ulceration – 3, leukopenia – 4 patients. Patients were treated initially with 2 infusions of rituximab (1000 mg) given once every two weeks with premedication (methylprednisolone (250 mg) and chlorpyramine). Then all patients received maintenance therapy with rituximab 500 mg every 6 months. Duration of treatment and follow-up was at least 3 years. Median follow-up was 45 months (36–90). Patients were evaluated, using immunologic, subjective parameters, salivary/lacrimal function at baseline and in 24 weeks and then every year during the follow-up. Patients were not concomitantly treated with another immunosuppressant agent or glucocorticoids daily.

Results: All patients were women with a mean age at diagnosis of 49 years [29–70] and median duration of disease was 6 years (1–20). The average cumulative dose of rituximab was 10000 mg (7000–12000 mg). The median European Sjögren's Syndrome disease activity index (ESSDAI) decreased from 2.5 (2–3) to 0 (0–1) ($p=0.01$) by the end of the study. The increase in salivation and lacrimation according to Schirmer test and tear film break-up time was insufficient, however, in all patients the size of the salivary glands normalised and the recurrent parotitis stopped. Furthermore, 7 patients with severe keratoconjunctivitis sicca improved the course of the disease. The healing of corneal ulceration in all patients was observed one year after the initiation of therapy. A significant decrease in the RF level (from 198 IU/ml (51–442) to 71 IU/ml,^{30–73} $p=0.002$) and gammaglobulins (from 28%±5% to 19,3%±3,5%, $p=0.001$) was observed one year after this study beginning. Unreliable decrease of immunoglobulins was noted in 23% of patients by the end of the follow-up, that did not increase the risk of secondary infections. We observed good tolerability of therapy, only 4 patients had mild infusion reactions.

Conclusions: Rituximab therapy is highly effective, well tolerated and helps to avoid long-term use of glucocorticoids/cytotoxic agents in pSS.

Disclosure of Interest: None declared

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AB0505

EARLY AND SUSTAINED REMISSION IN SLE CAN BE ACHIEVED BY USING PULSE METHYL-PREDNISOLONE, HYDROXYCHLOROQUINE AND LOW-MEDIUM DOSE-PREDNISONE

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Objectives: To compare the different therapeutic schemes used in two longitudinal cohorts of patients with Systemic Lupus Erythematosus (SLE): the Systemic Autoimmune Diseases Unit of Cruces University Hospital, Barakaldo, Spain (cohort C), using a low-medium dose prednisone scheme; and the Internal Medicine Department of Bordeaux, France (cohort B) which follows the standard treatment guidelines.

Methods: We included patients from both cohorts diagnosed with (SLE from year 2000), with a follow-up from the time of diagnosis (inception cohorts) and for at least 5 years. We analysed the different use of glucocorticoids (prednisone and pulse methylprednisolone), hydroxychloroquine (HCQ) and immunosuppressive drugs in both cohorts. To compare the efficacy of both therapeutic schemes, we analysed the rate of clinical remission and clinical remission on treatment, according to the DORIS definitions, during the 5 years of follow-up

Results: 173 patients were studied: Bordeaux (B): 81 and Cruces (C): 92. Baseline clinical variables were similar between both groups, including demographics, autoimmunity and organ involvement. The baseline SLEDAI was: 8 (B) vs. 7 (C), $p=0.06$. The proportion of patients in treatment with prednisone was similar from year 1: 79% (B) vs. 72% (C), $p=0.269$, to year 5: 63% (B) vs. 55% (C), $p=0.315$. However, patients in cohort B received higher doses of prednisone: mean maximum dose at year 1: 38 mg/d (B) vs. 14 mg/d (C), $p<0.05$; at year 5: 8 mg/d (B) vs. 3 mg/d (C), $p<0.05$; average dose of prednisone at year 1: 15.8 mg/d (B) vs. 4.4 mg/d (C), $p<0.05$; at year 5: 6.6 mg/d (B) vs. 3.2 mg/d (C), $p<0.05$. Methyl-prednisolone pulses were ever used in 26% (B) vs. 42% (C), $p<0.05$; the mean total pulses per patient was 3 (B) vs. 7 (C), $p<0.05$; however, the mean total dose of methyl-prednisolone per patient was similar 1725 mg (B) vs. 1635 mg (C), $p=0.835$, revealing a lower dose per pulse in patients from cohort C. The proportion of patients in treatment with HCQ was lower in cohort B at year 1: 80% (B) vs. 97% (C), $p<0.05$ and at year 5: 73% (B) vs. 99% (C), $p<0.05$. Methotrexate was used more frequently in cohort C ($p<0.05$) with no differences in cyclophosphamide, azathioprine and mycophenolate use.

Clinical remission in both cohorts was as follows: year 1: 25% (B) vs. 40% (C), $p<0.05$; year 2: 29% (B) vs. 42% (C), $p=0.07$; year 3: 37% (B) vs. 42% (C), $p=0.54$; year 4: 37% (B) vs. 48% (C), $p=0.15$; year 5: 36% (B) vs. 49% (C), $p=0.08$.

Clinical remission on treatment: year 1: 43% (B) vs. 84% (C), $p<0.05$; year 2: 70% (B) vs. 87% (C), $p<0.05$; year 3: 73% (B) vs. 88% (C), $p<0.05$; year 4: 73% (B) vs. 93% (C), $p<0.05$; year 5: 73% (B) vs. 93% (C), $p<0.05$.

Conclusions:

- The more frequent use of hydroxychloroquine, pulse methylprednisolone and methotrexate in the Cruces cohort resulted in reduced doses of oral prednisone.
- Patients from the Cruces cohort achieved clinical remission earlier and in a more sustained way during the follow-up.

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AB0506

HYDROXYCHLOROQUINE HAS NO PROTECTIVE EFFECT ON THE DEVELOPMENT OF SYSTEMIC LUPUS ERYTHEMATOSUS IN 7004 PATIENTS WITH PRIMARY SJÖGREN'S SYNDROME: A NATIONWIDE POPULATION-BASED STUDY

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Background: Hydroxychloroquine (HCQ) has been proposed to be associated with later onset of systemic lupus erythematosus (SLE)¹ and is widely used in patients with primary Sjögren's syndrome (pSS) which may evolve to SLE.² We want to explore the potentially protective role of HCQ in the development of SLE among patients with pSS.

Objectives: This study was conducted to assess whether exposure to HCQ in pSS patients is associated with a reduction in the development of SLE.

Methods: This retrospective cohort used claims data from the National Health Insurance Registry Database (NHIRD) in Taiwan. Patients with incident Sjögren's syndrome (SS) from 2000 to 2010 in the Registry of Catastrophic Illness Database (RCIPD) of the NHIRD, which was certified by two rheumatologists, were identified. The date when SS was diagnosed in the RCIPD was defined as the index date. Those who were diagnosed as having SLE, rheumatoid arthritis, polymyositis, dermatomyositis, or systemic sclerosis in the RCIPD before the index date were excluded. Other exclusion criteria included¹ patients who were diagnosed as having SLE in the RCIPD within one year after the index date,² patients who withdrew from the NHIRD within one year after the index date, and³ patients who used oral, intramuscular, or intravenous corticosteroids, methotrexate, azathioprine, leflunomide, sulfasalazine, cyclosporine, tacrolimus, mycophenolate, mercaptopurine, or cyclophosphamide for more than or equal to 90 days within one year before or after the index date. The included SS patients who used HCQ for more than or equal to 90 days within one year after the index date were eligible to HCQ group. The study endpoint was defined as newly-diagnosed SLE in RCIPD or withdraw from NHIRD during the 14 year follow-up period (January 1st, 2000 to December 31st, 2013).

Results: A total of 7004 pSS patients were identified. The mean follow-up time was 6.9 years in the HCQ group ($n=4282$) and 7.0 years in the non-HCQ group ($n=2722$). There were 22 newly-diagnosed SLE (0.5%) in the HCQ group and 16 (0.6%) in the non-HCQ group. The overall event rate of SLE was 8.78/10,000 person-years in the HCQ group and 9.83/10,000 person-years in the non-HCQ group (adjusted hazard ratio 0.97, 95% confidence interval 0.50–1.88, in a Cox proportional hazard model).

Conclusions: There is no protective effect of HCQ on the development of SLE in patients with pSS.

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AB0507

BELIMUMAB IN PATIENTS WITH SYSTEMIC LUPUS ERYTHEMATOSUS: OUTCOMES IN ROUTINE CLINICAL PRACTICE

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Background: Systemic lupus erythematosus (SLE) is a systemic autoimmune disease with a wide range of clinical manifestations. The persistence of activity of the disease and the prolonged use of corticosteroids are amongst the main predictors of accumulated organ damage in patients with SLE. Therefore, we need new strategies to induce long-lasting remission and minimise the adverse effects of standard medications.

Objectives: to assess the effectiveness and safety of Belimumab in actual clinical practice during the first year of treatment in patients with SLE.

Methods: retrospective observational study of patients treated with Belimumab. This study involves 6 hospitals in Castilla y León (Spain). It collects clinical and analytical data before the start of Belimumab, and 6 and 12 months after the initiation of the therapy. The data collected include the daily dose of prednisone received at different time points and the activity of the disease was classified as mild, moderate and severe based on SELENA-SLEDAI index. A reduction from baseline of 3 points on the SELENA-SLEDAI indicates meaningful symptomatic improvement.

Results: Among the twenty-five patients were included, with a mean age of 43.7 ± 12.2 years, 72% were female and 96% caucasian. The average time from diagnosis of SLE to Belimumab infusion was 9.5 ± 7.1 years; 32% were diagnosed with SLE < 5 years ago. Up to 56% of the patients had moderate disease activity and only 8% patients had very high activity of the disease. All but one of the patients had previously received an immunosuppressant (azathioprine in 50% of the cases) and 16% of the sample had not responded to rituximab. The most frequent reasons for initiating Belimumab were an ineffective previous treatment regimen (60%), the intend to decrease steroid use (56%), and worsening patient condition (52%); whereas the most frequent manifestation of SLE in these patients were arthritis (44%), followed by mucocutaneous (20%) and immunologic findings (20%). As for immunologic markers of activity, DNA was elevated by 40% and 68% of the patients showed hypocomplementemia, that dropped to 24% in both cases at 12 months. The mean score of the SELENA-SLEDAI index decreased from 9.5 to 6 in the first 6 months and to 5.2 in the 12 months of follow-up. A reduction in the initial mean steroid dose was also observed from 20 mg/day to 8.9 mg/day and 6.4 mg/day at 6 and 12 months respectively. Hence, the dose of steroid was reduced by 68% during the first year (p=0.06). This reduction was clinically significant, but it did not reach statistical significance in our study. Two patients (8%) had discontinued Belimumab within the first 6 months of therapy (1 pregnancy and 1 worsening proteinuria); 34.7% had discontinued it within the first 12 months, mostly due to ineffectiveness (62.5%). Two patients with severe renal involvement (>1 gr proteinuria/24 hour) were treated with Belimumab, allowing to reduce the steroids to a low dosis (<7.5 mg/day) at 12 months.

Conclusions: Belimumab appears to be effective, reducing disease activity as measured by the SELENA-SLEDAI Index and, also, the mean dose of steroids needed, mainly after 12 months of treatment. No significant adverse effects were reported as previous studies have shown.

Disclosure of Interest: None declared

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AB0508

FIXED, LOW-DOSE HYDROXYCHLOROQUINE VERSUS WEIGHT-ADJUSTED DOSE IN SYSTEMIC LUPUS ERYTHEMATOSUS PATIENTS WITH LOW ACTIVITY

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Background: Optimal hydroxychloroquine (HCQ) dose to reduce ocular toxicity risk is 5 mg/kg or actual weight daily, according to new recommendations. In systemic lupus erythematosus patients (SLE) with low or no disease activity, fixed low-dose HCQ might be equally effective in relapse prevention weight-adjusted doses, thus resulting in lower cumulative dose.

Objectives: Our aim was to compare a fixed dose of HCQ 200 mg daily with a weight-adjusted dose (5 mg/kg of actual weight daily) in SLE patients with low activity.

Methods: SLE activity was assessed using the SLE Disease Activity Index (SLEDAI-2K), the Safety of Oestrogen in Lupus Erythematosus National Assessment (SELENA)-SLEDAI and the Physician Global Assessment (PGA, 0–3 scale) in each visit. Low-activity SLE (LLDAS) was defined according to Franklyn et al: 1) a SLEDAI-2K score ≤ 4, 2) no new SLE-related activity events compared with the previous visit, 3) a PGA score ≤ 1, 4) prednisone dose ≤ 7.5 mg daily and 5) stable

doses of maintenance immunosuppressant therapy. LLDAS was evaluated at baseline and months 3 and 6. In order to adjust doses to weight, and given the impossibility of fractionating HCQ tablets, the adjusted dose was calculated for every week. For example, for 62 kg patient, the calculated dose would be 5 mg × 52 kg = 260 mg daily, which would mean 1820 mg weekly. Therefore, the patient would receive 400 mg daily for 2 days and 200 mg daily for 5 days every week. A relapse was defined as an increase of SLEDAI scores ≥ 3, according to current recommendations

Results: A total of 50 LLDAS patients were compared, 25 with a fixed dose and 25 with a weight-adjusted dose. No significant differences regarding body weight between groups were observed: 52 kg (41–58.5 kg) vs. 51 kg (44–55 kg). Baseline activity scale scores were not significantly different. No patient relapsed on follow-up in either of both groups. Finally, the mean HCQ cumulative dose at 6 months was reduced by approximately 9.6 grams.

Conclusions: In LLDAS patients, a fixed HCQ dose of 200 mg daily may be as effective as the weight-adjusted dose in preventing disease relapses, thus resulting in a decrease in the HCQ cumulative dose and, therefore, a reduction of the risk of ocular toxicity.

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AB0509

KZR-616, A SELECTIVE INHIBITOR OF THE IMMUNOPROTEASOME, SHOWS A PROMISING SAFETY AND TARGET INHIBITION PROFILE IN A PHASE I, DOUBLE-BLIND, SINGLE (SAD) AND MULTIPLE ASCENDING DOSE (MAD) STUDY IN HEALTHY VOLUNTEERS

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Background: Proteasome inhibition is a standard of care for plasma cell malignancies. Bortezomib targets the constitutive proteasome and immunoproteasome, and is effective in the treatment of Systemic Lupus Erythematosus (SLE) and lupus nephritis (LN), but is associated with hematologic (e.g. thrombocytopenia) and constitutional (e.g. peripheral neuropathy) adverse events (AEs).

Objectives: We report the safety, pharmacokinetics (PK), pharmacodynamics (PD) and immunomodulatory effects of KZR-616, a first-in-class selective inhibitor of the immunoproteasome, in healthy volunteers (HV) following single and repeat subcutaneous (SC) administration.

Methods: Cohorts (6 drug:2 placebo) received single or 4 weekly SC doses. Safety assessments, PK and PD were measured to Day 7 (SAD) or Day 28 (MAD). SAD cohorts included 7.5, 15, 30 and 60 mg (SC). MAD cohorts included 30, 45, 60 mg, and 2 intrasubject escalation cohorts with 1 dose at 30 mg and 3 doses at 45 mg. PK was measured by LC/MS². PD was measured using enzymatic and active site binding assays. Inflammatory cytokine release was measured following *ex vivo* stimulation of whole blood in HV receiving placebo or 45 mg KZR-616.

Results: 32 HV (24:8) were enrolled in 4 SAD cohorts. The most common AEs were injection site reactions (ISRs), which were generally mild and transient. No clinically-significant (CS) laboratory or ECG abnormalities and no dose limiting toxicities were observed in the SAD subjects. Following SC administration, drug exposure increased dose proportionally and was characterised by rapid absorption (T_{max} 15–30 min) and clearance (T_{1/2} ~2 hours). Inhibition of the immunoproteasome exceeded 80% at ≥ 30 mg with significant recovery noted over 7 days. Constitutive proteasome inhibition was <37% in all cohorts.

40 HV (30:10) were enrolled in 5 SC MAD cohorts. In the initial cohort of 60 mg, a systemic drug reaction (chills, elevated heart rate, nausea) occurred ~8 hours after the first dose in 4 subjects. Dosing for this cohort was stopped. Subsequent cohorts (initiated at 30 mg) received prophylactic treatment with antihistamines ± prednisone 1 hour prior to the first and second dose. No similar AEs occurred with repeat dosing of 45 mg. No CS laboratory or ECG abnormalities were seen in the remaining MAD cohorts. ISRs did not appear to increase in severity or frequency with repeat dosing. There were no AEs of peripheral neuropathy, and 45 mg was well tolerated across 3 cohorts.

Consistent PK was noted following repeat administration and no drug accumulation was observed. At 45 mg, inhibition of 2 key subunits of the immunoproteasome, LMP7 and LMP2, was ~95% and ~70%, respectively. Reduced *ex vivo* stimulated production of multiple cytokines (IL-23, IL-6, TNF-α, IL-17) was noted in subjects receiving repeat administration of 45 mg KZR-616.