start to one year in bm-TX, while 75.6 to 78.7 in tri-TX. Improvement of SvdHS demonstrated better result in bm-TX than in tri-TX significantly (<0.05).

<table>
<thead>
<tr>
<th>Table 1: Average values of each parameter and their p-values</th>
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<tr>
<td><strong>bm-TX</strong></td>
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<td>Women</td>
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<td>age</td>
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<tr>
<td>ACQA</td>
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<td>GGs use</td>
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<td>MTX use</td>
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<tr>
<td>DAS28-CRP</td>
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<tr>
<td>HAQ-DI</td>
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<td>SvdHS</td>
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<td>PS-VAS</td>
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</table>

bm-TX, a group of rheumatoid arthritis (RA) patient who is undertaken with biologic disease modifying anti-rheumatic drug (bDMARD) and methotrexate (MTX) therapy; tri-TX, a group of RA patient who is undertaken with combination of free conventional synthetic DMARDs therapy; p-value, statistical level of significance used with Mann-Whitney U test. Women express number and percentage in parenthesis. ACQA, anti-cyclic citrullinated peptide antibodies; GCs, glucocorticoid steroid; DAS28-CRP, 28-joints disease activity score with C-reactive protein; HAQ-DI, Health Assessment Questionnaire Disability Index; SvdHS, Sharp/van der Heijde Score; PS-VAS, pain score measured with visual analog scale.

Conclusions: PSM is useful technique to diminish artificial bias. tri-TX is one choice for RA patient, but not superior for clinical results compared to bm-TX.

REFERENCE:

Disclosure of Interest: None declared

SA10231

COMPARISON OF EFFICACY OF TOFACITINIB VS. ETANERCEPT TREATMENT IN RHEUMATOID ARTHRITIS PATIENTS WITH HIGH ACTIVITY DISEASE BY ULTRASOUND EVALUATION WITH POWER DOPPLER (1 YEAR TREATMENT PERIOD).

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Background: Modern clinical recommendations rule us to timely and rational treatment of rheumatoid arthritis (RA) patients with biologics or tofacitinib when traditional DMARDs failed in achievement of remission or low disease activity (LDA). Ultrasound power Doppler (PD) was recently recommended by some investigators for accuracy of evaluation of local inflammation in small joints to predict the possible flares of RA.

Objectives: To compare the efficacy of tofacitinib vs. etanercept in real clinical practice by complex evaluation including PD during 1-year treatment of RA patients with high disease activity.

Methods: In this randomized open study, we assign 30 patients to receive either etanercept 50 mg subcutaneous weekly (10 pts) or tofacitinib 5 mg BID orally (20 pts). There are 21 females and 9 males with severe RA (average DAS 28 >5,8). From 10 pts treated with etanercept 50 mg subcutaneous weekly (10 pts) or tofacitinib 5 mg BID orally (20 pts). There are 21 females and 9 males with severe RA (average DAS 28 >5,8). Improvement of SvdHS – decreased from 5.86 to 3.23 (p<0.001), 5 pts achieved remission, 3 – LDA. Number of painful and swollen joints decreased to 3–8 times. ESR and C-protein normalized in 8 patients in etanercept group and 12 pts in tofacitinib group. SDAI evaluation showed lowering the score of activity from range 37.10 to range 6.50 in etanercept group and from 40.78 to 14.25 in tofacitinib group. US dynamical: median GS score decreased from 6.5 to 2.5 (p<0.01) in etanercept group and from 8 to 3 (p<0.01) in tofacitinib group. Number of bone erosions still unchanged. In PD mode number of joints with hypervascularized synovium decreased from 3 to 0 (p<0.001) in both groups.

Conclusions: Integrated evaluation of efficacy of treatment of patients with severe RA showed that both etanercept and tofacitinib have good effect in achieving of remission or LDA (DAS28 and SDAI). Tofacitinib acts similar to etanercept in 3 months of therapy, but then its effect progressed more slowly. PD is additional method of monitoring of sinovial inflammation and shows us the significant regression of tissue hypervascularisation (activity of inflammation) by 6 months of treatment both etanercept and tofacitinib. Follow up of patients within the year and later on helps to adjust therapy.

Disclosure of Interest: None declared

SA10231

EFFECTS OF THE JAK1-SELECTIVE INHIBITOR FILGOTINIB ON GENE EXPRESSION PROFILE IN BLOOD OF PATIENTS WITH ACTIVE RHEUMATOID ARTHRITIS

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Background: Filgotinib (FIL), an oral selective JAK1 inhibitor, has shown good safety and efficacy in two phase 2b studies (background methotrexate (MTX), DAWRN1) and as monotherapy (DARWIN 2) in active rheumatoid arthritis (RA) patients with inadequate response to MTX1,2. We conducted a large-scale RNA sequencing study of genes expressed in blood samples from these studies.

Objectives: Identify RA-associated gene transcripts that are altered in response to FIL treatment.

Methods: PAxgene blood samples from 242 RA patients receiving either a stable dose of MTX and placebo (PBO) or FIL 200 mg once daily (QD, DAWRN1); or PBO, FIL 100 mg, or 200 mg monotherapy QD (DARWIN 2), were collected and analyzed at baseline, week 1 and/or week 12. RNA in whole blood was sequenced (Illumina HiSeq 2500) after globin depletion. Differential gene expression analysis was performed on all time-paired data after subtracting gene expression changes in the PBO group. Spearman’s rank correlation of gene expression to time, dose, and disease activity score (DAS28) were calculated on samples without missing values. A false-discovery rate (FDR) of 10% was applied for all analyses

Results: Top-ranked gene sets positively associated with DAS28 disease activity at baseline over both studies included interferon alpha (IFN-α) and IFN gamma (IFN-γ) response, IL6/JAK/STAT3 signaling, and toll-like receptor signaling pathways (FDR<10%). Of 197 genes that positively correlated with disease score (increased gene expression with increased DAS28, FDR<10%), 117 (59%) trended toward reduced expression at 12 weeks with FIL in both studies. These genes were enriched in pathways which included granulocyte and macrophage activation. Conversely, of 256 genes negatively correlated with disease score (FDR<10%), 169 (66%) trended toward increased expression post-FIL (figure 1). Of 14724 genes expressed at >1CPM in at least 5% of the samples, 607 were differentially expressed following FIL treatment in either DAWRN1 or DARWIN2 with 48 genes significant in both studies (FDR<10%). Genes reaching significance in at least one study showed consistent magnitude and direction of change in both studies and were enriched in JAK/STAT, innate and adaptive immunity, and autoimmune associated pathways. CISH, SOCS2, SOCS3, VWA5A,
Conclusions: RA patients treated with FIL show reproducible changes in gene expression consistent with modulation of JAK/STAT signaling and innate and adaptive immunity. FIL was shown to partially reverse the dysregulated gene expression profile associated with baseline DAS28 score, consistent with the efficacy observed in RA patients.

REFERENCES:


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SAT0232
REACTIVATION OF IMMUNE CHECKPOINTS BY AN EPITOME-SPECIFIC VACCINE REINSTATES TOLEROCENIC PATHWAYS AND INDUCES CLINICAL AMELIORATION IN PATIENTS WITH RHEUMATOID ARTHRITIS

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Background: Immune checkpoints like PD-1 that govern immune tolerance are attractive therapeutic targets in diseases driven by the dysregulation of tolerogenic pathways. We have previously reported that the induction of immune tolerance by epitope-specific immunotherapy with dnaJP1, a peptide sharing sequence homology to the HLA alleles implicated in the pathogenesis of rheumatoid arthritis (RA), results in clinical improvement in RA and represents a promising therapeutic intervention.

Objectives: In the present work, we adopt a holistic approach in deciphering the tolerogenic immune mechanisms underlying the efficacy of epitope-specific immunotherapy with dnaJP1. We hypothesize that clinical amelioration of RA by dnaJP1 is attributed to the reactivation of immune checkpoints that triggers immune mechanisms modulating immune tolerance and clinical control.

Methods: Peripheral Blood Mononuclear Cells (PBMCs) were obtained at the end of the Phase II trial (Day168), from clinical responders treated with dnaJP1 (n=6) and clinical non-responders treated with placebo (n=10). Gene expression analysis was performed by quantitative PCR. The T cell compartment was studied by multi-coloured flow cytometry using specifically designed antibody panels. Flow cytometry results were then analysed by clustering with Multi-Dimensional Automated Reduction and Visualization (MARVis).

Results: Analysis of the T cell immune system of dnaJP1 responders and placebo non-responders revealed a subset of CD4+FoxP3+ regulatory T (Treg) cells exclusively in dnaJP1 responders that displayed a higher expression of the inhibitory immune checkpoint receptor, PD-1. The expression of PD-1 contributes to an enhancement of the tolerogenicity of this Treg cell subset by upregulating the production of signature anti-inflammatory cytokines such as TGFβ. Lastly, our preliminary findings demonstrate that the concurrent use of Hydroxychloroquine (HCQ) exerts a synergistic effect in reinstating immune homeostasis by promoting the immunomodulatory capacity of antigen-presenting cells (APCs). The switch to a tolerogenic DC phenotype in the presence of HCQ in turn skews effector T cells towards a functionally protective phenotype by upregulating the expression of PD-1.

Conclusions: Our data exemplifies that the toggle between inflammation and tolerance is delicately controlled by a unique subset of Treg cells in which the immune checkpoint protein, PD-1 is switched on. We have also provided mechanistic knowledge on the synergistic relationship between HCQ and the clinical effectiveness of dnaJP1. Taken together, we demonstrate a vaccine-like therapeutic strategy that modifies the multidimensional perturbations in the auto-reactive immune system by reactivating immune checkpoints governing tolerogenic pathways.

Disclosure of Interest: None declared

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SAT0233
METHOTREXATE TREATMENT IN RHEUMATOID ARTHRITIS AND ELEVATED LIVER ENZYMES: A LONG-TERM FOLLOW-UP OF OCCURRENCE, PREDICTORS, SURVEILLANCE, AND OUTCOME IN CLINICAL PRACTICE

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Background: Hepatotoxicity is an important safety issue in long-term methotrexate (MTX) treatment. Guidelines, including the widely used American College of Rheumatology guidelines, therefore recommend testing of liver enzymes at intervals of 6–12 weeks in all MTX-treated patients with rheumatoid arthritis (RA), making this one of the most frequent screening tests in rheumatology care. Although a number of potential risk factors for liver toxicity have been identified, individual risk stratification is still not part of guidelines. Besides, it is unclear what proportion of all monitoring tests that captures liver enzyme elevations and what happens after an alanine aminotransferase (ALT) elevation in clinical practice.

Objectives: To assess predictors of ALT elevation in an unselected population of MTX-treated RA patients, describe monitoring of liver enzymes in clinical practice, including the handling and outcome of elevated ALT levels.

Methods: All RA patients starting MTX treatment January 2005–April 2013 at a rheumatology clinic, (Uppsala university hospital, Sweden) were identified. Clinical and laboratory data from onset of RA until MTX treatment stopped or the end of the study period September, 2013, were obtained from medical records and supplemented by a telephone interview. Predictors for ALT>1.5 the upper limit of normal (ULN) were identified by multiple regression analysis.

Results: The study comprised 213 RA patients starting MTX therapy. During a mean follow-up (MTX-treatment period) of 4.3 years, 6288 ALT tests were performed. ALT >ULN was observed in 84 (39%) of the patients and 7% of all tests. The strongest predictor for ALT >1.5 x ULN was a pre-treatment ALT elevation (mean observation period 1.5 years before MTX start) (adjusted OR=6.8, 95% CI 2.2–20.5). In the patients with pre-treatment ALT elevation, the mean time to first ALT elevation was shorter than in those without pre-treatment elevation (p<0.001), and all had recurrent elevations during MTX treatment. In all patients with ALT >ULN, re-elevations occurred in 70%, with similar proportions in those without active interventions and in those where e.g. MTX dose reduction was performed (73% vs. 67%; p=0.43). In patients who permanently stopped MTX due to ALT elevation (n=7), ALT >ULN recurred in 5 (71%) after stopping MTX. Two patients were eventually diagnosed with nonalcoholic fatty liver disease. No patient developed signs of hepatic failure.

Conclusions: Pre-treatment ALT elevation is a strong predictor for early and recurrent ALT elevations during therapy. Overall, re-elevations are common, but only a minority of performed ALT tests captures elevations. More individualized or alternative means to follow these patients could be considered to more effectively identify those with MTX-related liver toxicity, and those who despite recurrent ALT elevations could continue MTX treatment without risk for deleterious liver damage.

Disclosure of Interest: None declared