Fig 2: Positive Role of B Cells/Plasma Cells and Negative Role of Inflammation in Response to Obexelimab

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SAT0188

HIGH-DOSE STEROIDS ARE IMPORTANT CONTRIBUTORS TO THE INFECTION BURDEN OF PATIENTS WITH LUPUS NEPHRITIS

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Background: Infection remains a major cause of morbidity and mortality in patients with systemic lupus erythematosus (SLE) and lupus nephritis (LN) treated with systemic immunosuppression (IS).

Objectives: We sought to describe the infection profile in patients with LN treated with aggressive immunosuppression (induction and maintenance therapy) and to identify the associated risk factors.

Methods: Patients with LN followed in the Nephrology Department of Fundeni Clinical Institute, were retrospectively reviewed for any infection that occurred from initiation of induction therapy. Infections were graded (1-5) according to the Common Terminology Criteria for Adverse Events. Infection site and type of microorganism were also recorded. Univariate and multivariate Cox proportional hazard regression analysis were performed in order to identify independent risk factors for infection.

Results: The study cohort comprised 101 patients (86.1% females) with a mean age of 34 ± 14 years. Forty-eight patients (47.5%) had at least one infection with a total 92 episodes of infection occurring during a median follow-up of 17 months (IQR:8.5-52.5 months). The majority of patients (31 of 48) had infections during the first 12 months since IS treatment initiation. The most common site was lung infection (in 24.8% of patients), followed by urinary tract (20.8% of patients) and cutaneous/mucosal infections (11% of patients). Thirty-eight percent of patients had bacterial infections. Nineteen percent of patients had severe infections (grade 3 or higher) with 3.3% of infection-related deaths (3 patients). The most common induction regimen was cyclophosphamide in addition to corticosteroids (48.5%), with 44.6% of patients receiving pulse methylprednisolone and 45.5% of patients receiving more than 30mg/d of prednisone as the maximum oral dose. In univariate Cox regression analysis, female gender (HR 3.34; 95% CI, 1.03-10.8, p=0.04), pulse methylprednisolone (HR 2.9; 95% CI, 1.6-5.24, p=0.001), high-dose (≥30mg/day) oral corticosteroids (HR 4.22; 95% CI, 2.21-8.02, p=0.001) and SLEDAI score (HR 1.047; 95% CI, 1.012-1.084, p=0.008) were risk factors for infection. In multivariate Cox regression analysis, female gender (HR 6.35; 95%CI, 1.86-21.64, p=0.003), high-dose oral corticosteroids (HR 4.7; 95% CI, 2.25-9.87, p=0.003) and SLEDAI score (HR 1.046; 95% CI, 1.003-1.09, p=0.034) remained independent predictors of infection risk. Of the risk factors associated with severe infections (grade 3 or higher), in univariate analysis we identified younger age (HR 0.96, 95%CI, 0.92-0.99, p=0.035), neurological involvement (HR 2.59; 95%, 0.86-7.83, p=0.09), pulse methylprednisolone (HR 5.42; 95% CI, 1.79-16.35, p=0.003) and high-dose oral corticosteroids (HR 8.32;

95% CI, 2.4-28.77, p=0.001) as risk factors for infection. After multivariate adjustment, neurological involvement (HR 4.33; 95%, 1.29-14.51, p=0.01) and high-dose oral corticosteroids (HR 7.6; 95% CI, 1.6-35.39, p=0.01) were identified as independent predictors of infection risk.

Conclusion: A high-dose oral corticosteroid regimen increased the risk for any infection and for severe infections by 4.7-fold and 7.6-fold, respectively. In addition, female gender and a higher SLEDAI score were identified as risk factors for any infection, while neurological involvement was associated with an increased risk for severe infections.

References:

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SAT0189

SAMPLE SIZES AND RECRUITMENT RATES ARE DECREASING WHILE PLACEBO RESPONSE RATES ARE INCREASING IN CLINICAL TRIALS FOR SYSTEMIC LUPUS ERYTHEMATOSUS - A MANDATE FOR NEW STRATEGIES

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Background: Randomized controlled trials in Systemic Lupus (SLE) have shown disappointing results for decades. Key challenges may include the heterogenous population coupled with high placebo response rates.

Objectives: To evaluate trends in SLE study metrics over time and explore associations between primary endpoint failure and response in placebo/standard of care arms.

Methods: Data from Phase II or III trials which enrolled ≥ 100 patients with SLE and reported SRI-4 and/or BICLA responses after a minimum of 24 weeks were included in the analysis. Sample size, recruitment rates, regional patient distributions, and results in placebo arms (at 24-36 weeks or 48-52 weeks) were examined according to the start date of each study in order to determine trends over time. Placebo group SRI-4 response rates in studies that met their primary endpoint were compared with those that did not.

Results: Twenty-seven (14 phase II and 13 phase III) studies met the search criteria. Eleven of them met their primary endpoints. The study start dates ranged from Dec 2006 to Jan 2017. Mean/median total subject numbers were 461/349. Mean/median placebo subjects' age at baseline were 39.9/39.2 and SLEDAI: 10.6/10.6. Mean/median placebo SRI-4 responses at Week 24-36 were 47.2%/45.8% and 42.8%/43% at Week 48-52. For BICLA, the rates were 40.3%/37.2% at Week 24-36 and 33.2%/33.5% at Week 48-52.

As expected, lower placebo response was found in trials that met primary endpoints vs studies that did not (p=0.005). Total subject numbers and recruitment rates decreased over time while placebo SRI-4 response rates increased overall (Figure). However, there has been a greater range of placebo responses in more recent trials. Similar trends were observed in BICLA responses at Week 24-36 and 48-52, and in a corticosteroid reduction endpoint (percent of patients with reduction in steroid dose by ≥25% and to ≤7.5mg/day prednisone/equivalent) at Week 48-52. Enrollment of patients from North America decreased while proportions of Eastern Europeans increased over time (Figure).

Conclusion: High placebo response rates pose a continuing challenge in SLE studies and are associated with primary endpoint failures.

Clinical trial metrics have been changing over time, with declining size and recruitment rates, possibly due to competition from increasing numbers of studies.

Figure.

These trends should be considered while designing and conducting future trials. Attention to site training and data quality may be particularly important to control high placebo rates, especially as trial sizes decrease.

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SAT0190

CORTICOSTEROID AND OPIOID USE REMAIN HIGH IN SYSTEMIC LUPUS ERYTHEMATOSUS (SLE) PATIENTS RECEIVING BIOLOGIC THERAPY: A RETROSPECTIVE CLAIMS DATABASE ANALYSIS

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Background: SLE is managed by variable combinations of five drug classes: antimalarials, biologics, corticosteroids, non-steroidal anti-inflammatory agents, and immunosuppressants. Opioids are commonly prescribed to SLE patients despite not being effective for the management of long-term musculoskeletal pain.¹

Objectives: To describe corticosteroid and opioid use among SLE patients in the United States, and the impact of belimumab initiation on prescribing patterns.

Methods: This retrospective study used MarketScan administrative claims databases to select insured adults, age ≥18, with a diagnosis (ICD-9/10 710.0 & M32) of SLE between 1/1/2012 and 5/31/2018 (earliest SLE diagnosis = index date). Patients were followed from index through the earliest of health plan disenrollment or 5/31/2019 (minimum of 12 months). Corticosteroid use was measured in the 12 months following SLE index date. Average daily dose of oral corticosteroids in prednisone equivalents was measured for 12 months after corticosteroid initiation. Opioid use was measured overall, and by strength and length of treatment (chronic use defined as >90 days of supply). Oral corticosteroid and opioid use were compared in the 6 months before and after initiation of belimumab.

Results: Of 49,413 SLE patients eligible for analysis, mean [SD] age was 50.1 [14.0] years, 90.2% were female, and average follow-up was 3.6 [1.9] years. 89.8% of patients received any SLE treatment and 68.5% received corticosteroids. The average number of corticosteroid prescriptions was 4.6 [4.1] during 12 months of follow-up. 52.6% of patients had ≥1 claim for an opioid prescription in the 12 months after SLE index and 34.6% were identified as having chronic opioid treatment. Among patients with oral corticosteroid treatment and 12 months of study enrollment post-corticosteroid initiation, the average daily dose for oral corticosteroids was 19.4 [14.2] mg and 59.6% had a high average daily dose of >15mg (Figure 1). Among 1,710 patients with belimumab treatment and 6 months of study enrollment after the first prescription, use of oral corticosteroids decreased by 9.1% (p=0.001), average daily dose decreased from 14.5 [18.4] mg to 11.9 [18.0] mg (p<0.001) in the 6 months post initiation as compared to the 6 months prior. However, 48.6% of patients remained on a medium (7.5mg – <15mg) or high dose (≥15mg). Initiation of belimumab resulted in no change in opioid use (Table 1).

Table 1.

	Before Belimumab		After Belimumab		p-value, pre vs. post Belimumab
	(N = 1,710)		(N = 1,710)		
Patients with an oral steroid prescription (N, %)	1,242	72.6%	1,086	63.5%	0.001
Number of prescriptions (Mean, SD)	2.3	2.3	2.1	2.3	<0.001
Average daily dose (Mean, SD)	14.5	18.4	11.9	18.0	<0.001
Low average daily dose (>0 to <7.5mg) (N, %)	210	12.3%	255	14.9%	0.037
Medium average daily dose (7.5 - <15mg) (N, %)	389	22.7%	334	19.5%	0.041
High average daily dose (15mg or more) (N, %)	643	37.6%	497	29.1%	<0.001
Patients with an opioid prescription (N, %)	901	52.7%	861	50.4%	0.341
Weak opioids	356	20.8%	312	18.2%	0.089
Strong opioids	699	40.9%	695	40.6%	0.915
Acute Opioid Use	538	59.7%	486	56.4%	0.165
Chronic opioid use	363	40.3%	375	43.6%	0.165

Conclusion: These results suggest that a strikingly high proportion of patients with SLE are treated with corticosteroids to control the disease and opioid therapy to manage chronic pain. While there was no change in opioid use, corticosteroid use decreased following initiation of belimumab.

References:

[1] Chen SK, Feldman CH, Brill G, et al. Use of prescription opioids among patients with rheumatic diseases compared to patients with hypertension in the USA: a retrospective cohort study. *BMJ* 2019;9:e027495

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Figure 1: Steroid Dosing During the 12 Months Following Initiation of Oral Steroids

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SAT0191

PLASMA PROTEOMICS IDENTIFIES A PROTEIN SIGNATURE ASSOCIATED WITH RESPONSE TO RITUXIMAB IN PATIENTS WITH SLE

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Background: Rituximab (RTX) is B cell-depleting biological therapy used in the treatment of systemic lupus erythematosus (SLE). Response rates are typically around 50% and there are currently no robust biomarkers to identify which patients are more likely to respond.

Objectives: To determine whether proteomic analysis of baseline plasma samples could identify novel biomarkers of response to RTX in patients with active SLE.

Methods: Patients with SLE (≥ 4 ACR criteria) receiving RTX for active disease (BILAG A or 2 BILAG B scores) from the UK-based BILAG-BR register were included. Improvement at 12 months was defined as a reduction to ≤ 1 BILAG B score with no increase in either SLEDAI score or steroid dose. Proteomic analysis was performed on baseline plasma samples using sequential window acquisition of all theoretical fragment ion spectra mass spectrometry (SWATH-MS). Data were aligned and normalised to give relative protein abundance. A Lasso penalised logistic regression, with an outcome of improvement at 12 months, was used to perform the variable selection procedure using the R package 'glmnet'. The penalty metric was set at the value which minimised deviance in a 10-fold cross-validation procedure. Confounding variables of sex, age, ethnicity, oral steroid dose, and SLEDAI score had no penalty applied and were thus forcibly retained in the model. Protein-protein interaction networks were visualised using STRING v11.0.

Results: 70 patients of whom 63/70 (90%) were female with a median (IQR) age of 41 (32, 51) years and disease duration of 11 (6, 20) years at baseline were included. Patients had active disease with a median SLEDAI score of 10 (6, 16). All patients received RTX according to NHS England guidelines. Of 829 proteins, 815 were detected in at least 1 patient. We identified 9 proteins which were associated with clinical improvement at 12 months. A literature search identified that these proteins have relevance to T cell function, complement activation and lupus nephritis. Gender had the greatest weight in the model followed by Serpin Family A Member 10 (SERPINA10) and complement factor B (CFB). Protein interaction networks linked SERPINA10 to CFB by C3 complement (figure).