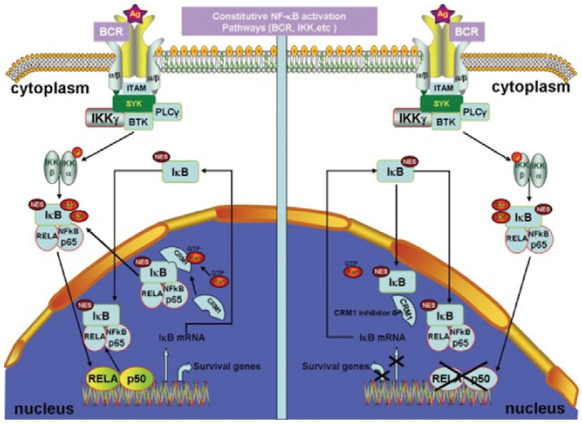


cells. It is likely that inhibition of the canonical NFκB pathway underlies KPT-350's inhibitory effect. Together, our findings suggest the potential of SINE compounds to have a significant impact on disease progression in SLE.

References:

[1] Figure - Zhang KJ and Wang M. Chin J Cancer Res 24(4): 380–393:2012.

Disclosure of Interest: J. Rangel-Moreno Grant/research support from: NIH Small Business Innovation Research grant, S. Cochran Employee of: Karyopharm Therapeutics, S. Tamir Shareholder of: Karyopharm Therapeutics, Employee of: Karyopharm Therapeutics, M. Lee Shareholder of: Karyopharm Therapeutics, Employee of: Karyopharm Therapeutics, S. Shacham Shareholder of: Karyopharm Therapeutics, Employee of: Karyopharm Therapeutics, J. Anolik Grant/research support from: NIH Small Business Innovation Research grant

DOI: 10.1136/annrheumdis-2017-eular.6054

OP0305 TYPE I IFN SYSTEM ACTIVATION IN NEWBORNS EXPOSED TO ANTI-RO/SSA AUTOANTIBODIES IN UTERO

M. Wahren[1], M. Hedlund[1], G.E. Thorlacius[1], M. Ivanchenko[1], N. Kyriakidis[1], L. Rönnblom[2], M.-L. Eloranta[2], A. Espinosa[1], S.-E. Sonesson[1]. *[1]Karolinska Institutet, Stockholm; [2]Uppsala university, Uppsala, Sweden*

Background: Overexpression of type I IFN-stimulated genes has been demonstrated in both SLE and SS, and induction of IFNα production in plasmacytoid dendritic cells by immune complexes containing RNA and autoantibodies, including Ro/SSA and La/SSB autoantibodies, has also been shown. During pregnancy, these autoantibodies pass over the placenta to the fetus, but it is not know if an IFN-activation takes place also in the fetus.

Objectives: In the present study, we investigated if the type I IFN system is activated in newborns exposed to anti-Ro/SSA autoantibodies *in utero*.

Methods: Anti-Ro/SSA positive mothers and their babies as well as healthy controls were included in the study. Maternal and cord blood drawn at birth was immediately separated into plasma and PBMC. mRNA expression was analyzed by microarrays, cell surface markers were assessed by flow cytometry and circulating IFNα levels by DELFIA.

Results: We observed increased expression of IFN-regulated genes and elevated plasma IFNα levels not only in anti-Ro/SSA positive women but also in their newborns, with maternal and fetal IFN scores showing a significant positive correlation (r=0.74, p=0.005). Increased expression of MHC class II was observed on $CD14^+$ monocytes of anti-Ro/SSA antibody-exposed babies, suggesting cellular activation. Notably, the IFN score of babies born to mothers receiving immunomodulatory treatment was similar to that of controls.

Conclusions: We demonstrate for the first time that anti-Ro/SSA antibody-exposed babies at risk for neonatal lupus have a pre-activated immune system with an IFN signature, elevated plasma IFNα, and increased MHC class II expression on circulating monocytes. Our data also suggest that maternal immunomodulatory treatment may modulate the IFN activity in the baby.

Disclosure of Interest: None declared

DOI: 10.1136/annrheumdis-2017-eular.6581

OP0306 DOWNREGULATION OF MICRORNAS IN PLASMACYTOID DENDRITIC CELLS IS ASSOCIATED WITH A TYPE I INTERFERON SIGNATURE IN SYSTEMIC LUPUS ERYTHEMATOSUS AND ANTIPHOSPHOLIPID SYNDROME

L.L. Van Den Hoogen[1,2], J.A. van Roon[1,2], R.D. Fritsch-Stork[2], C.P. Bekker[1,2], A. Pandit[1,2], M. Rossato[1,2], T.R. Radstake[1,2]. *[1]Laboratory of Translational Immunology; [2]Rheumatology and Clinical Immunology, UMC Utrecht, Utrecht, Netherlands*

Background: The most prominent alteration in the immune system of patients with SLE is a type I interferon (IFN) signature, which we recently also reported in patients with primary APS (PAPS). In SLE and APS, this signature is related to disease activity and vascular disease. Plasmacytoid dendritic cells (pDC) are considered key players in the pathogenesis of SLE and APS as they are major producers of type I IFNs. MicroRNAs (miRNAs) are short non-coding RNAs that modulate gene expression through RNA interference mechanisms and have been implicated in the dysregulation of immune cells in patients with autoimmune diseases. Here we investigated miRNA expression in pDC of patients with SLE and APS in relation to the type I IFN signature.

Objectives: To identify if pDC dysregulation in patients with SLE and APS is associated with alterations of their miRNA expression profile.

Methods: The frequency of circulating pDC was determined by flow cytometry in patients with SLE (n=49), SLE+APS (n=34) and PAPS (n=27) and healthy controls (HC, n=22). RNA was extracted from pDCs isolated from the peripheral blood of patients with SLE (n=20), SLE+APS (n=10), PAPS (n=10) and HC (n=12). pDC miRNA and transcriptome profiles were assessed by RT-qPCR by OpenArray and RNA-sequencing (RNAseq) respectively. Patients were stratified by the presence (IFN-high) or absence (IFN-low) of an IFN signature on the basis of RNAseq. pDC stimulated with TLR7 agonists were analyzed for changes in miRNA expression.

Results: The numbers of circulating pDC were reduced in peripheral blood of patients with SLE, SLE+APS and PAPS (all $p<0.001$) and did not differ among the patient groups. Among 131 expressed miRNAs, 36, 17 and 21 miRNAs were differentially expressed ($p<0.05$) in patients with SLE, SLE+APS and PAPS, respectively, as compared with HC. All but one of these miRNAs were downregulated in the patients versus HC. Only 1 miRNA was differentially expressed when comparing between SLE and SLE+APS patients and between SLE+APS and PAPS patients. No changes in expression of genes related to the biogenesis of miRNAs were observed in the pDC of the patient groups. RNAseq data revealed an IFN signature in pDC, which was strongest in SLE and SLE+APS patients. IFN-high (n=23) patients showed a stronger downregulation of miRNAs as compared with IFN-low (n=17) patients. A total of 9 miRNAs were differentially expressed between IFN-high and IFN-low patients. Pathway enrichment on targets of the top three miRNA ($p<0.001$) distinguishing between IFN-high and –low patients indicated that these miRNAs are potentially regulating pathways relevant for pDC function such as TLR signaling and endocytosis. Activation of pDCs by TLR7 agonists induced a downregulation of miRNAs in pDC, resembling the miRNA expression pattern seen in patients, in particular those with a high type I IFN signature.

Conclusions: Reduced numbers of circulating pDC and downregulation of miRNAs in pDC is shared between SLE, SLE+APS and PAPS patients. Altered miRNA expression in pDC is associated with the presence of a type I IFN signature in SLE and APS. Our data suggest that the reduced expression of a subset of miRNA underlies pDC dysregulation in SLE, SLE+APS and PAPS patients.

Disclosure of Interest: None declared

DOI: 10.1136/annrheumdis-2017-eular.2372

FRIDAY, 16 JUNE 2017

Comorbidities in rheumatoid arthritis

OP0307 TREATMENT OF BAFF TRANSGENIC MICE WITH ANTI-TNF: MONOCLONAL ANTI-TNF ARE ASSOCIATED WITH A HIGHER RISK OF LYMPHOMA THAN ETANERCEPT

G. Nocturne[1], L. Bineta[2], S. Boudaoud[2], J. Pascaud[2], R. Seror[1], C. Nicco[3], C. Chereau[3], F. Mackay[4], F. Vincent[4], T. Lazure[5], S. Ferlicot[5], L. Stimmer[6], S. Roulland[7], R. Krzysiek[8], S. Hacein-Bey[8], F. Batteux[3], X. Mariette[1]. *[1]Rheumatology; [2]INSERM U1184, le Kremlin Bicêtre; [3]U1016, Paris, France; [4]Melbourne University, Melbourne, Australia; [5]Pathology, le Kremlin Bicêtre; [6]CEA, Fontenay aux roses; [7]Marseille Luminy, Marseille; [8]Immunology, le Kremlin Bicêtre, France*

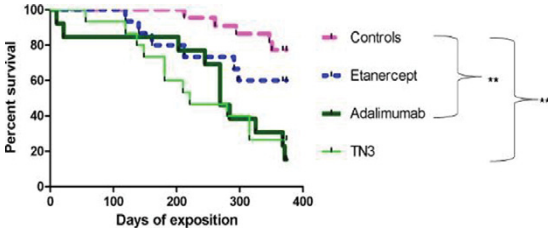
Background: Risk of lymhoma in patients with rheumatoid arthritis (RA) and disease activity is the main risk factor. The impact of treatment, notably of anti-TNF, is unclear: decreasing the risk of lymphoma by controlling activity or alterring anti-tumor immunosurveillance. Anti-TNF are not associated with an increased risk of lymphoma in large epidemiologic studies. However, the risk might vary according to the type or to the dose of anti-TNF.

Objectives: To assess if the risk of lymphoma might differ according to the type of anti-TNF, comparing monoclonal anti-TNF to the soluble receptor. For that, we used BAFF transgenic (Tg) mice as a model of autoimmunity-associated lymphomas. They develop lupus and Sjögren and 3% of them spontaneously developed lymphoma at 12–18 months

Methods: Six months aged BAFF-Tg mice were treated with anti-TNF for 12 months: etanercept (ETA) (n=15, 8 mg/kgx3/week), monoclonal anti-mouse TNF: TN3 19.12 (n=15, 20 mg/kg/week), adalimumab (ADA) (n=12, 20 mg/kg/week) or controls (n=22). Sera were assessed monthly. Crude mortality was compared among the different groups. Histological examination of the spleen was performed. The Fisher's exact test was used to compare the incidence of lymphoma among the groups.

Results: Adjunction of low dose of methotrexate during the 3 first days of treatment prevented immunization in the 3 groups for life. Using L929 cells, a cell line sensitive to TNF induced death, we confirmed that ADA was 8 to 12 times less efficient than ETA to inhibit soluble murine TNF. As expected, the mean level of ETA, TN3 and ADA were 7 μg/ml, 69 μ g/ml and 105 μg/ml, respectively. The

level of auto-antibodies and serum Ig did not significantly differ among the groups. However, crude mortality was significantly higher in mice treated with monoclonal anti-TNF compared to controls (p=0.0001 for ADA and p=0.0003 for TN3) but not for mice treated with ETA (Figure). Incidence of lymphoma was higher in mice treated with monoclonal anti-TNF: *5/15 (33%)* with TN3 (p=0.03/controls), *4/12 (33%)* with ADA (p=0.054/controls), *0/15* with ETA and *1/22 (5%)* in controls.



Conclusions: Higher mortality and increased risk of lymphoma were observed in BAFF Tg mice treated with monoclonal anti-TNF compared to etanercept. This result may be linked either to the different mechanism of action between the soluble receptor and the monoclonals or to a difference of trough level observed in the different groups even if higher levels of ADA was mandatory given the difference of effect on mouse TNF. This study demonstrates the negative impact of a prolonged anti-TNF treatment on the risk of lymphoma in the context of BAFF increase.

Disclosure of Interest: None declared

DOI: 10.1136/annrheumdis-2017-eular.5651

OP0308 TNF INHIBITOR TREATMENT AND RISK OF CANCER RECURRENCE IN PATIENTS WITH RHEUMATOID ARTHRITIS: A NATIONWIDE COHORT STUDY FROM SWEDEN

P. Raaschou, J. Söderling, J. Askling on behalf of the ARTIS study group. *Dept of Medicine, Karolinska Institute, Stockholm, Sweden*

Background: Clinical guidelines caution against the use of TNFi in individuals with a recent (5–10 years) history of cancer, but evidence of an increased risk of cancer recurrence is limited (1–2).

Objectives: We investigated the risk of recurrent solid non-skin cancer in patients with rheumatoid arthritis and TNFi-treatment, and if time between index-cancer and TNFi-start influence this risk.

Methods: 61.950 individuals with RA were identified in the Swedish national outpatient-care register Jan 2001-Dec 2014. Among these, 446 Individuals with at least one diagnosis of cancer (index cancer) prior to the start of TNFi-treatment were identified through linkage to the national cancer register and the ARTIS register of biologic treatment. Individuals (n=1.278) with a history of equally recent cancer of the same type and stage (invasive/in situ) were matched 3:1 to each patient starting TNFi against a background of solid cancer. Study participants were required to be in cancer remission during a period of 6 months prior to start of follow-up. The primary outcome was first recurrence or second primary of the same cancer type, identified through register-linkages until Dec 2014. Hazard ratios (HR) for recurrence or second primary were calculated using a Cox regression model with TNFi-treatment start (and a corresponding date among the matched biologics-naïve individuals) as start of follow-up. The final models were stratified for the matching variables sex, birth year, year of diagnosis of the index cancer and index cancer type and stage (invasive vs in situ), and adjusted for education level and comorbidities.

Results: The mean time from index cancer diagnosis until TNFi-treatment/start of follow-up was 9.9 and 9.5 years among the TNFi treated and their matched biologics-naïve controls, respectively. The mean follow-up (SD) from TNFi start was 4.9 (3.5) and 4.1 (3.1) years, respectively. The cancer stage distribution was similar between the two groups, apart from stage IV (0.6% among the TNFi-treated and 1.6% among the biologics-naïve). Thirty individuals (7%) among the 446 TNFi-treated developed a cancer recurrence (crude incidence rate 14/1000 person-years), compared with 89 (7%) among the 1.278 matched biologics-naive (crude incidence rate 17/1000 person-years). This corresponded to an adjusted HR for recurrent cancer of 0.69 (95% CI 0.42–1.12) in the matched analysis (table 1) comparing the TNFi treated to the biologics-naïve individuals. Stratified analyses indicated no increased risk associated with any specific cancer type with the possible exception of uterine cancer where HR for recurrence was 14.8 (95% CI 1.17–187.5), based on only 1 event among the TNFi-treated. HR for recurrence among individuals starting TNFi treatment within 5 year from index cancer was 0.67 (0.31–1.44).

Table 1 Number of patients, recurrent or second primary cancer, incidence rate per 1000 person-years (PY) and hazard ratios (HR) among TNFi treated patients with RA and their matched biologics-naïve comparators

Cancer	TNFi			Matched comparators			Adjusted* HR (95 % CI)
	N	Events (%)	IR per 1000 PY	N	Events (%)	IR per 1000 PY	
Overall	446	30 (6.7%)	13.8	1 278	89 (7.%)	17.0	0.69 (0.42-1.12)
Anorectal	29	0	0	69	4 (5.8%)	15.5	-
Breast	212	22 (10.4%)	19.9	633	46 (7.3%)	16.1	1.04 (0.57-1.89)
CNS	30	1 (3.3%)	7.0	81	3 (3.7%)	7.5	-
Colon	34	0	0	91	3 (3.3%)	11.3	-
Kidney	6	0	0	14	1 (7.1%)	16.4	-
Lung	3	1 (33.3%)	86.1	9	(.%)	0	-
Ovarial	29	1 (3.4%)	6.2	75	4 (5.3%)	12.8	-
Prostate	59	2 (3.4%)	8.7	175	17 (9.7%)	31.0	0.16 (0.03-1.00)
Urinary	16	2 (12.5%)	33.7	47	10 (21.3%)	65.5	0.80 (0.16-4.07)
Uterine	28	1 (3.6%)	6.2	84	1 (1.2%)	2.8	-

Cox regression stratified for the matching variables sex, birth year (±10 years), year of diagnosis (±5 years) of the index cancer, cancer type and stage at diagnosis (invasive vs in situ) of the index cancer, and adjusted for education and comorbidities. Within each matched strata, HRs could therefore be calculated only when events occurred among both TNFi-treated and biologics-naive.

Conclusions: Among patients with RA and a history of cancer, those selected to receive TNFi-treatment in clinical practice did not experience more cancer recurrences than patients with RA treated otherwise. We detected no differential risk depending on the timing of TNFi-start in relation to the index cancer. The generalizability of our findings to individuals with a very recent cancer, or a poor prognosis, remains unknown.

References:
[1] Raaschou P, et al. Ann Rheum Dis 2015;74:2137–2143.
[2] Mamtani R, et al. Arthritis Rheumatol 2016; 68: 2403–2411.

Disclosure of Interest: P. Raaschou: None declared, J. Söderling Grant/research support from: previous research projects fully or partly funded by Novo Nordisk and Combine Sweden, and has served as an external consultant to AbbVie, Merck and Novartis., J. Askling Grant/research support from: Abbvie, Pfizer, UCB, MSD, Roche, Lilly.

DOI: 10.1136/annrheumdis-2017-eular.5148

FRIDAY, 16 JUNE 2017

AxSpA: from bug to gut and to disease phenotype

OP0309 INTESTINAL SCLEROSTIN/SEROTONIN AXIS IS MODULATED BY DYSBIOSIS AND REGULATES ILC3 EXPANSION IN AS PATIENTS

F. Ciccia[1], G. Guggino[1], A. Rizzo[1], S. Milling[2], M. Luchetti[3], D. Baeten[4], R. Alessandro[1], G. Triolo[1]. *[1]University of Palermo, Palermo, Italy; [2]University of Glasgow, Glasgow, United Kingdom; [3]University Politecnica delle Marche, Ancona, Italy; [4]University of Amsterdam, Amsterdam, Netherlands*

Background: Sclerostin is an osteocyte-specific factor that binds to low-density lipoprotein receptor-related protein 5 (LRP5) inhibiting the Wnt signaling pathway and possibly contributing to the pathogenesis of Ankylosing spondylitis (AS). Subclinical gut inflammation observed in AS patients is characterized by the presence of dysbiosis and innate immune alterations. In the gut, LRP5 activation by unknown ligands inhibits serotonin production. Serotonin, by inducing glial derived neurotrophic factor (GDNF), controls ILC3 expansion, in the context of glial–ILC3–epithelial cell unit (GIECU). Sclerostin/serotonin axis has been never studied in AS.

Objectives: Aim of this study was to evaluate whether sclerostin is produced in the gut; to study the sclerostin/serotonin axis in AS and the effect of sclerostin on enterochromaffin cells (EC); to evaluate the presence of intestinal GIECU in AS and the role of serotonin in modulating the production of GDNF on isolated intestinal glial derived cells. We finally studied the effect of GDNF on ILC3.

Methods: Ileal, synovial and bone marrow (BM) expression of sclerostin, serotonin and GDNF were investigated by rt-PCR, immunohistochemistry and WB in 30 AS patients and 20 controls. Platelet and plasma unconjugated concentrations of serotonin were assessed by high-performance liquid chromatography (HPLC). Isolated bacteria from AS ileal biopsies were cultured with EC and serotonin expression evaluated by RT-PCR. Sclerostin and serotonin gut expression were evaluated in HLA-B27 TG rats before and after antibiotics treatment. EC were stimulated with sclerostin and the expression of THP1 assessed by RT-PCR. The presence of GIECU was studied by confocal microscopy analysis of GFAP/Tbet/Thy1. Isolated intestinal glial cells were stimulated with serotonin and the modulation of GDNF assessed by RT-PCR. The effect of GDNF on ILC3 was evaluated by flow cytometry.

Results: Sclerostin was produced in the gut and down-regulated in AS. Up-regulation of serotonin was observed in the gut, in the synovia and plasma, but not in BM of AS. Isolated intestinal bacteria from AS reduced EC serotonin production. Sclerostin down-regulation and serotonin over-expression were observed in the gut of HLA-B27 TG rats where Antibiotics increased intestinal sclerostin production and reduced serotonin expression. Treatment of isolated gut EC with sclerostin down-regulated the expression of THP1. GDNF was over-expressed in AS gut and confocal microscopy analysis demonstrated the existence of glial-ILC3-epithelial cells unit in AS patients. Finally, serotonin induces the release of GDNF by isolated intestinal glial cells and recombinant GDNF expanded RET^{+}ILC3.

Conclusions: here we demonstrate for the first time that intestinal sclerostin is the ligand of LRP5 and modulates the release of serotonin. Sclerostin/serotin axis is dysregulated in AS patients and HLA-B27 TG rats. In HLA-B27 TG rats, antibiotics restored sclerostin production and serotonin expression indicating a role of dysbiosis in modulating sclerostin/serotonin axis. Serotonin seems to be an important regulator of ILC3 expansion by inducing the production of GDNF by enteric glial cells, in the context of glial-ILC3-epithelial cells unit.

Disclosure of Interest: None declared