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AB0072

BIOMARKER CHANGES FOR PATIENTS WITH RHEUMATOID ARTHRITIS RECEIVING TOFACITINIB WITH METHOTREXATE OR GLUCOCORTICOID VS TOFACITINIB MONOTHERAPY

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Background: Tofacitinib is an oral Janus kinase inhibitor for the treatment of RA. Herpes zoster is more common in patients (pts) with RA vs the general population.¹ This risk increases with tofacitinib use² and appears to be further increased with concomitant use of csDMARDs such as methotrexate (MTX), or glucocorticoids (GC).³ The mechanism for these increases in risk may be linked to treatment-induced interferon (IFN) suppression,³ given that replication of the varicella zoster virus appears to be limited by IFN activity.⁴

Objectives: To evaluate whether treatment of RA with tofacitinib + MTX or GC suppresses IFN pathway proteins to a greater extent than treatment with tofacitinib monotherapy.

Methods: This was a post hoc analysis of pooled data from 1 Phase (P)2 (Japan study [NCT00687193]) and 2 P3 (ORAL Scan [NCT00847613]; ORAL Start [NCT01039688]) tofacitinib studies. Serum samples were collected at baseline (BL), Week (W)12 and/or W24 from pts with RA treated with tofacitinib 5 or 10 mg BID, given as monotherapy (Japan study; ORAL Start) or with stable doses of MTX (15–25 mg weekly for ≥6 weeks; ORAL Scan) and/or GC (≤10 mg/day prednisone or equivalent; all studies). A total of 376 proteins associated with cellular and inflammatory processes, including 6 IFN pathway proteins (CXCL10, CXCL9, CXCL11, IL-12, IFN γ and IL-20), were measured using a homogeneous solution-based assay (Olink Proseek[®] Multiplex Assay, Uppsala, Sweden). Changes in protein levels from BL to W12 (Japan study, ORAL Scan) and/or W24 (ORAL Scan, ORAL Start) were compared for tofacitinib monotherapy vs tofacitinib + MTX or GC using linear regression models. The dependent variable was change from BL in protein levels at W12 or W24. The independent variable was MTX or GC status. Age, gender, GC status (in MTX model) and BL protein levels and tofacitinib dose were covariates. Regressions were performed separately for each study; results for GC were combined via meta-analysis using fixed and random effect models. Significance was considered at $p < 0.1$ after controlling for false discovery rate (FDR). Data quality control included accounting for plate/batch defects and limits of detection, and removal of sample/analytes with excessive missing data.

Results: In total, 659 serum samples were collected from 321 pts. Of the 6 IFN pathway proteins, 2 (IFN γ and IL-20) were below the limit of detection. There was no strong evidence suggesting statistical differences between tofacitinib monotherapy and tofacitinib + MTX or GC in changes in levels of the 4 detectable IFN pathway proteins (CXCL10, CXCL9, CXCL11 and IL-12) from BL to W12 and/or W24. Significant differences were observed for 2 of the 370 other proteins: MMP-1 (FDR adjusted $p = 0.08$) and IL1Ra (FDR adjusted $p = 0.09$), where levels decreased from BL to W12 for tofacitinib + MTX to a greater extent than for tofacitinib monotherapy.

Conclusion: The results of this post hoc analysis suggest that tofacitinib + MTX or GC may not suppress circulating serum levels of IFN pathway proteins to a greater extent than tofacitinib monotherapy. Although there were differences at W12 for tofacitinib + MTX vs tofacitinib monotherapy in MMP-1 and IL1Ra, it is not yet clear whether these observations may be attributable to differences in the ethnicities of the study populations receiving these two treatment regimens (global vs Japan). Further analyses of biomarker changes with tofacitinib are ongoing.

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AB0073

RELATIONSHIPS BETWEEN CYTOKINE PROFILES AND TH17/TREG BALANCE IN PATIENTS WITH RHEUMATOID ARTHRITIS

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Background: Rheumatoid arthritis (RA) is an autoimmune inflammatory disease. Cytokines serve as the mediators of cellular differentiation, inflammation, immune pathology, and regulation of immune response in this disease.^[1] A previous study demonstrated that the imbalance between Th17 and Treg cells is an important mechanism which may lead to RA.^[2] However, the effect of cytokines on the balance of Th17/Treg cells in patients with RA remains unknown.

Objectives: To investigate the relationships between various cytokine levels and Th17/Treg balance in patients with RA.

Methods: The study include 75 RA patients, meeting the diagnostic classification criteria for RA revised by ACR in 1987 and with DAS28 scores were greater than 2.6, and 75 health controls. The absolute numbers of lymphocyte cell subsets and T subsets in peripheral blood were measured by Flow Cytometer (FCM). Serum levels of the following 6 cytokines were determined in the same samples using a cytometric beads array: Interleukin-2(IL-2), Interleukin-4(IL-4), Interleukin-6(IL-6), Interleukin-10(IL-10), Interferon- γ (INF- γ) and Tumor necrosis factor- α (TNF- α) for all RA patients.

Results: (1) Compared with healthy controls, the absolute counts of B cells ($P = 0.042$), the absolute counts of Th1 cells ($P = 0.031$) and the ratio of Th1/Th2 ($P = 0.000$) are significantly increased in RA patients. In contrast, the absolute counts of NK cells ($P = 0.032$) and the absolute count of Th2 cells ($P = 0.000$) were significantly decreased in the RA patient. (Figure1) (2) There was no significant difference in the absolute number of Th17 cells between the two groups, but absolute counts of Treg cells are significantly decreased in RA patients, the ratio of Th17/Treg also have obvious difference, which was higher in RA patients. (Figure1) (3) Among 75 RA patients, two cytokines were significantly associated with the ratio of Th17/Treg, IL-4 ($r = 0.264$, $P = 0.023$) and TNF- α ($r = 0.270$, $P = 0.020$), while other cytokines have no correlation. (Figure2)

Conclusion: Rheumatoid arthritis (RA) is a chronic disease involving various immune cells, our research show that decreased NK cells, Th2 cells and Treg cells; increased B cells, Th1 cells and the ratio of Th17/Treg may be key pathophysiological features in patients with RA. Meanwhile, the level of serum IL-4 and TNF- α may influence the ratio of Th17/Treg, that means we can maintain the patient's Th17/Treg immune balance by regulating the levels of such cytokines. Further researches are needed to elucidate the possible mechanisms with this phenomenon.

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Figure 1. The absolute number of B cell, NK cell, Th1 cell, Th2 cell, Treg cell in RA patients and health controls, Data are expressed as means ±SD.

Figure 2. Correlation of the serum levels of IL-4 and TNF- α with the ratio of Th17/Treg.

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AB0074

INTERRELATIONSHIP BETWEEN NICOTINIC ACETYLCHOLINE RECEPTOR AND CYTOKINE PRODUCTION NOTED FOLLOWING T-CELL ANTIGEN RECOGNITION AND ACTIVATION

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Background: T cells express muscarinic and nicotinic acetylcholine receptors (mAChRs, nAChRs) that increase intracellular Ca^{2+} [1] on stimulation. The expression of these receptors on macrophages and their activation by vagal stimulation has recently been the focus for novel arthritis treatment [2].

Objectives: Our aim in the present study was to assess the effect of various peptides, on cytokine production and nAChRs inhibition.

Methods: nAChR heterologous subunits were expressed in *Xenopus* oocytes and the inhibitory activity of various peptides at ACh-evoked currents were assessed. The effect of these peptides on T-cell antigen recognition and subsequent cytokine production was assessed using an antigen presentation assay (APA). Briefly, the 2B4.11 murine T cell hybridoma recognizing cytochrome c as the antigen was co-cultured with the antigen presenting B cell hybridoma line LK35.2 (I-Ek bearing) and pigeon cytochrome c in the absence or presence of peptide or several nAChRs antagonists, including mecamylamine (broad nAChR antagonist), waglerin-1 ($\alpha 1\beta 1\epsilon\delta$), α -bungarotoxin ($\alpha 7$), RgIA ($\alpha 9\alpha 10$), Vc1.1 ($\alpha 9\alpha 10$) and dihydro- β -erythroidine hydrobromide ($\alpha 4\beta 4$ and $\alpha 4\beta 2$). ELISA and real-time PCR were performed to measure cytokine protein levels and nAChRs T-cells mRNA express levels separately.

Results: At 10 μ M, peptide W32052 had modest 50-55 % inhibition of human (h) $\alpha 3\beta 2$ and $\alpha 4\beta 2$ nAChR subtypes, and 35% inhibition at $\alpha 9\alpha 10$. W32052 greatly inhibited chimeric rat $\alpha 1\beta 1\delta$ -mouse ϵ (85%) at 10 μ M. W32052 also inhibited IL-2, IL-6, TNF- α and GM-CSF production at 50 μ M in the APA. nAChRs antagonists, mecamylamine (100 μ M), RgIA (10 nM), Vc1.1 (17.5 μ M) and dihydro- β -erythroidine hydrobromide (10 μ M) could decrease IL-2 production. However, waglerin-1 and α -bungarotoxin did not affect IL-2 production in the APA.

Conclusion: W32052, an antagonist of nAChR, inhibits cytokine production following antigen recognition suggesting that there is a close link between T-cell antigen activation, ion channel regulation mediated by AChR and cytokine production. Further experiments are in progress.

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AB0075

EFFECT OF SIDAGURI EXTRACT (SIDA RHOMBIFOLIA L) ON URINARY CARBOXY-TERMINAL TELEPEPTIDES OF TYPE II COLLAGEN IN OSTEOARTHRITIC PATIENTS

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Background: Osteoarthritis is one of the most common joint diseases in Indonesia and elsewhere. Assessment of the effectiveness of osteoarthritis therapy with

biomarkers should be developed. One of the biomarker that can be used to assess the activity of osteoarthritis is *Urinary Carboxy-Terminal Telepeptides of Type II Collagen*. Indonesia is the center of world biodiversity, and Sidaguri is one of the traditional plants that is believed to have many benefits including its anti-inflammatory effect and the ability to decrease level of uric acid. The β -sitosterol is an active component in Sidaguri that has anti-inflammatory activity in osteoarthritis.

Objectives: To compare the effect of sidaguri and meloxicam therapy with meloxicam alone in decreasing the levels of urinary Carboxy-Terminal Telepeptides Of Type II Collagen in osteoarthritis patients.

Methods: This study was conducted on 24 patients with osteoarthritis at H. Adam Malik General Hospital Medan from April to June 2018. Subjects were divided into 2 groups, namely placebo and Sidaguri group. Levels of uCTX II were assessed before and after intervention. T- test was used to analyze the data using SPSS version 22.

Results: 83.3% of osteoarthritis patients in H. Adam Malik hospital who participated in this study were women with mean age 60.58 ± 9.74 years in the placebo group and 63.08 ± 6.14 years in the sidaguri group. The results showed that subjects receiving Sidaguri showed significant decrease in uCTX II before and after intervention (521.42 ± 369.99 vs 330.75 ± 163.49 ng/mmol, $p = 0.033$). Meanwhile, in the placebo group also found decreased levels of uCTX II but it was not statistically significant (286.17 ± 163.82 vs. 218.25 ± 75.05 ng/mmol, $p = 0.238$). In addition, there was a significant difference between the mean of the two groups after the intervention ($p = 0.046$).

Conclusion: There was a significant decrease in uCTX II levels in osteoarthritis patients who received Sidaguri extract for 30 days compared to the placebo group.

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AB0076

CAN DIFFERENT INTERLEUKIN LEVELS PREDICT RESPONSE TO BIOLOGICAL TREATMENT IN PATIENTS WITH RHEUMATOID ARTHRITIS?

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Background: The cytokine family interleukin IL-17 has an important pro-inflammatory role; stimulating tumour necrosis factor (TNF), interleukin IL-1 and IL-6 production. It is subclassified into IL-17A, IL-17F and IL-17AF¹. The interleukin IL-10 acts by blocking the secretion of pro-inflammatory cytokines². We hypothesised that patients whose disease activity is not adequately controlled by TNF therapies in Rheumatoid Arthritis (RA) may have IL-17 driven disease and that lower IL-10 levels may play a permissive role.

Objectives: To determine if pre-treatment or 3 month IL-17/IL-10 concentrations correlate with treatment response to anti-TNF drugs by 6 months of treatment.

Methods: Data was collected from the Biologics in Rheumatoid Arthritis Genetics and Genomics Study Syndicate (BRAGGSS). Patients were followed up at pre-treatment (baseline), 3 months, 6 months and 12 months with bloods, questionnaires and clinical data obtained. Patients were eligible for inclusion if commencing on adalimumab or etanercept and were designated good or poor EULAR responder status at 6-months. Wilcoxon rank sum compared interleukin levels at pre-treatment and 3 months- according to EULAR classification by 6 months. Logistic regression was carried out adjusting for gender, baseline DMARD use and disease activity scores (DAS-28).