SAT0259 HIGH PLASMA CONCENTRATION OF MYCOPHENOLATE ACID IN EARLY PHASE OF INDUCTION THERAPY PREDICTS GOOD RENAL OUTCOME IN LUPUS NEPHRITIS CLASS III OR IV

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Background: Mychophenolate mofetil (MMF) is recommended as initial induction treatment for most cases of lupus nephritis (LN) class III-IV. Although the association between area under the concentration-versus-time curve (AUC) of myochophenolate acid (MPA) and therapeutic efficacy has been well shown in renal transplantation, it has been poorly investigated in LN. Furthermore, MMF interacts with multiple factors and its concentration may be decreased by high prednisolone (PSL) dose, low serum albumin level and low creatinine clearance. Since these factors dramatically change in induction phase of LN, the plasma concentration of MPA may also change by fixed dose of MMF administration. Here, we measured AUC_{0-12} of MPA at different phases of induction treatment, early and middle, and prospectively investigated which concentration predicted future renal response in LN class III-IV.
Objectives: To investigate the relationship between the plasma concentration of MPA in early or middle phase of induction therapy and future renal response.
Methods: We prospectively enrolled patients with biopsy proven LN class III or IV who hospitalized from Apr to Oct 2016. As induction therapy, PSL was started at dose of 1mg/kg/day and tapered to 10mg/day by 12 weeks. Fixed dose of MMF at 2,000mg/day was continuously introduced. We measured 2 points of MPA plasma concentration depending on the phase of induction therapy, at early (week 2) and middle (week 12). We evaluated the association between these concentration and complete renal response (CR) rate at week 12.
Results: Six patients were enrolled. AUC_{0-12} between the early and the middle phase was not correlated (R^2=0.17, p=0.7), but that of the early phase tended to be lower (47.4±25.6 vs 58.9±19.1 mgh/L). All the patients with high AUC_{0-12} (over 40mgh/L) at the early phase achieved CR at week 12 (Figure 1). But we could not find any association between AUC_{0-12} at middle phase and CR rate at week 12.

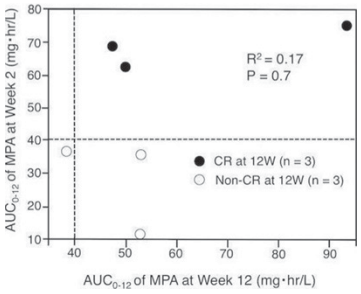

Figure 1

Conclusions: High AUC_{0-12} of MPA at the early phase of induction therapy might predict good renal response.
Disclosure of Interest: None declared
DOI: 10.1136/annrheumdis-2017-eular.4622

SAT0260 OVARIAN FUNCTION PRESERVATION WITH GONADOTROPIN-RELEASING HORMONE ANALOGUES IN PATIENTS WITH SYSTEMIC LUPUS ERYTHEMATOSUS TREATED WITH CYCLOPHOSPHAMIDE

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Background: The fertility in childbearing Systemic Lupus Erythematosus (SLE) patients can be impaired due to several conditions. In particular, treatment with alkylating agents, as cyclophosphamide (CYC), could determine menstrual irregularities and premature ovarian failure (POF). Gonadotropin-releasing hormone analogues (GnRH-a) is one of the preventive strategy suggested by the recently published EULAR recommendations (1). They are characterized by good safety profile and effectiveness in reducing POF rate in patients with malignancies and autoimmune diseases. So far, only few studies have been published focusing on the use of GnRH-a to prevent POF in SLE women receiving CYC treatment.
Objectives: In the present case-control study, we aimed at evaluating the efficacy of GnRH-a on the ovarian function preservation in SLE patients treated with CYC.
Methods: We enrolled consecutive SLE patients, fulfilled the 1997 ACR revised criteria treated with CYC in the period between 2005 and 2012, receiving GnRH-a (GnRH-a+). As control, SLE patients treated with CYC not receiving GnRH-a (GnRH-a-) were assessed. Clinical and laboratory data were collected in a standardized, computerized and electronically filled form. Ovarian function was assessed by the evaluation of FSH and estradiol level (E2). GnRH-a (triptorelin 3.75 mg/monthly intramuscularly) was prescribed. SLE patients treated with CYC were followed after the treatment every six months during the first year and then annually.
Results: Thirty-tree SLE patients treated by CYC were evaluated in the present analysis: 75.7% of patients were treated for lupus nephritis. Among [FC1] these, 18 GnRH-a+ (mean±SD age 29.3±7.6 years; mean±SD disease duration 7.2±4.2 years) and 15 GnRH-a- (mean±SD age 31.0±10.5 years; mean±SD disease duration 6.3±7.4 years). The mean±SD SLEDAI-2K score in GnRH-a+ patients was 10.1±3.7, in GnRH-a- patients 8.3±3.3 (p=NS). Moreover, no differences were identified concerning the duration of CYC treatment (GnRH-a+: 6.1±2.8 months *versus* GnRH-a- 6.1±2.2 months, p=NS) and follow-up (GnRH-a+: 8.11±2.2 years versus GnRH-a- 9.3±7.2 years, p=NS). The prevalence of POF was significantly higher in GnRH-a- (5 patients, 33.3%) in comparison with GnRH-a+ (2 patients, 11.1%, P=0.0002). A significantly higher mean age at the time of CYC treatment was observed in patients developing POF (37.7±5.9 years) in comparison with those not developing this complication (28.0±8.5 years, p=0.008). Moreover, the use of GnRH-a seems to be protective also in terms of menstrual cycle regularity: the cycle remained regular during treatment in 83.3% of GnRH-a+ and only in 33.3% of GnRH-a- (p=0.003). During the follow-up, 3 patients in the GnRH-a+ group underwent pregnancy, with a good outcome.
Conclusions: The results of the present study showed the protective role of GnRH-a for the preservation of ovarian function in SLE patients treated by CYC. Furthermore, the age resulted the only risk factor associated with POF development.
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Disclosure of Interest: None declared
DOI: 10.1136/annrheumdis-2017-eular.6381

SAT0261 REFRACTORY SYSTEMIC LUPUS ERYTHEMATOSUS IS MAINLY ASSOCIATED WITH THE DECREASED NUMBER OF REGULATORY T CELLS AND LOW-DOSE IL-2 COMBINED WITH RAPAMYCIN CAN EFFICIENTLY RECOVERY THE BALANCE OF TH17/REGULATORY T CELLS

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Background: Refractory system lupus erythematosus (SLE) still relies on aggressive treatment with high-dose glucocorticoids and immunosuppressive agents,but a significant proportion of patients persist with activity or relapse and show serious side-effects by the treatment.However, the imbalance of Th17 cells and regulatory T (Treg) cells in peripheral blood of patients with SLE may be an important factor in the pathogenesis of SLE.Because low-dose IL-2 can selectively enhance Treg function while avoiding the activation of effector T cells and rapamycin can promote the proliferation of Treg cells[1–2],the combination of the low-dose IL-2 and rapamycin has been considered to treat refractory SLE for the purpose of remission.
Objectives: To observe the effect of low-dose IL-2 combined with rapamycin on the balance of Th17/Treg cells in patients with refractory SLE.
Methods: Eighty-two refractory SLE patients (80 women and 2 men),with a mean duration of 72.41±37.52 months and mean age of 36.22±12.48 years, were enrolled.They are in line with the standard of ACR in 1997,who are treated with glucocorticoid and immunosuppressant for more than one year, but the subjects continues to rise to a peak.After the eligible patients are given IL-2 and rapamycin in combination therapy with conventional therapy at 0, 6, 12, 24 week respectively after medication.The clinical symptoms, blood routine, urine routine, ESR, Th17 cells, Treg cells, Th17/Treg cells and the dosage of corticosteroids and immunosuppressant are registered one by one.
Results: At 24 week after treatment,28.9% patients with refractory SLE were relieved.Low-dose IL-2 combined with rapamycin leaded to an increase in the absolute counts of Treg cells in refractory SLE patients,from a median of 12.98 cells/ul (at week 0) to 22.1 cells/ul (at week 24) (P=0.002).The ratio of Th17/Treg cells shows a reduction from a median of 0.44 at week 0 to 0.29 at week 24 (P=0.029).No significant difference was observed in the absolute counts of Th17 after combined treatment.At week 24, the mean dosage of prednisone which refractory SLE patients were receiving decreased from 17.20 mg/d to 8.87 mg/d.And the categories of DMARDs use were also reduced ($P<0.05$).
Conclusions: Our results suggest that refractory SLE is major associated with the decreased number of Treg but not that of Th17.The Th17 and Treg cells in the peripheral blood of patients with refractory SLE tends to balance due to the significantly increase the number of Treg cells after low-dose IL-2 combined with rapamycin treatment.Low-dose IL-2 combined with rapamycin treatment can reduce the dosage of glucocorticoid and DMARDs.
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Disclosure of Interest: None declared
DOI: 10.1136/annrheumdis-2017-eular.4552

SATURDAY, 17 JUNE 2017

SLE, Sjögren's and APS - clinical aspects (other than treatment)

SAT0262 BCL2-ASSOCIATED ATHANOGENE 3 PROTEIN IS ASSOCIATED WITH B-CELL HYPERACTIVITY INCLUDING LYMPHOMA IN PRIMARY SJÖGREN'S SYNDROME

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Background: Bcl2-associated athanogene 3 (BAG-3) is a co-chaperone protein that interacts with the ATPase domain on heat-shock protein 70. BAG-3 is involved is several biologic processes including apoptosis, cytoskeleton organization and autophagy and, therefore, it has been extensively investigated in the field of tumorigenesis (1). In particular, BAG-3 expression is constitutive in human primary tumors including leukemias and lymphomas and it is induced in different normal cell types, including leukocytes, by a variety of stimuli. BAG-3 is able to induce and maintain cell proliferation, resistance to therapy and cell motility, namely metastatization. On this basis, a role of BAG-3 in chronic inflammatory diseases may be postulated, but data on this topic are not available.
Objectives: The purpose of our study was to investigate the expression of BAG-3 in primary Sjogren's syndrome (pSS) and the relationship with clinical and serological features.
Methods: BAG-3 concentration was assessed in the serum of 103 patients with pSS according to the 2002 American-European classification criteria and in 40 sex and age matched healthy donors (HD). Clinical and serological records were collected and statistical analysis was performed with SPSS 21.0.
Results: Twenty-six pSS patients were positive for BAG-3 (BAG-3+), with serum levels ranging from 32.1 to 950 pg/ml. When setting the cut-off value according to the highest value found in HD (300 pg/ml), we identified 13 pSS patients displaying a peculiar clinical serological phenotype. In detail, in this subgroup of pSS patients the prevalence of purpura, low C4, both anti-Ro and anti-La autontibodies, rheumatoid factor and lymphoma was higher, when compared to pSS patients with BAG-3 levels $<$300 pg/ml or BAG-3- (all $p<0.05$). Furthermore, they displayed less frequently sicca symptoms such as xerostomia and xerophtalmia (both $p<0.05$). Binary logistic regression analysis revealed that pSS patients with BAG-3 levels $>$300 pg/ml had on odds ratio (OR) of 12 (95% CI 1.9–86, p=0.009) for lymphoma and this association was independent of the presence of purpura, a well know marker of lymphoma in pSS. When including low complement, another feature associated with lymphoma, in the multivariable analysis, both low C4 and BAG-3 levels $>$300 pg/ml resulted independently associated to lymphoma (OR=24 and 12.4 respectively).
Conclusions: Our study assessed for the first time serum BAG-3 levels in a large cohort of pSS patients. The results showed that the highest levels of BAG-3 identify a peculiar clinical and serological pSS phenotype, as consequence of a B-cell hyperactivity. Since it is known that BAG-3 is an anti-apoptotic protein playing a pivotal role in cell survival, and that B-cell hyperactivity in pSS is the consequence of coordinated and integrated actions of several stimuli and appropriate cytokines, our results may suggest that BAG-3 overexpression is involved in B-cell proliferation and activity, as well as in oligoclonal and monoclonal expansion in pSS.
References:
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Disclosure of Interest: None declared
DOI: 10.1136/annrheumdis-2017-eular.3587

SAT0263 NEOPLASIA IN PATIENTS WITH SYSTEMIC LUPUS ERYTHEMATOSUS IN SPAIN: RELESSER REGISTRY DATA

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Background: There is limited evidence on the risk of neoplasia in autoimmune diseases such as systemic lupus erythematosus.
Objectives: The objective of this study is to analyze the incidence of cancer in the Spanish population with SLE and the factors associated in its development: RelesSER Registry Data.
Methods: We calculated the incidence density of malignant neoplasms, the standardized incidence ratio and the average time to develop the first neoplasm after diagnosis of SLE in patients of the SLE registry of the Spanish Rheumatology Society (RelesSER) fulfilling ACR97 criteria. We carried out a bivariate analysis of the associated factors to neoplasms and multivariate by logistic regression.
Results: A total of 3607 patients (90.4% female) were included. We registered 140 neoplasms in women (4.3%) and 14 in men (4%) ($p<0.821$). Incidence density 7.3/1000 patient-years (95% CI:4.85–10.98) (7.39 in patient-years women and 6.93 in men) without significant differences. After stratification by gender and age, cancer appeared in 3.2% of the women aged under 45 versus 3.8% of the men; 4.1% of women aged 45–65 years versus 5.9% of men and a 5.3% of women 65 and older versus 2.5% of men the same age. The standardized incidence ratio (SIR) was 2.16; 1.51 in men and 2.38 in women, highest for women under 65 years old. The SIR for $>$65 years was 0.98; 0.59 in men and 1.55 in women.
The average time until de development of the first malignant neoplasm was 10 years (RI:5.75–17.00), being lower in women [9.5 (RI: 5.00–17.0) years] than in men [12.5 (8.75–17.5)] and in patients under 45 years versus over 45 years [8.0 (RI: 5.00–16.00)].
Malignant neoplasms were the cause of death in 10% of the patients (15/154), predominantly hematological and breast cancers, both at 19% followed by lung cancer in 14.3%.
Factors associated to malignant neoplasms in the bivariate analysis are shown in (table 1). No immunosuppressive therapy was associated with the development of neoplasms. In the multivariate model, adjusted for age and time of disease duration, age was the only significant variable (OR:1.030; 95% CI: 1.003–1.059; p=0.029) with a trend for ACE inhibitors use (OR:1.866; 95% CI: 0.808–4.306; p=0.144), SLEDAI (last visit) (OR: 0.904; 95% CI: 0.806–1.015; p=0.089, SLICC/ACR DI) (without neoplasias) (OR: 1.160; 95% CI: 0.961- 1.401; p=0.123), and duration of the disease in months (OR: 1.003; 95% CI: 1.000–1.006; p=0.068).

Table 1

	Cáncer	Control	*p*
Gender, men %	4	96	0.821
Gender, women %	4.3	95.7	0.821
Mean age at first criterion, years (DS)	38.35 (16.01)	32.72(14.29)	<0.001
Diagnostic age SLE, years (DS)	40.37 (15.68)	34.75 (14.46)	<0.001
Age at last evaluation, years, mean (DS)	57.74 (14.38)	46.17 (14.58)	<0.001
Disease duration (months), mean (DS)	208.71 (102.95)	140.1 (99.69)	<0.001
Follow-up in Rheumatology (months), mean (DS)	170. 1 (90.75)	118.12 (86.90)	<0.001
Sjogren´s syndrome, %	20.5	14.1	0.029
SLEDAI, median [p25-p75]	1.00 [0.00-3.25]	2.0 [0.00-4.00]	0.026
KATZ, median [p25-p75]	3 [2-4]	2 [1-3]	0.001
SLICC*, median [p25-p75]	1.00 [0.00-3.00]	0.00 [0.00-1.00]	<0.001
CHARLSON*, median [p25-p75]	3 [2.00-4.00]	1 [1.00-3.00]	<0.001
Time on antimalarals (months) median [p25-p75]	78.00 (27.75-136.50)	60.00 (24.00-119.00)	0.099

Conclusions: The incidence of neoplasia in Spanish women with SLE is higher than expected for age and gender. Malignant neoplasms were the cause of death in 10% of the patients, predominating hematological and breast cancers followed by lung cancer.
Acknowledgements: The RelesSER registry has been supported by the FIS (ISCIII) - European Regional Development Fund (FEDER), fellowship PI11/02857. It has also been partially funded by: GSK, UCB, Roche and Novartis.
Disclosure of Interest: None declared
DOI: 10.1136/annrheumdis-2017-eular.4474

SAT0264 VALVULOPATHY AND PULMONARY HYPERTENSION IN A SERIES OF PATIENTS WITH ANTIPHOSPHOLIPID SYNDROME

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Objectives: To evaluate the prevalence of cardiac valvular involvement and