Oral Presentations

New perspectives on therapeutic immune tolerance.

OP0002

IMMTOR NANOPARTICLES ENHANCE THE TOLEROGENTIC ENVIRONMENT OF THE LIVER IN MICE

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Background: Tolerogenic ImmTOR biodegradable nanoparticles encapsulating rapamycin have been shown to mitigate the formation of anti-drug antibodies against pegadricase, a pegylated uricase enzyme, which enabled monthly dosing and sustained reduction of serum uric acid levels in a Phase 2 clinical trial of SEL-212, a combination of pegadricase + ImmTOR, in patients with symptomatic gout with hyperuricemia. Prior mechanism of action studies showed selective biodistribution of ImmTOR to the spleen and liver following intravenous (IV) administration in mice. In the spleen, ImmTOR has been demonstrated to induce tolerogenic dendritic cells and antigen-specific regulatory T cells and inhibit antigen-specific B cell activation. Splenectomized mice showed a partial but incomplete abrogation of the tolerogenic immune response mediated by ImmTOR.

Objectives: Here we evaluated the ability of ImmTOR to enhance the tolerogenic environment in the liver.

Results: All the major resident populations of liver cells, including liver sinusoidal endothelial cells (LSECs), Kupffer cells (KC), stellate cells (SC), and hepatocytes, actively took up fluorescent-labeled ImmTOR particles, which resulted in downregulation of MHC class II and co-stimulatory molecules and upregulation of the PD-L1 checkpoint molecule. The LSEC, known to play an important role in hepatic tolerance induction, emerged as a key target cell for ImmTOR. The tolerogenic environment led to a multi-pronged modulation of hepatic T cell populations, resulting in an increase in T cells with a regulatory phenotype, upregulation of PD-1 on CD4⁺ and CD8⁺ T cells, and the emergence of a large population of CD4⁺CD8⁻ (double negative) T cell population. Modulation of T cell phenotype was seen to a lesser extent after administration by empty nanoparticles, but not free rapamycin. The upregulation of PD-1, but not the appearance of double negative T cells, was inhibited by antibodies against PD-L1 or CTLA-4.

Conclusion: These results suggest that the liver may contribute to the tolerogenic properties of ImmTOR in mitigating anti-drug antibody responses to biological therapies, such as pegadricase.

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Autoimmune diseases by abnormal T cell function.

OP0003

AUTOREACTIVE CD4+ T CELLS AND THEIR TCR REPERTOIRE IN PR3-ANCA ASSOCIATED VASCULITIS

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Background: ANCA-associated vasculitis (AAV) with proteinase 3 (PR3) ANCA is genetically associated with HLA-DP [1], is often relapsing in nature, and has a predisposition for kidneys, lungs and ear-nose-throat involvement [2]. Despite the presence of PR3+ANCA, indicating CD4+T-cell help in the disease, the knowledge about autoreactive CD4+T cells is scarce. Activated T cells have been shown at site of inflammation [3] and involvement of proinflammatory cytokines in circulation is also reported [4, 5].

Objectives: Identification of autoreactive T cells may help to identify the drivers of the immune responses and chronicity. We therefore aimed to investigate PR3-specific CD4+T-cell responses in peripheral blood of AAV patients with a focus on both phenotype and T-cell receptor (TCR) repertoires.

Methods: The study included sixty-six patients: 26 with active PR3 autoantibody+ AAV, 21 with inactive but PR3+ AAV and 19 with inactive PR3- AAV. *In-vitro* cultures with PR3 protein were established to assess antigen-specific cytokine responses in a 3-color fluorospot assay. Deep immunophenotyping was performed by flow cytometry. Antigen-responsive CD4+ T cells were isolated and

single cell TCRαβ sequences were generated and analyzed from PR3+ AAV patients (n=5) using a previously published protocol [6].

Results: PBMCs from AAV patients demonstrated an HLA-DP associated cytokine responses to PR3 stimulation including IFN-γ and IL-10, but not IL-17A. This T-cell autoreactivity was found to be confined to a highly differentiated CD4+ T cell population characterized by perforin and GPR56 expression, implicating a cytotoxic feature of the response. Active disease involved a reduction in expression of several markers associated with cytotoxicity amongst the CD4+GPR56+ T cells. Their frequency was also negatively associated with the doses of prednisolone. A similar phenotype was shared with T cells activated by human cytomegalovirus (HCMV) peptides in the same patient cohort. Single cell sequencing of paired alpha beta T-cell receptors (TCRs) revealed different patterns of gene usage between PR3 and HCMV reactive T cells. Moreover, we could identify shared (public) PR3-reactive T-cell clones between different HLA-DPB1*04:01+ patients.

Conclusion: PR3 is an autoantigen which provokes ANCA responses in AAV patients. Our study identified PR3-reactive CD4+ T cells at the level of their phenotype and TCR repertoire. The autoreactive CD4+ T cells, present in both active and inactive disease, implicate chronic antigen exposure and the persistence of long-lived T-cell clones. The presence of public autoreactive clones between HLA-DPB1*04:01+ patients suggests an active role for these cells in pathogenesis of AAV and validates the link with predisposed genotype.

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OP0004

AUTOIMMUNE AND INFLAMMATORY MANIFESTATIONS IN COMMON VARIABLE IMMUNODEFICIENCY DISORDERS

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Background: Common variable immunodeficiency (CVID) disorders are the second most frequent immunodeficiency worldwide and autoimmune diseases (AD) are present in 20% of such patients, cytopenia being the most frequent manifestation [1]. Defects in central and peripheral tolerance, activation/proliferation of B cells, and hypogammaglobulinemia are key features of the disease, along with a reduction in CD4+T cells, abnormalities in Treg and defective secretion of regulatory cytokines, that could perpetuate autoimmune - autoinflammatory phenomena.

Objectives: To describe immune and inflammatory disorders in our CVID cohort. **Methods:** Retrospective analysis of 33 patients who fulfill the European Society for Immunodeficiencies (ESID) Registry – Work criteria for CVID diagnosis [2] treated in the immunodeficiency unit of our tertiary university hospital. After getting an informed consent form, medical records were revised to obtain clinical, analytical and immunological data.

Results: Of the 33 CVID patients analysed, 11 had some autoimmune/inflammatory manifestation. Seven patients presented autoimmune thrombocytopenia (AIT), and one of them also had non-severe neutropenia. Two patients also had seronegative spondyloarthritis, one patient had cutaneous psoriasis, and

two patients had alopecia. There were no cases of type 1 diabetes, vitiligo or thyroid disorders. Interestingly, four patients had lung involvement, two of them with granulomatous-lymphocytic interstitial lung disease (GLILD), one with organising pneumonia and one with usual interstitial pneumonia. Five of the eleven patients required immunosuppressive treatment, mostly with steroids. One case of AIT required concomitant treatment with azathioprine and the patient with psoriasis was treated with methotrexate. In six patients, autoimmune disorder was the first manifestation.

Conclusion: 33% of the CVID patients had autoimmune or inflammatory manifestations in our cohort; six patients had one immune/inflammatory phenomena, four had two different disorders and one patient presented with three different ones. The most frequent manifestation was AIT, as seen in previous reports. In six cases, the autoimmune-inflammatory manifestation was the first symptom attributable to CVID. In conclusion, AD are common in CVID patients, so clinicians must be aware of possible immunodeficiencies in this type of patients.

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What the rheumatologist needs to know to interpret studies in 2021

OP0005

DIETARY HYPERINSULINEMIC POTENTIAL AND RISK OF INCIDENT GOUT: 3 PROSPECTIVE COHORT STUDIES OF US MEN AND WOMEN

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Background: Gout and the metabolic (insulin resistance) syndrome frequently coexist. Intravenous insulin has been shown to raise serum urate (SU) levels in physiologic studies and a Mendelian Randomization study also showed a causal role of insulin on the risk of gout. However, it is unknown whether habitual hyperinsulinemic dietary intake confers gout risk.

Objectives: Prospectively examine the relation between two distinct insulin-related dietary indices and risk of incident gout in three large cohorts of US women and men over 30 years.

Methods: We studied 164,090 women from Nurses Health Study I (1986-2016) and II (1989-2017) and 40,598 men from Health Professionals Follow-up Study (1986-2016), who were free of gout at baseline. Dietary intake and covariates were assessed by validated questionnaires every 4 years. Insulinemic potential of diet was evaluated using 1) food-based empirical dietary index for

hyperinsulinemia (EDIH) score that was pre-defined based on circulating C-peptide levels¹ and reflects *insulin resistance*²; and 2) dietary insulin index (DII), which reflects *transient, postprandial insulin secretion*.² We assigned EDIH and DII scores for each participant, adjusted for total energy intake, and prospectively examined the association between scores and incident gout (using ACR survey criteria for gout³), adjusting for potential confounders.

Results: We ascertained 2,874 incident gout cases over 5,124,490 person-years of follow-up. In pooled multivariable-adjusted analyses, those in the highest EDIH quintile had 1.76-times (95% CI: 1.56 to 1.99) higher gout risk, compared with the lowest (Table 1). This attenuated with further adjustment for BMI (a likely causal intermediate) but remained positive (RR 1.30, 1.15 to 1.48). DII scores were inversely associated with gout risk (RR 0.66, 0.58 to 0.74) (Table 1).

Conclusion: EDIH scores, reflecting chronic hyperinsulinemia (i.e., greater insulin resistance with reduced clearance), were positively associated with the risk of incident gout, even beyond the pathway through adiposity. Conversely, higher DII scores, which reflect short-term, postprandial elevations in insulin levels (and also greater insulin clearance and sensitivity) conferred a lower risk. This corroborates human physiologic experiments and Mendelian Randomization studies showing insulin resistance can increase SU levels by decreasing renal excretion of urate, and supports lowering insulinemic potential of diet as a strategy to reduce gout risk.

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Opening Plenary Abstract session

OP0006

ASSOCIATIONS OF BASELINE USE OF BIOLOGIC OR TARGETED SYNTHETIC DMARDS WITH COVID-19 SEVERITY IN RHEUMATOID ARTHRITIS: RESULTS FROM THE COVID-19 GLOBAL RHEUMATOLOGY ALLIANCE

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Table 1. Risk Ratio (95% CI) of Gout According to Quintiles of Insulin-Related Dietary Index

EDIH (measure of insulin resistance)						
	Q1: lowest circulating insulin levels	Q2	Q3	Q4	Q5: highest circulating insulin levels	P for trend
N cases	430	482	598	631	733	
Person-years	1,025,129	1,025,285	1,025,574	1,025,301	1,023,651	
Age-adjusted RR	1.00 (Ref)	1.13 (1.00-1.29)	1.43 (1.26-1.61)	1.53 (1.36-1.73)	1.85 (1.64-2.09)	<.0001
MV-Adjusted [*] RR	1.00 (Ref)	1.11 (0.98-1.27)	1.39 (1.22-1.57)	1.47 (1.30-1.67)	1.76 (1.56-1.99)	<.0001
MV-Adjusted ^{**} RR (+ BMI)	1.00 (Ref)	1.03 (0.90-1.17)	1.21 (1.06-1.37)	1.21 (1.07-1.37)	1.30 (1.15-1.48)	<.0001
Dietary Insulin Index (measure of transient, post-prandial secretion and sensitivity)						
	Q1: lowest insulin sensitivity	Q2	Q3	Q4	Q5: greatest insulin sensitivity	P for trend
N cases	783	611	527	498	455	
Person-years	1,024,763	1,025,730	1,025,075	1,025,538	1,023,834	
Age-adjusted RR	1.00 (Ref)	0.79 (0.71-0.88)	0.69 (0.62-0.77)	0.65 (0.58-0.73)	0.59 (0.53-0.66)	<.0001
MV-Adjusted [*] RR	1.00 (Ref)	0.79 (0.71-0.88)	0.69 (0.62-0.77)	0.66 (0.59-0.74)	0.60 (0.53-0.67)	<.0001
MV-Adjusted ^{**} RR (+ BMI)	1.00 (Ref)	0.78 (0.70-0.87)	0.69 (0.62-0.77)	0.67 (0.60-0.75)	0.66 (0.58-0.74)	<.0001

*Multivariable (MV) models adjusted for age (month), White race, smoking, menopause (women only), hormone use (women only), physical activity, history of hypertension, and diuretic use **MV + BMI models further adjusted for BMI (a likely causal intermediate)