APCDD1, DNASE1L3, and PIM3 correlated with both duration of treatment and FIL dose (FDR<10%). CISH and SOCS confirm JAK pathway modulation.

Figure 1 Heatmap of 453 DAS28-correlated genes and the corresponding change in gene expression with 12 wk FIL in Phase2b RA studies

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.

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SAT0232

REACTIVATION OF IMMUNE CHECKPOINTS BY AN EPITOPE-SPECIFIC VACCINE REINSTATES TOLEROGENIC 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 in a fully human context. We hypothesize that clinical amelioration of RA by dnaJP1 immunotherapy 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 immunomes 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. In addition, we observed a corresponding reshaping of the effector T (Teff) cell compartment in which the expression of pro-inflammatory cytokines such as IL-17A and IFNγ was downregulated. Importantly, epitope-specific immunotherapy also induced a subset of active antigen-experienced memory T cells (CD4+CD45RO+CD69+) which sustains the tolerogenic immune response by secreting 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 multitudinous 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 8–12 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.

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