchester, United Kingdom; ⁵Pfizer Inc, Inflammation and Immunology, Montreal, QC, Canada; ⁶Pfizer Inc, Inflammation and Immunology, New York, NY, United States of America; ⁷Pfizer Inc, Inflammation and Immunology, Collegeville, PA, United States of America

Background: The Phase 3b/4 study ORAL Shift demonstrated sustained efficacy and safety of tofacitinib modified-release (MR) 11 mg once daily (QD) following methotrexate (MTX) withdrawal that was non-inferior to continued tofacitinib + MTX use (per DAS28-4[ESR]), in patients (pts) with rheumatoid arthritis (RA) who achieved CDAI-defined low disease activity (LDA) with tofacitinib + MTX at Week (W)24.¹

Objectives: To assess the performance of alternative disease activity measures at W24 (randomisation) and W48 (study endpoint) in ORAL Shift.

Methods: ORAL Shift (NCT02831855) enrolled pts aged ≥18 years with moderate to severe RA and an inadequate response to MTX. Pts received open-label tofacitinib MR 11 mg QD + MTX for 24 weeks. Achievement of CDAI LDA (≤10) at W24 was set as the criteria for entry to the 24-week double-blind MTX withdrawal phase, with pts randomised 1:1 to receive tofacitinib MR 11 mg QD + placebo (PBO) (ie blinded MTX withdrawal) or continue tofacitinib + MTX. In this post hoc analysis, efficacy analyses were performed in 8 subgroups defined by achievement of various disease activity criteria at W24: DAS28-4(ESR) remission (≤2.6) or LDA (≤3.2); DAS28-4(CRP) <2.6 or ≤3.2; RAPID3 remission (≤3) or LDA (≤6); CDAI remission (≤2.8); and SDAI remission (≤3.3). For each subgroup, the proportion of pts who achieved the corresponding disease activity criterion at W48 was calculated, with a 95% confidence interval (CI) estimated using the normal approximation to the binomial distribution. The change (Δ) from W24 to W48 in least squares (LS) mean DAS28-4(ESR) and DAS28-4(CRP) was also calculated in each subgroup, with a 95% CI for the difference between treatment groups estimated using a mixed model with repeated measures. Nominal p values were calculated and are presented with no formal statistical hypothesis testing formulated.

Results: Overall, 694 pts entered the open-label phase of ORAL Shift, and 530 were randomised and received treatment in the double-blind phase; 264 and 266 pts received tofacitinib + PBO and tofacitinib + MTX, respectively (Figure 1a). Considering those pts who were randomised and treated, the proportion of pts achieving each disease activity criterion at W24 varied, but was similar between treatments within each subgroup (Figure 1a). Among pts who met each disease activity criterion at W24, generally the majority of pts in both treatment groups also met the same criterion at W48 (Figure 1b). Numerically more pts receiving tofacitinib + MTX vs tofacitinib + PBO continued to meet the corresponding criterion at W48. Regardless of the disease activity criterion met at W24, differences between treatment groups in LS mean ΔDAS28-4(ESR) (Figure 1c) and ΔDAS28-4(CRP) (data not shown) from W24 to W48 favoured tofacitinib + MTX vs tofacitinib + PBO.

Figure 1a: Summary of subgroup populations, based on disease activity criterion met at W24. 1b: W24 response rate for each disease activity criterion, in pts who met corresponding criterion at W24 and c) difference between treatment groups in LS mean ΔDAS28-4(ESR) from W24 to W48, stratified by disease activity criterion met at W24

Figure 1a: Summary of subgroup populations, based on disease activity criterion met at W24. 1b: W24 response rate for each disease activity criterion, in pts who met corresponding criterion at W24 and c) difference between treatment groups in LS mean ΔDAS28-4(ESR) from W24 to W48, stratified by disease activity criterion met at W24

Conclusion: This post hoc analysis of data from pts randomised and treated in ORAL Shift demonstrated that, regardless of the disease activity state criterion met at W24, generally a majority of pts receiving tofacitinib maintained achievement of the corresponding disease activity criterion at W48, with or without continued MTX. Differences between treatment groups in LS mean ΔDAS28-4(ESR) from W24 to W48, as defined by achievement of LDA or remission with a variety of disease activity measures, were less than a change of 1.2, which is considered to be the threshold for a minimal clinically important improvement.²

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POS0087

LONG-TERM SAFETY AND EFFICACY OF UPADACITINIB OR ADALIMUMAB IN PATIENTS WITH RHEUMATOID ARTHRITIS: RESULTS AT 3 YEARS FROM THE SELECT-COMPARE STUDY

R. Fleischmann¹, E. Mysler², L. Bessette³, C. Peterfy⁴, P. Durez⁵, Y. Tanaka⁶, J. Swierkot⁷, N. Khan⁸, X. Bu⁹, Y. Li¹⁰, I. H. Song¹¹. ¹Univ of Texas Southwestern Med Center, Metroplex Clinical Research Center, Dallas, United States of America; ²Organización Médica de Investigación, Rheumatology, Buenos Aires, Argentina; ³Laval University, Rheumatology, Quebec, Canada; ⁴Spire Sciences Inc, Boca Raton, United States of America; ⁵Institut de Recherche Expérimentale et Clinique, UCL Saint-Luc, Pôle de Recherche en Rhumatologie, Brussels, Belgium; ⁶University of Occupational and Environmental Health, The First Department of Internal Medicine, Kitakyushu, Japan; ⁷Wrocław Medical University, Department of Rheumatology and Internal Medicine, Wrocław, Poland; ⁸AbbVie, Immunology, North Chicago, United States of America

Background: In the SELECT-COMPARE study, the Janus kinase inhibitor, upadacitinib (UPA), demonstrated significant improvements in the signs and symptoms of rheumatoid arthritis (RA) when administered at 15mg once daily (QD) on background methotrexate (MTX) compared with adalimumab (ADA) plus MTX at Week 12 that were maintained through 72 weeks in patients with prior inadequate response to MTX.¹

Objectives: To assess the long-term safety and efficacy of UPA vs ADA over 3 years in the ongoing long-term extension (LTE).

Methods: Patients receiving background MTX were randomized 2:2:1 to UPA 15mg QD, placebo (PBO), or ADA 40mg every other week. Between Weeks 14-26, rescue was mandated for either lack of response (<20% improvement in tender or swollen joint counts: Weeks 14, 18, 22) or failure to achieve a targeted disease outcome (CDAI low disease activity: Week 26). Patients who completed the 48-week double-blind period could enter an LTE for up to 10 years total. This analysis describes patients through 3 years of treatment. Treatment-emergent adverse events (TEAEs) per 100 patient years (PY), including events of special interest (AESI), were summarized up to 3 years based on exposure to UPA and to ADA. Efficacy was analyzed by original randomized groups. Patients who were rescued or prematurely discontinued study drug were categorized as non-responders for visits after rescue or discontinuation. Descriptive analyses were performed without formal statistical comparisons.

Results: In total, 651, 651, and 327 patients were randomized at baseline to receive UPA, PBO, and ADA, respectively. Between Weeks 14-26, 252 (39%) patients were rescued from UPA to ADA, 159 (49%) were rescued from ADA to UPA, and all PBO patients were switched to UPA by Week 26.¹ A higher proportion of patients randomized to UPA completed 3 years without rescue compared to those randomized to ADA (47% vs 36%, respectively). UPA was generally well-tolerated as assessed by the rates of TEAEs, including serious AEs, AEs leading to discontinuation of study drug, and AESIs, including serious and opportunistic infections, malignancies, adjudicated major adverse cardiac events or venous thromboembolism; Figure 1). Consistent with previous analyses, the event rates of AESIs were generally comparable between the UPA and

ADA groups, while herpes zoster, lymphopenia, hepatic disorder, and CPK elevation were reported at higher rates with UPA. Consistent with earlier time points, greater proportions of patients randomized to UPA achieved low disease activity and remission at 3 years based on CDAI, as well as DAS28(CRP) ≤ 3.2 or < 2.6 , compared with patients randomized to ADA (Table 1).

Conclusion: The safety profile of UPA was consistent with the results reported previously and with the integrated Phase 3 safety analysis.^{1,2} Higher levels of clinical response continued to be observed with UPA vs ADA through 3 years of treatment.

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Figure. Exposure-adjusted Event and Incidence Rates of Treatment-emergent AEs Over 3 Years

ADA, adalimumab; AE, adverse event; CI, confidence interval; CPK, creatine phosphokinase; EAER, exposure-adjusted event rates; EOW, every other week; MACE, major adverse cardiovascular event; NMSC, non-melanoma skin cancer; PY, patient years; QD, once daily; UPA, upadacitinib; VTE, venous thromboembolism. Exposure adjusted incidence rates (EAIR) are reported for malignancy, MACE, VTE, and deaths; exposure adjusted event rates (EAER) are reported for the remaining events.
^aExcluded tuberculosis and herpes zoster.
^bHerpes zoster: majority of cases on UPA were non-serious and involved 1 or 2 dermatomes.
^cCPK elevation: most were mild or moderate and asymptomatic, with no reports of rhabdomyolysis.
^dHepatic disorders: majority were transaminase elevations.
^eIncludes treatment-emergent and non-treatment emergent deaths.

Table 1. Efficacy Endpoints at 3 Years (NRI)

Endpoints, % (95% CI)	UPA 15 mg QD N=651*	ADA 40 mg EOW N=327*
CDAI ≤ 10	39 (36, 43)	29 (24, 34)
CDAI ≤ 2.8	24 (21, 28)	17 (12, 21)
DAS28(CRP) ≤ 3.2	37 (33, 41)	26 (21, 31)
DAS28(CRP) < 2.6	32 (29, 36)	22 (17, 26)

ADA, adalimumab; CI, confidence interval; DAS28(CRP), Disease Activity Score for 28-joints C-Reactive Protein; CDAI, clinical disease activity index; EOW, every other week; NRI, non-responder imputation; QD, once daily; UPA, upadacitinib. *Patients who were rescued prior to/at Week 26 were considered non-responders. 252/651 and 159/327 patients were rescued of those randomized to UPA and ADA, respectively.

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POS0088

EFFICACY OF JANUS KINASE INHIBITORS FOR DIFFICULT-TO-TREAT RA IN CLINICAL PRACTICE

M. Kamiya¹, D. Togawa¹, S. Mori¹, K. Yamazaki¹. ¹Nara Hospital, Kindai University, Orthopaedic Surgery and Rheumatology, Ikoma City, Japan

Background: In 20-30% of rheumatoid arthritis (RA) patients, the first biologic disease-modifying antirheumatic drugs (bDMARDs) (generally tumour necrosis factor inhibitors (TNFis)) is ineffective, and among the patients who do not respond to therapy, 20% is faced with secondary ineffectiveness within the first 2 years of treatment [1]. In practice, when refractory RA is present, of which the definition implies previous use of at least two bDMARDs (generally TNFis), the next treatment choice often made is a bDMARD of another class (non-TNFis) [2]. On the other hand, patients who are inadequately responding to bDMARDs need new treatment options because subsequent bDMARD treatment reduces their response [3]. Janus Kinase inhibitors (JAKis) are the first targeted synthetic DMARDs (tsDMARD) licensed for the treatment of RA with comparable efficacy to bDMARDs. Unlike the single cytokine targeting approach of bDMARDs, JAKis are specifically designed to inhibit intracellular signalling molecules common to the receptors of multiple inflammatory cytokines implicated in RA pathogenesis.

Objectives: Difficult-to-treat (D2T) RA is defined as refractory to two or more b/ts DMARDs with different mechanisms of action, with active and progressive disease, as published by Eular(4). We evaluated real world efficacy of approved JAKis and factors that may help to continue them in patients with D2T RA.

Methods: Patients who had inadequate response to two or more bDMARDs (including both TNFis and non-TNFis) at our hospital by December 2019 were defined as D2T RA, and patients who switched to JAKis were retrospectively investigated. The drug retention rate was determined by Kaplan-Meier method, and the difference was tested by Logrank test. Multiple regression analysis was used as the statistical method to predict continuation of JAKis for more than 1 year, with patient background (age, gender, during the disease, number of bDMARDs used, with or without methotrexate and/or glucocorticoids, disease activity score assessing 28 joints using erythrocyte sedimentation rate) presence of rheumatoid factor/anti-CCP antibody, matrix metalloproteinase 3 value, Health Assessment Questionnaire disability index) at the time of initiation as an explanatory variable.

Results: A total of 915 bDMARDs had been administered to 394 RA patients. The retention rate of bDMARDs and the number of bDMARDs used were 89.3% and 1.48 bDMARDs at 1 year, 67.7% and 2.27 bDMARDs at 5 years, and 52.0% and 3.15 bDMARDs at 10 years, respectively. The retention rate of JAKis at 1 year was 60.2% in 65 patients with tofacitinib (TOF) and 67.2% in 70 patients with baricitinib (BAR) (P=0.38). Among them, the drug retention rate in D2T RA patients was 50.8% in 38 TOF patients and 66.3% in 35 BAR patients with no significant difference (P=0.30). There were no patient background factors that significantly predicted continuation at 1 year for any JAKis.

Conclusion: Despite the limited number of patients and the retrospective nature of the study, TOF and BAR were shown to be effective options for D2T RA, regardless of patient background such as disease activity or number of bDMARDs used. Other JAKis and switches between JAKis need to be investigated in the future.

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