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

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Background: Tofacitinib is an oral Janus kinase inhibitor for the treatment of RA. Infection is a common and often serious complication of RA. Understanding the potential mechanisms involving tofacitinib and infections may help to improve disease management.

Methods: This was a post hoc analysis of pooled data from 1 Phase II (P) Japan study (NCT00867193) and 3 P (ORAL Scan [NCT00847613]; ORAL Start [NCT01039888]) 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 BD, given as monotherapy (Japan study; ORAL Start) or with stable doses of MTX (15–25 mg weekly for ≥12 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, IFNγ, 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<0.05 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 (IFNγ 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 in the patients 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.

REFERENCES
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 (nAChRs, nACRs) that increase intracellular Ca2+[1] on stimulation. The expression of these receptors on macrophages and their activation by vagnal stimulation has recently been focused for novel arthritis treatment [2].

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

Methods: nACRs 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 a frequent cytokine production was assessed using an antigen presentation assay assessed. The effect of these peptides on T-cell antigen recognition and subsequent cytokine production was assessed using an antigen presentation assay (APA).

Results: At 10μM, peptide W32052 had modest 50-55% inhibition of human (h)αβ2 and hαβ2 nACR subtypes, and 35% inhibition at hoh2x10. W32052 greatly inhibited chimeric rat α1β10 mouse ε (85%) at 10μM. W32052 also inhibited IL-2, IL-6, TNF-α and GM-CSF production at 50μM in the APA. nACRs antagonists, mecamylamine (100μM), RIA (10nM), Vc1.1 (90μM) and dihydro-β-erythroidine hydrobromide (αβδ4 and αβδ2), ELISA and real-time PCR were performed to measure cytokine protein levels and nACRs T-cells mRNA express levels separately.

Conclusions: We found that W32052, an antagonist of nACR, 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.

REFERENCES

Disclosure of Interests: None declared


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-17A2. The interleukin IL-10 acts by blocking the secretion of pro-inflammatory cytokines3. 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/LL-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 DMDAR use and disease activity scores (DAS-28).

Disclosure of Interests: None declared