activity states [remission (SLEDAI-2K=0) and lupus low disease activity state (LLDAS)], accrual of irreversible damage (SLICC damage index, SDI), number and severity of flares, and side-effects. Analyses were performed at quarterly intervals and only patients with at least 3 months of follow-up were included in the study.

Results: A total of 56 patients were included [53 women (94.6%), mean (SD) age 46.3 (12.7) years]. Evidence of serologic activity (low C3/C4 and/or high anti-ds DNA) was evident in 30 patients (53.5%). Most frequent manifestations were arthritis (82.1%), inflammatory rash (73.2%), active hair loss (57.1%), mucosal ulcers (26.8%) and leukopenia (10.7%).

Median (range) duration of follow-up was 9.1 (2.9 - 34.6) months. We observed a significant decrease in the SLEDAI-2K, physician global assessment (PGA) and daily prednisone dose over time, starting as early as 3 months after belimumab initiation (Table 1). This effect was significantly more pronounced in patients who were serologically active (SA) at baseline, even after exclusion of the serologic component of the SLEDAI [median (range) *clinical* SLEDAI-2K for SA patients: 7 (1–24) at baseline vs. 2 (0–16) at 6 months and 2 (0–16) at 12 months, $p<0.0001$ and p=0.013, respectively; for serologically inactive patients: 6 (2–23) at baseline vs. 6 (0–14) at 6 months and 5 (0–18) at 12 months, p=0.017 and p=0.024, respectively]. For patients with $\geq$12 months of follow-up (n=20), belimumab treatment resulted in a significant decrease in flare rate [median (range) total number of flares for the 12 months before and after belimumab treatment, 3 (0–7) and 0 (0–2), respectively, $p<0.0001$). 10 patients (17.8%) discontinued belimumab due to inefficacy after a median (range) 7.1 (5.5 - 20.4) months of therapy and 5 patients discontinued due to planned pregnancy. There were no drug discontinuations due to side-effects.

Table 1. Changes in disease activity and daily prednisone dose during treatment with belimumab

	Baseline (reference) n=56	3 months n=56	6 months n=47	9 months n=26	12 months n=22	18 months n=10	p value
SLEDAI, median (range)	8 (2-28)	6 (0-24)*	4 (0-20)*	4 (0-18)*	4 (0-18)*	3 (0-14)**	*p<0.001 **p=0.01
	Baseline (reference)	3 months	6 months	9 months	12 months	18 months	p value
PGA, median (range)	1.9 (1-3)	1.5 (0.3-3)*	1.5 (0.5-3)*	1.5 (0-2.2)*	1.15 (0-3)*	1 (0-2)***	*p<0.001 **p=0.18 ***p=0.01
	Baseline (reference)	3 months	6 months	9 months	12 months	18 months	p value
Pr dose, median (range)	7.5 (0-40)	7.5 (0-30)*	5 (0-25)*	5 (0-10)*	5 (0-30)**	4.3 (0-7.5)***	*p<0.001 **p=0.001 ***p=0.021
Low disease activity states, n(%)	Baseline	3 months	6 months	9 months	12 months	18 months	
LLDAS	0 (0)	10 (17.9)	15 (31.9)	10 (34.5)	5 (21.7)	4 (40)	
Remission	0 (0)	3 (5.4)	4 (7.1)	3 (5.4)	4 (7.1)	2 (3.6)	

Conclusions: In real-life clinical settings, belimumab is efficacious in controlling disease activity of SLE and permitting tapering of glucocorticoid dose. Similar to data from RCTs, this effect seems to be more pronounced in serologically active patients.

Disclosure of Interest: None declared

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AB0443 INFUSION REACTIONS TO RITUXIMAB IN SYSTEMIC LUPUS ERYTHEMATOSUS: A RETROSPECTIVE ANALYSIS

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Background: B-cell depletion with Rituximab (RTX) has been used since since 2000 in the treatment of Systemic Lupus Erythematosus (SLE). An issue with the use of RTX is the attrition rate due reactions during of following infusions. This can prevent re-treatment with RTX in patients with a good initial response to RTX and in whom other treatments had failed, this is especially important in SLE patients with limited biologic options.

Objectives: To identify the rates and patient characteristics of infusion reactions to RTX in patients with SLE.

Methods: A retrospective analysis of the SLE patient cohort receiving RTX at University College London Hospitals via examination of patient records was used to determine if there was a clinically significant reaction (from clinic letters or discharge summary) for each RTX infusion. One cycle of RTX refers to 2 infusions given 2 weeks apart. A descriptive analysis of the reaction was recorded as was the decision making surrounding the infusions.

Results: Records from 151 RTX-treated patients were reviewed with 13 excluded due to missing data. 138 remaining patients (130 females and 8 males, mean age (1st infusion) =33 years; range: 16–73) received a total of 478 individual RTX infusions (between 1–9 cycles). Prior to 2007, standard of care was to receive Cyclophosphamide (CYC) with each cycle. The total rate of infusion reactions was 5.85% (23 patients had 28 reactions). Of these 4 (50%) were males, 19 females (14.6%; *p*=0.009, Chi square). Average number of cycles in those without, compared to with a reaction was 1.61 vs 1.64. With 1st dose, 7 patients (25%) had reactions, 19 with 2nd (67.9%). 3 patients were retreated (1 twice); 2/3 had further reactions and the 3rd two further cycles without issues. Most were not retreated. Reactions ranged from mild to severe (Table 1). A total of 24 RTX reactions were categorized into: Immediate- unlikely immune mediated 4; likely cytokine release 7; IgE mediated 5; and bone pain reactions 2. Delayed-early (24–48hours) 1; and late (>48hours) 5; by a Clinical Allergist. 4 reactions were excluded from this analysis; 1 death as likely CYC induced (but occurred within 24 hours of RTX) and 3 due to lack of data.

Table 1. Severity of Infusion Reactions

Severity of reaction	Number of patients	% of total infusion reactions	Retreated?
Death	1	3.6%	N
Severe	3	10.7%	Y – 1 (had further reaction)
Moderate	7	25.0%	Y – 1 (2 further cycles)
Mild	8	28.6%	Y – 1 (2 further cycles)
Delayed	5	17.9%	Y – 1 (1 further cycle)
Unclassified	4	14.3%	N

Mild (infusion resumed/completed), Moderate (had to cease infusion reaction), Severe (hospital admission), Delayed/serum sickness.

Conclusions: The number of previous cycles was similar in patients who reacted versus those who did not. Patients were most likely to experience a clinically significant reaction with the second infusion. Males had higher incidence of reactions. Most (19%) were immediate and the majority (79%) of immediate and delayed reactions occurred during 1st (10) and 2nd (9) cycles. The total rate of infusion reactions in this cohort was lower than previously reported however this is likely contributed to by the limitations of a retrospective review. However 64% of reactions (11/17) in this cohort were significant, necessitating cessation of infusion or hospital admission.

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AB0444 EFFECT OF RITUXIMAB ON A SALIVARY GLAND ULTRASOUND SCORE IN PRIMARY SJÖGREN'S SYNDROME: RESULTS OF THE TRACTISS MULTICENTRE RANDOMISED TRIAL SUB-STUDY

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Background: B lymphocytes are important in the pathogenesis of primary Sjögren's syndrome (PSS), but two phase III trials (TEARS and TRACTISS) of the B cell depleting agent rituximab (RTX) failed to show an effect on their primary endpoints in PSS. Whilst RTX may lack efficacy in a non-stratified PSS population, other possible explanations for these negative results include the choice and timing of primary outcome. In a small single-site salivary gland ultrasound (SGUS) substudy in TEARS, more subjects in the RTX arm demonstrated improvement in parotid gland echostructure. Importantly, SGUS is an operator-dependent technique.

Objectives: To compare the effects of RTX versus placebo on SGUS in PSS, in a multicentre, multiobserver substudy of TRACTISS.

Methods: Subjects consenting to SGUS were randomised to 1000mg RTX or placebo given at weeks 0, 2, 24 and 26, and scanned at baseline and weeks 16 and 48. Sonographers completed a 0–11 total ultrasound score (TUS) comprising domains of echogenicity, homogeneity, glandular definition, glands involved, and size of hypoechoic foci. Baseline-adjusted values of TUS were analysed over time, modelling change from baseline at each time point. For each TUS domain we fitted a repeated measures logistic regression model to model the odds of a response in the RTX arm (defined as a 1 point improvement) as a function of the baseline score, age category, disease duration and time point.

Results: 66 patients (49.6% of the total study population) consented to SGUS, and 52 (39.1%; n=26 RTX and n=26 placebo) completed the baseline and at least one follow-up visit. Estimated baseline-adjusted TUS at week 16 was 6.2 (95% CI 5.4–7.0) for placebo and 5.0 (95% CI 4.4–5.6) for RTX, and at week 48, 6.1 (95% CI 5.5–6.6) and 4.8 (95% CI 4.2–5.4) respectively. Estimated between group differences (RTX-placebo) in baseline adjusted TUS were -1.2 (95% CI -2.1 to -0.3; p=0.0099) and -1.2 (95% CI -2.0 to –0.5; p=0.0023) at weeks 16 and 48. Glandular definition was the only domain to show statistically significant improvement with an OR of 6.8 (95% CI 1.1–43.0; p=0.043) at week 16 and 10.3 (95% CI 1.0–105.9; p=0.050) at week 48. Improvement of $\geq$1 point in TUS was associated with improvement in oral dryness VAS at week 16 (diff=15.9; CI 1.5 to 30.3; p=0.030) but not week 48 in the RTX arm.

Conclusions: TUS differed between study arms, favouring RTX. This encourages further research into SGUS as an imaging biomarker in PSS clinical trials.
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AB0445 HYDROXYCHLOROQUINE'S IMPACT IN RENAL BIOPSY AND OUTCOMES OF LUPUS NEPHRITIS

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Background: Given its immunomodulatory effects, hydroxychloroquine use is recommended in systemic lupus erythematosus (SLE). It is associated with a lower rate of appearance and of relapse of lupus nephritis (LN). LN is classically classified using ISN/RPS classification, but others indexes, such as the ones described by Austin and Hill, allow for the quantification of SLE activity in the kidney tissue.
Objectives: To analyze the association between the use of hydroxychloroquine and the activity of LN in the kidney biopsy.
Methods: Retrospective single center study of consecutive SLE and biopsy proven LN patients, diagnosed from 2010 to 2016. We evaluated the following outcomes: clinical remission, renal function and proteinuria at end of follow-up (g/24h). Complete remission was defined as a reduction of proteinuria to <0,5g/24h, inactive urinary sediment and serum creatinine <115% of baseline; partial remission same parameters, except proteinuria <1g/24h if initial value <3h/24h, or reduction to <3g/24h if initial value >3g/24h. Kidney biopsies were evaluated by the INS/RPS LN classification and the morphological indexes described by Austin and Hill, obtained after histomorphological review of renal biopsies. The studied predictor was the use of hydroxychloroquine. Statistical analysis was performed with STATA software, using one-way ANOVA, Qui2 and Pearson/Sperman test were appropriate.
Results: During 6 years, there were 46 biopsy-proven LN cases, 84,8% (n=39) woman, median 35 years old (27–42,5) and 57,6% (n=19) caucasian. 39 patients were already known to have SLE, 7,44 (1,13–12,3) years previously. Of those 39 patients, 46% were under hydroxychloroquine and 77% under other immunosuppression.
The median follow-up was 31,9 (13,2–45,6) months. Based on biopsy findings, 35 patients were started on immunosuppression – induction in 50% of cases with MMF and in 50% with cyclophosphamide; maintenance in 81% with MMF, the rest with azathioprine. Complete remission was achieved in 58% of patients, 27% achieving partial remission. We observed 4 LN relapses. At the end of FUP, we saw a 96% (n=44) patient survival, with a median serum creatinine of 0,8 mg/dl (0,7–0,99), eGFR 99,8 ml/min (71,2–116,8) and proteinuria of 0,6 g/24h (0,2–1,6). From those 46 patients, 30 were under immunosuppressive therapy at time of LN presentation, and 60% (n=18) were also under hydroxychloroquine. Table 1 summarizes the clinical findings:
With the use of hydroxychloroquine, we observed a lower histomorphological activity, as represented by a lower Hill biopsy index, and tendency towards lower Activity index. We also saw a tendency towards lower proteinuria.
Conclusions: Our data reinforces the recommendations of using hydroxychloroquine for its adjuvant role in SLE patients, as we saw a lower histomorphological activity in kidney biopsy, and a trend towards lower proteinuria.
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AB0446 ADDITIVE INHIBITION OF INTERFERONS, B AND T CELL ACTIVATION AND TFH-RELATED CYTOKINE CXCL13 BY LEFLUNOMIDE AND HYDROXYCHLOROQUINE SUPPORTS RATIONALE FOR COMBINATION THERAPY IN PSS PATIENTS

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Background: T and B cell-driven immunity is critically involved in immunopathology of pSS. Recently we demonstrated synergistic T and B-cell activation upon T cell triggering and TLR7/9-driven B cell activation in pSS patients, accompanied by synergistic induction of immunoglobulins and IFN-γ- and IL-17-producing T cells[1]. In addition, TLR7/9-expressing activated pDCs associated with increased type I IFNs and IFN-inducible genes are increased pSS patients. Several studies have shown that the DMARDs leflunomide and hydroxycholoroquine inhibit immune activation in pSS but only show moderate efficacy. However, LEF and HCQ target different pathways with overlapping, but also potentially additive mechanisms, where LEF primarily targets T and B cells and HCQ TLR7/9-driven B cell and pDC activation.
Objectives: To assess the additive effects of LEF and HCQ on CD4 T- and B-cell activation and production of interferons IFN-α and IFN-γ, Tfh-related cytokine CXCL13, as well as IgG and IgM *in vitro* employing SEB/TLR9-triggered PBMC.
Methods: PBMCs of healthy individuals (n=9) and of pSS patients (n=8) were cultured with antigen (SEB), TLR9 and their combination, in presence or absence of LEF, HCQ and their combination in clinical relevant concentrations. Proliferation of T and B cells and release of IFN-α, IFN-γ, CXCL13, IgG and IgM were measured.
Results: In line with robust T and B cell activation, IFN-γ, IFNα, CXCL13, IgG and IgM production was achieved by a combination of SEB and TLR9 (all at least $p<0.001$). LEF dose dependently inhibited B and T cell proliferation, Interferon, CXCL13 and immunoglobulin production. HCQ dose dependently inhibited B cell proliferation, IFN-α, CXCL13, and immunoglobulin production. T cell proliferation and IFN-γ production were inhibited by HCQ only at higher concentrations. At several suboptimal concentrations LEF and HCQ additively inhibited T cell proliferation both in healthy individuals and in pSS patients. (Figure 1). Significant additive effects were seen for all outcome measures except IFN-α. Since IFNa was already robustly inhibited by HCQ alone (eg.for pSS 90% at 3.3 μM, $p<0.001$), only trends towards additive effects were observed.

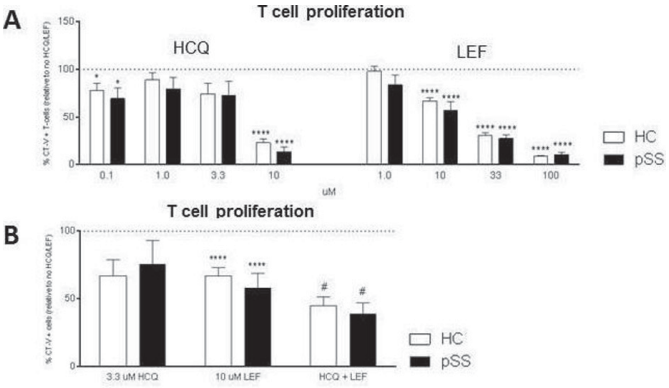

Figure 1. HCQ and LEF additively inhibit T cell activation. T cell proliferation is dose dependently inhibited by LEF and by HCQ at 0.1 and 10 μM **(A).** Significant additive inhibition of T cell proliferation is achieved by combination of suboptimal concentrations of LEF and HCQ both in HC and pSS patients **(B).** *and **** indicates statistical significance of p<0.05 and p<0.0001 resp. vs control, # indicates statistical significance of p<0.05 of the combination vs each of the single drugs.

Conclusions: LEF and HCQ robustly inhibited proliferation of T and B cells, cytokine production and immunoglobulin production with clear additive efficacy in both healthy individuals as in pSS patients. These data support the potential surplus value of combination therapy with LEF and HCQ for patients with pSS.
References:
[1] Bikker et al. Interleukin-7 and Toll-Like Receptor 7 induce synergistic B cell and T cell activation. PLoS ONE 9(4): e94756.
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AB0447 ANTIMALARIALS IMPROVE SURVIVAL OF SYSTEMIC LUPUS ERYTHEMATOSUS ON CHOLESTEROL: RESULTS OF A FIFTEEN-YEAR CHINESE MULTICENTER RETROSPECTIVE STUDY IN JIANGSU PROVINCE

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Abstract AB0445 – Table 1

Hydroxychloroquine use	Class II	Class III	Class IV	Class V	Hill Biopsy Index	Activity Index	Chronicity Index	End of FUP eGFR (ml/min)	End of FUP serum creatinine (mg/dl)	End of FUP proteinuria (g/24h)
Yes (n=18)	39%	28%	28%	22%	0,86 (0,2 – 1,8)	1 (0 – 4,25)	0,75 (0 – 3,25)	99,8 (81,9 – 112,1)	0,74 (0,7 – 0,8)	0,3 (0,1 – 0,6)
No (n=12)	8%	17%	58%	33%	1,52 (0,98 – 2,01)	7,25 (1,38 – 9)	2,25 (0,13 – 5,25)	98,6 (56,4 – 120,3)	0,78 (0,7 – 1,3)	0,75 (0,15 – 2,6)
p-value	0,09	NS	NS	NS	0,03	0,07	NS	NS	NS	0,09