showed that caspase-3 scores were significantly higher in biopsies treated with tPDT compared to those incubated with buffer ($p=0.009$).

Conclusions FAP-tPDT induces cell death of FAP-positive activated fibroblasts in synovial tissue from RA patients. This is a first indication that FAP-targeted PDT can be a feasible new treatment strategy in RA.

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EFFECTS OF RESVERATROL AND A NOVEL RESVERATROL-SALICYLATE HYBRID MOLECULE ON ACTIVATION OF HUMAN CD4⁺ T-CELLS

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Career situation of first and presenting author Student for a master or a PhD.

Introduction T-cells are assumed to be crucially involved in the pathogenesis of systemic autoimmune diseases such as rheumatoid arthritis (RA). Consequently, substances modulating T-cell activation may have therapeutic benefit in RA and related rheumatic diseases. Resveratrol is a natural occurring polyphenol mainly produced in plants. The beneficial effects of resveratrol are due to its anti-inflammatory, anti-carcinogenic and anti-oxidant activities.

Objectives To compare the effects of resveratrol and a novel resveratrol-salicylate hybrid molecule termed C-10 (Aldawsari FS *et al*, 2016) on human CD4⁺ T-cells.

Methods CD4⁺ T-cells were isolated from healthy donors and pre-incubated with different concentrations of resveratrol or C-10 before being stimulated with anti-CD3/anti-CD28 antibodies. After 24 hour and 72 hour, respectively, cell culture supernatants were harvested and IL-2, IFN- γ and TNF- α release was quantified by ELISA. Proliferation rate was measured by thymidine incorporation. In addition, the up-regulation of the early activation markers CD25, CD69, CD71 and CD98 was analyzed and phosphorylation of signal transduction molecules were determined by western blot and/or flow cytometry.

Results Inhibition of IL-2, IFN- γ and particularly TNF- α release was significantly more effective when the cells were treated with C-10 as compared to resveratrol. Moreover, the proliferation rate was significantly more decreased in the presence of C-10. The expression of CD25, CD69, CD71 and CD98hc was reduced to a similar degree by both compounds. Furthermore, phosphorylation of Akt and STAT-5 was substantially attenuated by C-10 and to a lesser degree also by resveratrol. All T cell subsets investigated (Th1, Th2, Th17) were affected at a similar degree but the most pronounced effect was seen in naïve T cells.

Conclusions Our data demonstrate that C-10 suppressed cytokine secretion and proliferation more effectively than resveratrol. Both compounds influence the phosphorylation of important signalling molecules. The effect exerted on STAT-5 activation may be the key mechanism for inhibition of T cell activation. Thus, the resveratrol-salicylate hybrid molecule C-10 might be considered a candidate drug for treatment of RA and other T-cell driven autoimmune diseases.

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CLINICAL AND IMMUNOLOGICAL EFFECTS OF TOFACITINIB THERAPY IN RHEUMATOID ARTHRITIS

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Career situation of first and presenting author Student for a master or a PhD.

Introduction During the treatment of rheumatoid arthritis (RA) we intend to achieve remission or low disease activity. In this regard, the most effective way is targeted therapy. Oral JAK inhibitor, tofacitinib appeared as a new therapeutic option, beside biological therapies, which has already proven its safety and effectiveness in RA.

Objectives The aim of this study was to assess the clinical and immunological effects of one-year tofacitinib therapy in patients with RA.

Methods Altogether 30 RA patients with active disease were recruited and treated with tofacitinib in this 12 months follow-up study. Mean duration of rheumatoid arthritis were 7.7 $\pm$ 5.0 years. Half of the patients haven't received biological treatment prior tofacitinib therapy, other half of the patients switched to tofacitinib therapy after completing washout. 15 patients received 2 $\times$ 5 mg and 15 patients received 2 $\times$ 10 mg tofacitinib daily for 12 months. Assessments were performed at baseline, month 6 and 12. Levels of CRP and IgM rheumatoid factor (RF) antibodies were measured by quantitative nephelometry and levels of anti-CCP assessed by ELISA. Lymphocyte subsets (CD3⁺, CD4⁺, CD8⁺ T cells, CD19⁺ B cells and CD56⁺/CD3⁻ NK cells) were assessed by cytofluorimetry. In addition, disease activity (DAS28), age and disease duration were also measured.

Results Tofacitinib therapy was clinically effective, significant improvements in physical function were observed in 26 patients. 4 patients (two from both arms) quit the study due to inefficacy. There were significant decrease in levels of DAS28 ($p<0.001$), CRP ($p<0.001$) and HAQ value ($p<0.05$) in 12 months. There were no changes in levels of RF and anti-CCP. Numbers and ratio of CD3⁺ and CD4⁺ T cells were significantly decreased ($p<0.05$), however significant increase was seen in the numbers and ratio of CD19⁺ B cells after 12 months ($p<0.05$). There were no significant changes in numbers and ratio of NK cells. There was significant correlation between absolute number of CD8⁺ T cells and disease

duration at baseline ($R=0.466$, $p=0.009$). There were no other significant correlations.

Conclusions One year tofacitinib therapy effectively reduced disease activity and systemic inflammation. The therapy also improved functional capacity. JAK inhibition significantly decreased the number and ratio of CD3+ and CD4+ T cells and increased number and ratio of CD19+ B cells in 12 months. Tofacitinib is a safe and effective treatment for rheumatoid arthritis. It makes an effect, partly, via modifying lymphocyte subsets.

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Disclosure of Interest None declared.

P134/032 SELECTIVE EXPANSION OF A THYMIC-DERIVED AND FUNCTIONALLY COMPETENT REGULATORY T CELL POPULATION BY LOW-DOSE IL-2 THERAPY IN PATIENTS WITH REFRACTORY SLE

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Career situation of first and presenting author Instructor.

Objectives An acquired deficiency of interleukin-2 (IL-2) and related defects in regulatory T cell (Treg) homeostasis play a crucial role in the pathogenesis of SLE. Here, we report the responses of Treg and other lymphocyte subsets to low-dose IL-2 therapy observed during an open-label, uncontrolled, dose adaption, phase 1/2a single-center clinical trial in patients with active and refractory SLE.

Methods 12 patients with active and refractory SLE (SLEDAI ≥ 6) were treated at our site with a low-dose IL-2 regimen consisting of four separate treatment cycles each with daily subcutaneous injections of recombinant human IL-2 (aldesleukin) at single daily doses of either 0.75, 1.5 or 3.0 million IU for five consecutive days. Cells from peripheral blood were analyzed by flow cytometry before and one day after each treatment cycle.

Results All patients showed highly significant cycle- and dose-dependent increases in the proportions and absolute numbers of CD3+CD4+FoxP3+CD127^{lo} Treg and of CD25^{hi} expressing cells among Treg. By contrast, we observed no relevant changes in the absolute numbers of CD3+CD4+FoxP3 conventional T cells (Tcon), of CD3+CD8+ T cells, of CD3+CD56+NK T cells and of CD3-CD56+NK cells. The IL-2 expanded Treg population displayed a preserved suppressive capacity and expressed high levels of the Treg-associated molecules Helios, CD39 and CD137. In addition, we noted robust and dose-dependent increases in the proportions of Treg expressing the proliferation marker Ki67. Although significant increases in the proportions of Ki67⁺ cells among Tcon and also among other lymphocyte subsets were observed at the end of each treatment cycle, the calculated ratio between Ki67⁺ Treg and Ki67⁺ Tcon continuously increased and was significantly higher at the end of the treatment phase, suggesting a preferential targeting of the Treg population.

Conclusions Low-dose IL-2 therapy promotes the selective expansion of a functionally competent and thymic-derived Treg population in patients with refractory SLE. This study also provides novel insights into the pharmacodynamics and the broad biologic effects of low-dose IL-2 therapy.

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P136 THE EFFECTS OF LY294002, THE PHOSPHOINOSITIDE 3-KINASE INHIBITOR, ON NEUTROPHIL APOPTOSIS IN PATIENTS WITH RHEUMATOID ARTHRITIS AND COLLAGEN-INDUCED ARTHRITIS IN MICE

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Career situation of first and presenting author Young investigator.

Introduction Neutrophils act as a first line in host defense, they also play important roles on acute and chronic inflammation. Rheumatoid arthritis (RA) is a chronic inflammatory autoimmune disease characterized by persistent joint inflammation.¹ Previous studies have shown that delayed apoptosis of neutrophils correlated with the pathogenesis of RA.²

Objectives The aim of this study was to investigate the effects of LY294002, the phosphoinositide 3-kinase (PI3K) inhibitor, on neutrophil apoptosis in RA patients and collagen-induced arthritis (CIA) in mice.

Methods The peripheral blood from untreated RA patients who satisfy the 1987 ACR classification criteria for RA (n=20) and healthy volunteers (HC) (n=10) were used to isolate neutrophils by density gradient centrifugation. The neutrophils were cultured with or without LY294002 *in vitro* for 18 hour. The rate of neutrophils apoptosis were analyzed by flow cytometry. The intracellular protein levels of PI3K-Akt pathway in neutrophils were measured by Western blot. CIA mice were treated with vehicle or LY294002, and the incidence, arthritis score, histological assessment as well as the apoptosis rate of neutrophils from peripheral blood and marrow were analyzed.

Results The peripheral blood neutrophils apoptosis delayed in RA patients as compared with neutrophils from HC. As compared with the HC, the expression of phosphorylation PI3K (p-PI3K) and p-Akt were increased in RA patients. LY294002 could significantly promote neutrophils apoptosis in peripheral blood from RA patients. LY294002 blocked the activation of PI3K-Akt and inhibited the expression of p-Akt. Moreover, LY294002 treatment delayed the onset, reduced the severity of arthritis in CIA mice. We also found that neutrophils from both peripheral blood and bone marrow delayed apoptosis in CIA mice as compared with the control group, and LY294002 treatment facilitated the neutrophil apoptosis from peripheral blood and marrow in CIA mice.

Conclusions This data suggested that delayed apoptosis of neutrophils, which might through the activation of PI3K-Akt