pts with SLE and for those with moderate and severe disease vs. matched controls. For example, for pts with severe SLE vs. controls, mean costs for hospital stays, outpatient prescriptions, and other benefits were € 4335 vs. € 1,414, € 2582 vs. € 1,087, and € 1068 vs. € 691, respectively, in 2009.

Conclusions: In Germany, the economic burden of moderate and severe SLE was greater than that of sociodemographic- and morbidity-adjusted controls between 2009 and 2014. Pts with SLE incurred greater HCRU and total annual medical costs vs. matched controls. HCRU increased with increasing SLE disease severity, with the greatest burden among pts with severe disease. New treatments could reduce HCRU and future costs.

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FRI0319 A PRACTICAL SIMPLE DOSE ESCALATION REGIMEN FOR MILD HYDROXYCHLOROQUINE-INDUCED HYPERSENSITIVITY REACTION

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Background: In a recent Japanese clinical trial of hydroxychloroquine (HCQ), HCQ-induced hypersensitivity reaction occurred in 4.9% (5/103) including a case of Stevens-Johnson syndrome.¹ Several desensitisation methods were proposed, however the protocols were very complicated for routine practice.² Recently, a simple dose-escalation regimen of sulfamethoxazole-trimethoprim (SMX-TMP) showed better tolerability than standard dosing.³

Objectives: To investigate the incidence and risk factors of HCQ-induced hypersensitivity and propose a simple dose-escalation regimen for HCQ-induced hypersensitivity.

Methods: This is a single-centre, retrospective study. The subjects were Japanese SLE patients who started HCQ between Apr 1, 2009 and June 30, 2017 at Tokyo Metropolitan Tama Medical Centre. HCQ was prescribed with a dosage of 6.5 mg/ideal body weight (IBW) kg or less. We identified the cases of HCQ-induced hypersensitivity by reviewing electronic medical charts and pictures taken by patients or physicians. We diagnosed with HCQ-induced hypersensitivity if generalised eruption occurred within a month of starting HCQ and resolved completely after withdrawal of HCQ. We used the simple dose escalation regimen, starting from 40 mg/day with weekly increments by 40 mg, for patients with HCQ-induced hypersensitivity who did not require hospitalisation or systemic administration of glucocorticoids. We compared the clinical parameters (age, sex, dosage/actual or ideal body weight, starting dose, use of immunosuppressives, use of SMX-TMP, profile of autoantibodies) between patients with HCQ-induced hypersensitivity and those without HCQ-induced hypersensitivity. We also evaluated the success rate of our dose escalation regimen.

Results: Total 234 SLE patients were analysed. HCQ-induced hypersensitivity reaction were identified in 20 cases (8.5%). All cases developed mild generalised maculopapular rashes 17 (IQR 7.8–28.8) days after initiation of HCQ. No patient required hospitalisation or systemic glucocorticoid therapy. Among the clinical parameters compared, only anti-Sm antibody was associated with HCQ-induced hypersensitivity (table 1). HCQ was restarted in 10 patients using the simple dose escalation regimen. Among them 9 patients successfully continued HCQ and only one discontinued due to reappearance of mild hypersensitivity reaction.

	Patients with HCQ-induced hypersensitivity (n=20)	Patients without HCQ-induced hypersensitivity (n=214)	P value
Age, years (IQR)	38 (28-46)	40 (30-52)	0.490
Female, %	85.0	93.5	0.163
Body weight, kg (IQR)	50 (45-55)	52 (47-60)	0.178
Starting dose / IBW, mg/kg (IQR)	5.1 (4.0-6.0)	5.3 (4.5-5.9)	0.620
BAR (IQR)	20.3 (18.2-21.8)	20.8 (18.9-23.3)	0.241
HCQ starting dose			
- 100mg, %	5.0	0.5	
- 150mg	0	0.5	
- 200mg, %	45.0	43.0	
- 300mg, %	45.0	51.4	
- 400mg, %	5.0	4.7	
Usage of steroids, %	95.0	88.3	0.363
Dose of steroids, mg (IQR)	6.0 (5.0-12.5)	6.0 (4.0-9.0)	0.284
Usage of immunosuppressant, %	50.0	50.9	0.904
Usage of SMX-TMP, %	25.0	21.5	0.725
Liver dysfunction, %	9 (45.0)	0.5 (1/213)	0.759
Kidney dysfunction, %	10.0 (2/20)	5.6 (12/213)	0.432
Positive anti-dsDNA antibody, %	63.2 (12/19)	70.8 (149/209)	0.485
Positive anti-Sm antibody, %	60.0 (12/20)	34.2 (69/202)	0.022
Positive anti-RNP antibody, %	66.7 (10/15)	48.9 (85/174)	0.185
Positive anti-SSA antibody, %	40.0 (8/20)	55.5 (111/200)	0.185

Conclusions: HCQ-induced hypersensitivity reaction typically presents with mild generalised eruption 1–4 weeks after starting HCQ. Restarting HCQ with the simple dose escalation regimen may be a practical option for patients with mild HCQ-induced hypersensitivity reaction.

REFERENCES:

- [1] Yokogawa N, et al. Effects of Hydroxychloroquine in Patients With Cutaneous Lupus Erythematosus: A Multicenter, Double-Blind, Randomized, Parallel-Group Trial. *Arthritis Rheumatol* 2017;69:791–799.
- [2] Tal Y, et al. Hydroxychloroquine desensitization, an effective method to overcome hypersensitivity-a multicenter experience. *Lupus* 2017;1961203317735185.
- [3] Utsunomiya M, et al. Optimal regimens of sulfamethoxazole-trimethoprim for chemoprophylaxis of Pneumocystis pneumonia in patients with systemic rheumatic diseases: results from a non-blinded, randomized controlled trial. *Arthritis Res Ther* 2017;19:7.

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FRI0320 ANTIMALARIALS PROTECTIVE EFFECTS IN SYSTEMIC LUPUS ERYTHEMATOSUS IN CHINA

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Background: Hydroxychloroquine (HCQ) and chloroquine (CQ), both known as antimalarial drugs, have become fundamental therapeutic elements in systemic lupus erythematosus (SLE) in these decades. However, their specific benefits on organs or in a large cohort of Chinese SLE patients haven't been elucidated.

Objectives: This retrospective multicenter study sought to examine the potential protective roles of antimalarials in a large retrospect multicenter study of SLE patients in China.

Methods: Data were collected from 1372 patients' first and following hospitalizations during 1999 to 2009. Laboratory variables, medications, disease activity, organ involvements, and survival statuses were analysed according to antimalarial usage.

Results: Antimalarials improved the survival of SLE patients as an independent predictor (HR 0.503, p=0.000). Using antimalarials protected patients with longer disease duration (>2 years), SLEDAI (>15) on admission, high SLEDAI (>10) on discharge, organ involvements (cardiopulmonary, gastrointestinal, renal, hematologic), anti-dsDNA positive, and no application of cyclophosphamide. In second hospitalisation, compared to non-users, SLE patients who had been treating with antimalarial drugs had lower levels of total cholesterol (TC) (4.47 (0.13) mmol/L vs 5.03 (0.21) mmol/L, p=0.027) and less chance of anaemia (46.5% vs 58.2%, p=0.033).

Conclusions: Using antimalarials benefits outcomes of SLE patients through multiple facets in Chinese patients.

Disclosure of Interest: None declared

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FRI0321 SURVIVAL RATE AND CAUSES OF WITHDRAWAL OF BELIMUMAB TREATMENT IN SLE IN A REAL LIFE SETTING

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Background: Systemic Lupus Erythematosus (SLE) is a chronic disease requiring long-term treatment. Even though immunosuppressive therapies improved the survival rate, a great percentage of SLE patients exhibit a persistently active disease, or disease flares. Belimumab (BLM), is currently the only biological drug

approved for the treatment of active SLE patients not responding to standard of care, without active kidney or neuropsychiatric (NP) involvement.

Objectives: Aim of the study was to analyse 36 months survival of BLM treatment, causes of withdrawal in a monocentric cohort of SLE patients followed-up in a daily practice setting.

Methods: The study was proposed to all the patients starting BLM. After the informed consent was obtained, demographic, clinical and serological data, indication to BLM and concomitant therapies were registered. At baseline and at 6,12,24,36 months of follow-up, disease activity (SLEDAI 2K), DAS28, C3 and C4 levels, anti-dsDNA status and weekly dose of glucocorticoids were recorded. Data were expressed as median-interquartile range; after 6,12,24,36 months, differences in all parameters compared to baseline were evaluated (Student t test). The treatment survival was evaluated by Kaplan-Meier analysis. P value<0.05 were considered significant.

Results: We enrolled 39 Caucasian individual, 38 females, 1 male, with median age of 43 (IQR 7.5) years and median disease duration 14.5 (5.5) years. Indications for starting BLM were: mucocutaneous involvement (n=11,28%), arthritis (n=25,64%), systemic symptoms (n=3,7%) and lung involvement (1 pt,2%). At baseline, all the patients were taking PDN;97% hydroxychloroquine,23% mycophenolate mofetil,23% azathioprine, 5% cyclosporine, 7% methotrexate and 2% thalidomide. Table 1 summarises trend of SLEDAI 2K, C3 and C4, DAS28 (for articular involvement), prednisone dose and percentage of patients positive for anti-dsDNA during the follow-up. Fourteen out of the 39 patients (35.8%) reached 12 months of observation and only 4 the 24 months, 3 the 36 months. Figure 1 shows the survival curve of Belimumab. In 8 patients (20%) adverse events were the cause of BLM withdrawal (severe infection in one patient, severe bradycardia in one and acute infusion reaction in another one). In 4 patients (10%) BLM was discontinued for lack of efficacy (articular and skin manifestations) after 4, 8, 12 and 23 months respectively; in 6 patients (15%) for loss of efficacy; one patient developed a severe NP flare after 2nd BLM infusion and was admitted in our hospital for depression. One patient was lost during the follow-up. Two patients withdrew BLM therapy to plan a pregnancy. We found significant reduction of PDN week levels, and improvement of C4 and aDNA levels at T6; as for disease activity, we found significant reduction of DAS28 at T6, and of SLEDAI-2k at T6 and T12.

	T0	T6	T12
N° of patients	39	25	14
PDN mg/sett	52.5 (39.5)	35 (17.5)	35 (0)
SLEDAI 2K	6 (3.5)	2 (2)	2 (0.75)
C3	79 (19.75)	84.5 (17.5)	73.5 (9.75)
C4	13.5 (12.75)	7 (10) §	10 (10.25)
aDNA(%)	100	20	5
DAS28	4.32 (0.7)	3.3 (1.33)	3 (0.65)

Abstract FRI0321 – Figure 1. the figure shows patients mantaining treatment with Belimumab

Conclusions: In our monocentric cohort of SLE patients, BLM demonstrated to be effective on disease activity and serology and led to a significant decrease of glucocorticoids dose; the main causes of BLM withdrawal were adverse events or disease flares.

Disclosure of Interest: None declared

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FRI0322

RATIONALE FOR THE ATACEPT DOSE FOR A PHASE III STUDY IN PATIENTS WITH HIGHLY ACTIVE AND AUTO-ANTIBODY POSITIVE SLE

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Background: Atacept targets the B-cell stimulating factors BLyS and APRIL, and is currently in clinical development for the treatment of patients (pts) with active, auto-antibody positive SLE.

Objectives: Here, we evaluated integrated nonclinical, clinical and exposure-response (E-R) data from atacept studies to determine an appropriate atacept dose for a Phase (P) III study in SLE pts with high disease activity (HDA).

Methods: Nonclinical efficacy and pharmacokinetic (PK)/pharmacodynamic data for atacept were obtained from two murine models: An F1 hybrid NZBWF1/J spontaneous SLE model (given mouse Fc-protein control or mouse TACI-Fc 5 mg/kg intraperitoneal [IP] three times per week) and a 4-Hydroxy-3-nitrophenyl-acetyl-Keyhole Limpet Haemocyanin (NP-KLH) vaccinated C57BL/6 model to assess immunomodulation (given control protein 10 mg/kg or atacept 1, 3 or 10 mg/kg IP every third day). Clinical PK, efficacy, safety and E-R data were obtained from a PI PK study in healthy participants (Study 022; single dose atacept: 25, 75 or 150 mg) and two PII studies in pts with autoantibody-positive SLE (APRIL-SLE [EudraCT 2007-003698-13] and ADDRESS II [EudraCT 2013-002773-21]; randomization [1:1:1] to once weekly [QW] subcutaneous [SC] injections of atacept [75 or 150 mg] or placebo [PBO]). In APRIL-SLE, the primary endpoint was the proportion of pts with BILAG A/B flare over 52 weeks. In ADDRESS II, the primary endpoint was SRI-4 response at Week 24. SRI-6 response was analysed post-hoc in pts with HDA (SLEDAI-2K≥10) at Screening. A population PK model was established using data from the PI and PII studies. Population PK model-derived exposure vs probability of clinical response (BILAG A/B flare, SRI-4, SRI-6) was assessed, and an exploratory analysis of exposure vs safety performed.

Results: TACI-Fc 5 mg/kg prevented proteinuria development and glomerular damage in the F1 hybrid NZBWF1/J spontaneous SLE model. Anti-KLH IgG decreased markedly in atacept-treated NP-KLH vaccinated mice (>50% reduction vs control protein at all doses), with mean atacept serum trough concentrations (C_{min}) of ~2.3 µg/mL (1 mg/kg), ~5 µg/mL (3 mg/kg) and ~8.5 µg/mL (10 mg/kg). In post-hoc analyses of the proportion of pts with BILAG A/B flare and time to flare in APRIL-SLE, and SRI-4 and SRI-6 response in SLE pts with HDA in ADDRESS II, treatment with atacept 150 mg QW demonstrated greater clinical response vs PBO. In both studies, atacept E-R relationships based on population PK-derived exposure were observed. For maximal flare reduction, an atacept exposure of $AUC \geq 1 \text{ mg} \cdot \text{hr/mL}$ was identified. This exposure was more achievable with 150 than 75 mg (60% vs 15% probability) and corresponded to an atacept C_{min} of 5 µg/mL, which was similar to the C_{min} values observed in the NP-KLH vaccinated mouse model. Both atacept 150 and 75 mg had acceptable safety profiles in SLE pts, with no apparent E-R relationship observed for serious infections.

Conclusions: Integrated nonclinical, clinical and E-R data demonstrate an acceptable benefit-risk profile for atacept in SLE pts with HDA and support the selection of the 150 mg QW dose for a PIII study.

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