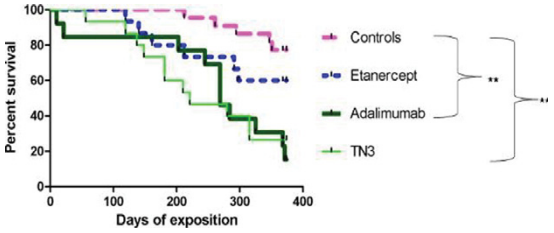
level of auto-antibodies and serum Ig did not significantly differ among the groups. However, crude mortality was significantly higher in mice treated with monoclonal anti-TNF compared to controls (p=0.0001 for ADA and p=0.0003 for TN3) but not for mice treated with ETA (Figure). Incidence of lymphoma 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

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

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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.

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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

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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

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Pregnancy meets rheumatic patients

OP0310 PREGNANCY OUTCOME IN WOMEN WITH SYSTEMIC LUPUS ERYTHEMATOSUS, A MULTICENTER COHORT-STUDY

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Background: Systemic lupus erythematosus (SLE) predominantly affects women during their fertile period. During pregnancy SLE patients are prone to pregnancy complications and may experience increased disease activity.
Objectives: To investigate disease activity around/during pregnancy and pregnancy complications in a European cohort according to antiphospholipid antibody (aPL) status. Additionally data on lifetime pregnancy outcomes and comparison of first and consecutive pregnancies were analyzed.
Methods: All ongoing pregnancies of >16 weeks gestation of SLE patients (according to the ACR revised criteria) receiving joint care from rheumatologists and gynecologists in two tertiary centers in the Netherlands between 2000–2015 were included. Disease activity (using SELENA-SLE(P)DAI around and during pregnancy), flare rate according to the SELENA- SLEDAI definitions and pregnancy complications were assessed by medical chart review.
Results: From 96 women (84% Caucasian) 144 pregnancies were included. Before (<6 months), during and after pregnancy (<6 months) the median SELENA-SLE(P)DAI score was 2 and mild/moderate flare rates were 6.3%, 18.8% and 13.9% respectively. Three patients developed a severe flare during pregnancy, 2 patients postpartum; all were aPL negative. Severe maternal complications (preeclampsia, eclampsia or HELLP-syndrome) occurred in 16.2% of aPL negative, 21.4% of aPL positive SLE patients, and in 30.8% of SLE patients with antiphospholipid syndrome (APS) (GEE; no significant differences between groups). HELLP-syndrome occurred in 23.1% of SLE patients with APS and in 3.1% of SLE patients without APS (Chi-Square; p<0.01). The perinatal complications intrauterine fetal death, preterm birth, small-for-gestational age and neonatal lupus occurred in 4.1%, 32.7%, 14.8%, 1.4%, respectively (GEE; no significant differences between groups). Maternal and perinatal complication rates were similar in first (18.5% and 41.4%) and consecutive (17.6% and 35.1%) pregnancies (Chi-Square; p=0.88 and p=0.44). Of all patients, 42.7% developed a complication during all of their pregnancies (obstetrical history included).
Conclusions: This is the first study in patients with SLE demonstrating that incidence rates of pregnancy complications do not decrease in consecutive pregnancies compared to first pregnancies, in contrast to findings in the general population. Except for HELLP-syndrome, pregnancy complications were not significant different between aPL groups. Despite overall low disease activity and the absence of aPL in the majority of patients, almost half of the patients developed a complication during their pregnancies.
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OP0311 HIGH MATERNAL EXPRESSION OF SIGLEC1 ON CD14+ MONOCYTES AS A SURROGATE MARKER OF A TYPE I INTERFERON SIGNATURE IS A RISK FACTOR FOR THE DEVELOPMENT OF AUTOIMMUNE CONGENITAL HEART BLOCK

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Background: Autoimmune congenital heart block (CHB) is a severe manifestation of neonatal lupus syndrome that is associated with placental transcytosis of maternal autoantibodies directed against the ribonucleoproteins Ro/SS-A and, to a lesser extent, La/SS-B.(1) Around 2/3 of affected mothers are diagnosed with either systemic lupus erythematosus (SLE) or primary Sjögren's syndrome (pSS),(2) which are both pathogenically driven by an upregulation of type I interferons (IFN).(3)
Objectives: Although the pleiotropic effects of type I IFN on the immune system are well documented, a potential role of type I IFN in the development of CHB has not yet been investigated. This study therefore aimed to compare maternal levels of type I IFN activation in affected and unaffected mothers, in order to provide first insights into a potential role of type I IFN in CHB development.
Methods: Blood samples, clinical data and serological parameters from 9 women with CHB pregnancies, 15 pregnant women with antibodies against Ro/SS-A but without a CHB complication ("Disease Controls", DC), and another 30 healthy pregnant women without the respective autoantibodies as controls were studied. Plasma levels of IFN-α (ELISA), interferon-gamma induced protein 10 (IP-10) (Bioplex®) and the expression of SIGLEC1 on CD14+ monocytes (flow cytometry) were analysed.
Results: Pregnant females with a CHB complication had a significantly higher expression of SIGLEC1 (p=0.0034) and IFN-α (p=0.014), but not of IP-10 (p=0.14, all MWU), compared to the DC group. Receiver operating curve (ROC) analysis between the CHB group and the DC group showed that a SIGLEC1 median fluorescence intensity (MFI) of >904 could distinguish between the groups with a sensitivity of 100% and a specificity of 64%, and a concentration of IFN-α >0.70 pg/ml with a sensitivity of 67% and a specificity of 86%. Healthy pregnant females without the respective autoantibodies had the lowest levels for all three parameters. In a cohort of 5 females, both the expression of SIGLEC1 and plasma levels of IFN-α were reduced by hydroxychloroquine and oral glucocorticoids.

Table 1. Antibody profiles

	CHB pregnancies (n=9)	Disease controls (n=14)	Healthy controls (n=30)
Anti-Ro (SS-A), n (%)	9 (100%)	14 (100%)	0
– anti-Ro52, n (%)	7 (78%)	12 (86%)	0
– anti-Ro60, n (%)	9 (100%)	8 (57%)	0
Anti-La (SS-B), n (%)	2 (22%)	4 (29%)	0

Conclusions: This is the first study to report increased type I IFN activation in pregnant females with a CHB complication. Also, we show here that IFN-α directed therapy, e.g. with hydroxychloroquine, may be especially beneficial in these females.
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Neuronal and hormonal alterations in arthritis

OP0312 A PROTEOMIC SIGNATURE OF FATIGUE IN PRIMARY SJÖGREN'S SYNDROME

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Background: Fatigue is a frequent and often disabling phenomenon in patients with chronic inflammatory and immunological diseases, neurodegenerative diseases, and cancer. The underlying biological mechanisms of fatigue are largely unknown and hypotheses are conflicting. It is important to uncover the pathophysiology and identify signalling pathways that generate and regulate this substantial phenomenon.
Objectives: Based on the hypothesis that fatigue originates from cerebral processes, we investigated whether relevant proteins and/or signaling pathways for fatigue could be revealed in the cerebrospinal fluid (CSF) of patients with primary Sjögren's syndrome.
Methods: Label-free shotgun mass spectrometry was performed to analyze the CSF proteome of 20 patients with primary Sjögren's syndrome. Fatigue was measured with the fatigue Visual Analogue Scale (fVAS).
Results: After depletion of high-abundance proteins, more than 800 proteins were identified and quantitated. Multivariate analyses showed that patients with low and high fatigue could be separated based on their CSF protein profiles, and 15 proteins were selected as top discriminatory proteins. Among these were apolipoprotein A4, hemopexin, pigment epithelium derived factor, secretogranin-1, secretogranin-3, selenium-binding protein 1, and complement factor B.
The figure shows the top network from Ingenuity Pathway Analysis (IPA) with 14 of