Methods: Fifteen severe, refractory SLE patients were included and followed for 2 years. Patients received RTX at week 0 and 2 and BLM at week 4, 6, 8 and then 4-weekly until week 104. Clinical response was assessed by achievement of low level of disease activity (LLDAS). By using specific antibody assays and high sensitivity flowcytometry (HS-FACS), we longitudinally followed, respectively, levels of SLE-specific ANAs and B-cell subsets.

Results: Ten patients (67%) showed a good clinical response after 24 weeks, referred to as 'responders'. Two of these patients (13%) switched treatment after 24 weeks due to a pregnancy wish and 8 patients (53%) continued study treatment throughout the complete 2 years of follow-up. Five patients (33%) discontinued treatment due to persistent LN (n=2), major flare (n=2) or relapsing minor flare (n=1), together referred to as 'non-responders'. Responders achieved LLDAS at a median of 24 weeks [range 12-36] and remained in LLDAS for 76 weeks [56-92] out of 104 weeks of follow-up. In 7 patients with active LN, 6 attained a complete renal response. In responders, ANAs showed significant and specific reduction throughout 2 years with achievement of seronegative anti-dsDNA immunofluorescence in 6 out of 6 anti-dsDNA positive patients at baseline while total IgG, anti-tetanus and anti-rubella antibodies remained stable. By using HS-FACS, a median decrease of 97% [-99;+35] CD19+ B-cell depletion was achieved at 24 weeks. Long-term follow-up showed that B-cell repopulation was inhibited throughout 2 years with a persistent median decrease of 84% [-92;+22] compared to baseline. Further analysis of B-cell subsets revealed that in the responders, double negative (DN) B cells (CD27-IgD-) reached maximum depletion at 4 weeks (median 1.09×10^6 cells/liter [range 0.23×10^6 - 4.31×10^6]), which lasted up to week 72 with a median of 1.26×10^6 cells/liter [0.79×10^6 - 4.11×10^6] at week 72, similar to values at nadir. This was in contrast to non-responders, where maximum depletion of DN B-cells was reached at 12 weeks (0.48×10^6 [0.17×10^6 - 5.86×10^6]), after which these cells increased to 2.29×10^6 [0.49×10^6 - 4.39×10^6] at 24 weeks.

Conclusion: Over 2 years follow-up, RTX+BLM for severe, refractory SLE patients prevented complete B-cell repopulation with persistent and specific reduction of ANAs. Clinical response was observed in 67% of patients and treatment discontinuation due to high disease activity was associated with early repopulation of DN B-cells. These data warrant further studies on clinical and immunological benefits of combination treatment RTX+BLM.

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OP0043

WITHDRAWAL OF A LOW DOSE (5 MG) OF CORTICOSTEROIDS IN SYSTEMIC LUPUS IN REMISSION FOR MORE THAN A YEAR IS AT RISK OF RELAPSE – THE CORTICOLUP TRIAL

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Background: Glucocorticoids (GCs) are a mainstay of treatment for patients with SLE but are associated with significant adverse effects. Some SLE patients are maintained for a long-term under a low dose of prednisone to prevent relapse. There is no scientific data to sustain this therapeutic strategy.

Objectives: We hypothesized that maintaining a daily dose of 5 mg prednisone in patients with an inactive SLE for at least a year would prevent the risk of relapse.

Methods: The CORTICOLUP study (NCT0255817) was a prospective randomized, open-labeled, controlled, monocentric study sought to compare

maintenance vs withdrawing of low-dose of prednisone (5mg) to reduce SLE flares, conducted from January 2014 to March 2017. Inclusion criteria were SLE patients **who during the year** preceding the inclusion had 1/an inactive SLE defined by a SLEDAI-2K score ≤ 4 , a BILAG-2004 index C, D or E in all systems and a PGA =0 and 2/a stable SLE treatment including prednisone 5 mg daily. The primary end point was the number of patients with flares during 12 months of follow-up defined by the revised-SELENA SLEDAI Flare Index (rSFI). Secondary outcomes were occurrence of a BILAG scores A or B ≥ 1 , clinical SLEDAI-2k >0 , PGA ≥ 0.5 and increase of the SLICC damage index (SDI). All patients were included in the intention-to-treat analysis.

Results: A total of 124 patients (61 in the maintenance group and 63 in the withdrawal group) were included. No patients were lost to follow up. At baseline there were no significant differences between the maintenance and the withdrawal group with respect to: duration of SLE [mean ($\pm$ standard deviation) duration of 11.8 (± 0.9) versus 13.1 (± 1.0) years], duration of remission [55.7 (± 5.8) vs 67.5 (± 6.8) months], HCQ treatment [98.2% vs 100.0%], immunosuppressive drugs [27.9% vs 25.4%], previous renal involvement [34.4% vs 41.3%], low C3 [16.4% vs 15.9%], positive Farr test [47.5% vs 46.0%], and SDI [mean index of 0.5 (± 0.1) vs 0.7 (± 0.2)].

There were significantly more flares in the withdrawal group compared to the maintenance group (17 flares versus 4, $p=0.0034$ using the Fisher's exact test). Mild or moderate flares were more frequent in the withdrawal group compared to the maintenance group (12 vs 3, $p=0.029$). The occurrence of severe flare was not significantly different between the two groups (5 vs 1, $p=0.208$). More than two-thirds of the flares in the withdrawal group occurred within the first six months. Within the withdrawal group, using forest plot analysis, no significant association was found between the occurrence of a flare and age, sex, duration of SLE, duration of SLE remission, duration of GCs treatment, immunosuppressants and serological SLE activity at randomization. Four patients in the withdrawal group and none in the maintenance group experienced damage: 2 osteoporosis bone fractures, 1 hydroxychloroquine retinopathy and 1 cataract.

Conclusion: Withdrawal of low dose of steroids in patients with inactive SLE and stable therapeutic regimen for more than a year is associated with a high risk of relapse.

Disclosure of Interests: None declared

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OP0044

A SYSTEMATIC REVIEW AND META-ANALYSIS OF THE GONADOTOXIC EFFECTS OF CYCLOPHOSPHAMIDE AND BENEFITS OF GONADOTROPIN RELEASING HORMONE ANALOGUES IN WOMEN OF CHILD-BEARING AGE WITH AUTOIMMUNE RHEUMATIC DISEASE

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Background: Premature ovarian insufficiency (POI) is a side effect of intravenous cyclophosphamide (i.v.CYC), which is the treatment of choice for many severe manifestations of autoimmune rheumatic disease (ARD) (1). The risk of POI post-CYC appears to be dependent on cumulative dose and patient age but has not been precisely quantified. Gonadotropin Releasing Hormone Analogues (GnRHa) may reduce this risk (2). Studies however, on GnRHa and CYC use in ARD patients have been limited in size and/or by combined analysis with patients receiving CYC for malignancies.

Objectives: In order to more precisely categorise the risk of POI in ARD patients, and determine whether GnRHa are effective in reducing this risk, we performed a systematic review to assess the risk of sustained amenorrhoea with i.v.CYC in ARD and a meta-analysis of the efficacy of GnRHa in reducing this risk.

Methods: Using Preferred Reporting Items for Systematic Reviews and Meta-Analyses principles, we searched English language papers using Pubmed, MEDLINE, EMBASE and the Cochrane Library to April 2018. We included all studies

that reported the incidence of sustained amenorrhoea (defined as at least 12 months of amenorrhoea) during i.v.CYC treatment in patients with ARD; and those that assessed sustained amenorrhoea in patients receiving GnRhA and i.v.CYC, compared to controls receiving i.v.CYC alone.

Results: 1099 articles were identified and their titles and abstracts screened, following which 81 papers were selected for full text review. 31 studies were then identified that addressed the risk of sustained amenorrhoea with i.v.CYC in n=1382 patients with ARD. The majority of these patients had systemic lupus erythematosus (1326 out of 1382 patients, 96.0%). The mean age was 24.9 (range 13-36.1) years. Sustained amenorrhoea occurred in 269 patients (19.5%, range 0-54% depending on age and cumulative cyclophosphamide dose). The rate of sustained amenorrhoea significantly positively correlated with increasing cumulative cyclophosphamide dose, and occurred in patients with a mean age ranging from 13-36.1 years at mean cumulative doses ranging from 1-20.1g. A further 3 studies assessed ARD patients given i.v.CYC +/- GnRhA, including 56 patients (mean age range 23.9-25.6 years) receiving GnRhA and i.v.CYC, and 37 controls (mean age range 25-29.4 years) given i.v.CYC only. Sustained amenorrhoea occurred in 2/56 (3.6%) patients treated with GnRhA, compared to 15/37 (40.5%) of controls. The pooled odds ratio of sustained amenorrhoea with GnRhA and i.v.CYC compared to i.v.CYC alone was 0.0543 (95%CI 0.0115-0.2576, p=0.0002). The number needed to treat was 2.7 (95%CI 2.0-4.4) and the absolute risk reduction was 37.0% (95%CI 35.6-38.4%).

Conclusion: Although the risk of POI with i.v.CYC was associated with increasing age, it was observed across all age groups and from cumulative doses of 1g or more. GnRhA markedly reduced this risk in ARD, and therefore should be considered for concomitant use with i.v.CYC in all women of child-bearing age with ARD.

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OP0045

ABATACEPT TREATMENT OF PATIENTS WITH EARLY ACTIVE PRIMARY SJÖGREN'S SYNDROME – A RANDOMIZED, DOUBLE-BLIND PLACEBO-CONTROLLED PHASE III STUDY (ASAP-III)

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Background: Effective systemic treatment is not yet available for primary Sjögren syndrome (pSS). Abatacept (CTLA-4-Ig) targets the CD80/CD86:CD28 costimulatory pathway required for full T-cell activation and T-cell dependent activation of B-cells. IV abatacept was shown to be safe, well tolerated, and to decrease disease activity in an open-label study of 15 pSS patients.¹

Objectives: To assess the efficacy and safety of subcutaneous (SC) abatacept vs. placebo in patients with early active pSS.

Methods: The Abatacept Sjögren Active Patients phase III (ASAP-III) study is a monocenter, investigator-initiated, double-blind, placebo-controlled trial (NCT02067910). ASAP-III included 80 adult patients with biopsy-proven pSS, fulfilling the AECG and ACR/EULAR criteria, with a disease duration of ≤7 years and moderate to high EULAR Sjögren's syndrome disease activity score (ESSDAI ≥5). Patients were randomized in a 1:1 ratio to receive weekly SC abatacept (125 mg) or placebo for 24 weeks (figure 1). After the double-blind phase, all patients were treated with abatacept in a 24-week open label phase. Concomitant use of other DMARDs was not permitted, with the exception of a stable dose of prednisone (≤10mg). Rescue therapy with prednisone or cyclophosphamide was permitted after week 12. Participants visited

our pSS tertiary referral center nine times, to be evaluated by a multidisciplinary team of rheumatologists, ophthalmologists, and oral and maxillofacial surgeons.

The primary endpoint is ESSDAI at 24 weeks. Secondary outcomes over 24 and 48 weeks include clinical, patient reported, functional, histological, laboratory, ultrasound, and microbiome parameters, and the occurrence of (serious) adverse events and treatment discontinuation.

Results: Baseline characteristics of participants are shown in table 1. Database lock for the blinded stage is planned in March 2019. Subsequently, the first intention-to-treat analyses will be performed, focusing on the ESSDAI and EULAR Sjögren Syndrome Patient Reported Index (ESSPRI), quality of life (EQ-5D), unstimulated and stimulated whole salivary flow (UWS, SWS), Schirmer test, Ocular Staining Score (OSS), serological parameters (RF, IgG), and safety parameters.

Conclusion: The ASAP-III trial was designed to assess the clinical efficacy and safety of SC abatacept in pSS patients with short disease duration and active disease. The 24-week results will be available during the EULAR congress 2019.

Figure 1. Design of the ASAP-III study.

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Table 1: Baseline characteristics of participants (n=80)

Characteristics	Value
Age (years), mean±SD	48.8±15.6
Female, n (%)	74 (93)
Disease duration (years), median (IQR)	2.0 (1.0-4.0)
Anti-Ro/SSA, n (%)	71 (89)
Previous use of DMARDs, n (%)	34 (42.5)
Use of prednisone, n (%)	1 (2)
ESSDAI, median (IQR)	13 (8-17)
ESSPRI, mean±SD	6.7±1.6
EQ-5D index, median (IQR)	0.71 (0.57-0.84)
UWS (ml/min), median (IQR)	0.05 (0.01-0.13)
SWS (ml/min), median (IQR)	0.16 (0.04-0.35)
OSS*, mean±SD	4.5±3.4
Schirmer* (mm/5 min), median (IQR)	3 (0-10)
IgG (g/L), median (IQR)	18.2 (14.4-25.9)
RF (IU/ml), median (IQR)	25 (5-71)

* Average of left and right eye.

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OP0046

MULTICENTRIC STUDY COMPARING CYCLOSPORINE, MYCOPHENOLATE MOFETIL AND AZATHIOPRINE IN THE MAINTENANCE THERAPY OF LUPUS NEPHRITIS: 10 YEARS FOLLOW UP

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Background: The most effective drug for the maintenance therapy of severe forms of lupus nephritis (LN) is still a matter of debate.