SAT0237

EFFICACY OF BARICITINIB IN PATIENTS WITH RHEUMATOID ARTHRITIS WHO FAILED 2 OR MORE DMARDs

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Background: Baricitinib (Bari) is an oral Janus Kinase (JAK)1/JAK2 inhibitor in development for patients with active rheumatoid arthritis (RA). In Phase 3 studies, Bari has demonstrated clinical efficacy and has a favorable safety profile.

Objectives: To evaluate Bari 2- and 4-mg in patients who have failed multiple DMARDs, across several studies.

Methods: Data from the subgroup of patients who had failed ≥ 2 DMARDs, including approx. one-half of patients in RA-BUILD (csDMARD-IR) and RA-BEAM (MTX-IR) and all patients from RA-BEACON (bDMARD-IR) were assessed, post hoc, for comparison of Bari 2-mg and 4-mg to placebo across time points using the following measures: ACR20, ACR50, ACR70, SDAI, CDAI, DAS28-CRP, HAQ-DI, and radiographic assessment of structural damage (mTSS), as well as safety. For patients who had failed ≥ 2 DMARDs from RA-BEAM, a comparison was also made between Bari 4-mg and adalimumab.

Results: In the ≥ 2 DMARD-IR populations from RA-BEACON, RA-BUILD, and RA-BEAM, $>95\%$ had failed MTX as one of the DMARDs. Compared to PBO in this population, Bari resulted in statistically significantly greater improvement in efficacy measures at Week 24, including physical function (Table). In the ≥ 2 DMARD-IR population from RA-BEAM (all patients received background MTX), Bari 4-mg was associated with greater improvements compared to adalimumab (table 1 and figure 1). Compared to PBO, Bari 4-mg statistically significantly inhibited structural progression at Week 24 in the ≥ 2 DMARD-IR subsets of RA-BEAM and RA-BUILD. The overall safety profile of Bari 4-mg in the ≥ 2 DMARD-IR population was consistent with findings from the overall baricitinib-treated population.

^{*}Data are the proportion (%) of pts who achieved the response at Week 24 (non-responder imputation), unless otherwise indicated. [§]Approximately 56% of patients in RA-BUILD and 54% of patients in RA-BEAM failed ≥ 2 DMARDs. Δ =least squares mean change from baseline (modified last observation carried forward). [¶]mTSS data are as randomized using last observation carried forward. ^{*} $p \leq 0.05$, ^{**} $p \leq 0.01$, ^{***} $p \leq 0.001$ for Bari 4-mg or Bari 2-mg vs. PBO; [†] $p \leq 0.05$ Bari 4-mg vs. ADA

Conclusions: These data demonstrate that a dose response is present between Bari 2-mg and Bari 4-mg, with both doses providing benefit in the patients who failed multiple DMARDs in the phase 3 program by improving signs and symptoms, physical function, and structure.

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SAT0238

RAPID ELEVATION OF ERYTHROCYTE METHOTREXATE-POLYGLUTAMATE3 (MTX-PG3) LEVELS RELATED TO THE EFFICACY OF MTX IN PATIENTS WITH RHEUMATOID ARTHRITIS (RA).

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Background: MTX is transported into cells and retained long after polyglutamation. Recently, it has been described that the response to MTX treatment is related to the intracellular MTX-polyglutamate (MTX-PG) levels, but little is known about its details and determinants¹.

Objectives: To clarify the association of erythrocyte concentrations of MTX-PGs (PG1 to PG4) with the efficacy of MTX in 35 MTX naïve patients with RA.

Methods: We measured erythrocyte MTX-PGs at 4, 12, 24, and 48 weeks after administration of MTX using liquid chromatography (LC)-mass spectrometry (MS)/MS assay. The associations of MTX-PG concentrations with disease activity and the 9 SNPs including 5 SNPs reported for associations with MTX-efficacy were analyzed.

Results: As shown in the figure, MTX-PG1 and PG2 elevated at week 4, and total MTX-PGs as well as MTX-PG3 and MTX-PG4 increased until week 12. The MTX-PG2 fraction (as percentage of total) was 26% to 29% and almost constant throughout the course. MTX-PG3 and MTX-PG4 fractions were gradually elevated over time, although MTX-PG1 fraction was decreased. A negative association of Disease Activity Score in 28 joints (DAS28) at week 4, 12 and 24 was observed with levels of MTX-PG2 ($p=0.008$), MTX-PG3 ($p=0.0045$), MTX-PG4 ($p=0.0142$) and total MTX-PG ($p=0.023$). On the other hand, Δ DAS28 (change in DAS28 scores from baseline) was positively correlated to fraction of MTX-PG3 ($p=0.011$) but negatively correlated to that of MTX-PG1 ($p=0.0071$). At week 12 and 24, MTX-PG2 fraction was higher ($p=0.0783$) in the patients who achieved the EULAR good response criteria than in those who did not.

MTX-PG3 levels were associated with SLC19A1c.80G>A and FMO2_c.585A>G, and the fraction of MTX-PG2 in total MTX-PGs was associated with GGH c.452C>T and with FMO2_c.585A>G.

Erythrocyte concentrations (nmol/ml) of total MTX-PGs and the PG2 fractions (%) in total MTX-PGs

Conclusions: This study suggests that rapid elevation of erythrocyte MTX-PG3 levels from MTX-PG1 through MTX-PG2 and higher distribution of MTX-PG3 is