Conclusions: LN exosomes can enhance the proliferation and secretion of mesangial cells in which PI3K/AKT pathway is activated. This tip us exosomes may involve in the pathogenesis of LN.

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FRIDAY, 15 JUNE 2018

SLE, Sjögren's and APS – clinical aspects (other than treatment)

FRIO302 SYSTEMIC LUPUS ERYTHEMATOSUS-ASSOCIATED THROMBOTIC MICROANGIOPATHIES IN 60 PATIENTS: CLINICAL FEATURES, PROGNOSIS AND TREATMENT IN A FRENCH MULTICENTRIC COHORT

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Background: The occurrence of a TMA during SLE is a rare event that complicates 1% to 4% of lupus. The full spectrum of TMA can be encountered in the course of SLE: acquired thrombotic thrombocytopenic purpura (TTP), TMA associated with glomerulonephritis (TMA GN), atypical hemolytic uremic syndrome (aHUS), microangiopathic antiphospholipid syndrome (MAPS; defined or probable catastrophic antiphospholipid syndrome) or HELLP syndrome during pregnancy.

Objectives: To describe the clinical phenotype of TMA in lupus, to specify the prognosis and to identify factors allowing early classification and management of the different subtypes.

Methods: We performed a French multicentric retrospective study from January 1987 to December 2017 in units of internal medicine, nephrology and ICU. Inclusion criteria associated SLE defined by the ACR and/or SLICC criteria and a TMA defined either by the presence of microangiopathic anaemia and peripheral thrombocytopenia, either by histological signs of TMA.

Results: 68 events of TMA occurred in 60 SLE patients; median age was 24 years; 56 women (F/M ratio: 14). Diagnosis of SLE was assessed at a paediatric age in 24 (35.8%) patients. Clinical manifestations of SLE were: acute cutaneous lupus (n=48, 71%), arthritis (n=36, 53%), pleuritis (n=13, 19%), pericarditis (n=25, 37%), renal involvement (n=39, 57% including 20 class IV glomerulonephritis) and auto-immune cytopenia (n=22, 32%). Triggering factors of TMA were: lupus flare (n=38), infections (n=12), pregnancy and peripartum (n=3), or therapeutic rupture (n=4). Clinical and biological features at diagnosis of each subtypes of TMA are presented in table 1. A platelet count lower than 28 000/mm³ was predictive of TTP diagnosis (Se=90,5%, Sp=88,5%), likewise a creatinine plasma level greater than 100 µmol/L was predictive of TMA GN (Se=88,5%, Sp=85%). The treatment of TMA included (alone or in combination): corticosteroids in all cases, plasma exchange (n=52), cyclophosphamide (n=28), Rituximab (n=15), Eculizumab (n=2), antiplatelet agent (n=36), and/or effective anticoagulation (n=26). The median duration of follow-up was 150 months. Among TMA GN patients, the final median GFR was 58 mL/min (range: 0–120) with 5 individuals on chronic dialysis and 1 kidney transplant. Among TTP patients, one died from TMA, whereas the final median GFR of survivors (n=59) was 97 mL/min (range: 64–150), without any patient requiring dialysis.

Table 1 Comparisons of clinical and laboratory data in different subtypes of TMA in SLE

	TTP	TMA GN	MAPS	HELLP syndrome	Anti-factor II autoantibody
Number of events	28	28	12	5	1
Gender (female/male)	18/10	13/15	11/1	3/2	1/0
Age at diagnosis of SLE (median [range], years)	24.3 [7-46]	23/3	14.3 [3-51]	24 [18-30]	30
Age at diagnosis of TMA (median [range], years)	24 [3-52]	27.5 [18-56]	41 [28-59]	29 [24-34]	30
Number with neurological disorder (%)	12 (46)	15 (50)	2 (17)	2 (57)	1
Number with acute renal failure (%)	12 (46)	26 (100)	12 (100)	2 (57)	0
Hb (median ± SE, g/L)	7.2 ± 2.3	7.35 ± 1.8	6.79 ± 1.3	6.3 ± 2.3	6.4
Haematocrit (median [range], %)	18.3 [7-40]	18.5 [10-43]	14.2 [10-41]	10 [10-31]	41
Creatinine levels (median ± SE, µmol/L)	80 ± 36.4*	309 ± 206*	128 ± 280	187 ± 142	36
CS (median ± SE)	0.90 ± 0.24*	0.3 ± 0.22*	0.79 ± 0.25	1.1 ± 0.4	1.19
Anti-ONA (median ± SE, ELISA R.U.)	200 ± 241	232 ± 220	300 ± 160	100 ± 140	31
ADAMTS13 activity (median ± SE, %)	9 ± 2*	48 ± 24*	42 ± 10	Not available	65
Urine protein (median ± SE, g/24h)	0.3 ± 1.3*	4 ± 2.3*	2 ± 2.3	3 ± 1.7	0.1
Hematuria (number of patients, %)	9 (34)	17 (64)	5 (42)	0	0
aCL positivity (number of patients, %)	9 (34)	4 (15)	11 (92)	0	0
Anti-beta2GPI (number of patients, %)	1 (3)	1 (3)	1 (8)	1 (25)	0

Abbreviations: SLE = systemic lupus erythematosus, TMA = thrombotic microangiopathy, Hb = hemoglobin, aCL = anticardiolipin, TMA GN = thrombotic microangiopathy associated with glomerulonephritis, MAPS = microangiopathic antiphospholipid syndrome, HELLP = hemolysis, elevated liver enzymes, low platelets.

* p < 0,05 in comparison between patient suffering from TTP or TMA GN with the rest of the cohort.

Conclusions: SLE-associated TMA is a heterogeneous syndrome. TTP with a decreased ADAMTS13 activity and a low platelets level (<28000/mm³) have a good renal prognosis, whereas TMA GN with a high creatinine level (>100 µmol/L)

have a poor renal prognosis. Early subtypes classification is mandatory for the clinician to provide prompt and appropriate management of this life-threatening complication.

Disclosure of Interest: None declared

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SLE, Sjögren's and APS – treatment

FRI0303 EFFICACY AND SAFETY OF USTEKINUMAB IN PATIENTS WITH ACTIVE SYSTEMIC LUPUS ERYTHEMATOSUS: RESULTS OF A PHASE 2, RANDOMISED PLACEBO-CONTROLLED STUDY

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Background: IL12 and IL23 have been linked to SLE pathogenesis.

Objectives: The anti-IL12/23 monoclonal antibody ustekinumab (UST) was evaluated in pts with active SLE.

Methods: We conducted a Ph2, PBO-controlled study in 102 pts with active SLE. Pts were randomised(3:2) to UST IV~6 mg/kg or PBO at wk0, followed by UST SC 90 mg or PBO injections q8w, both added to standard care. Primary endpoint was proportion of pts achieving SLE responder index(SRI)–4 response at wk24. Secondary endpoints were change from baseline(BL) in SLEDAI-2K, PGA and BICLA response. Additional pre-specified endpoint analyses included no BILAG worsening(defined as no new BILAG A and ≤1 new BILAG B) and BILAG flare (≥1 new BILAG A or ≥2 new BILAG B).

Results: SRI-4 response occurred in 60% UST vs 31% PBO pts(p=0.005) at wk24 (table 1). UST pts had greater median change from BL in SLEDAI-2K and PGA vs PBO. No difference was observed in BICLA response at wk24; however, in the UST group vs PBO, more pts had no BILAG worsening, and the risk of a new BILAG flare was significantly lower(HR 0.11 [95% CI 0.01–0.94];p=0.0078). UST demonstrated improvement in musculoskeletal and mucocutaneous disease features vs PBO (table 1). Through wk24, 78% UST vs 67% PBO pts had ≥1 AE; 8.3%–9.5%, respectively, had ≥1 SAE; there were no deaths. The overall safety profile was comparable between UST and PBO.

Abstract FRI0303 – Table 1. Efficacy Results at Wk 24.

	PBO	UST
Pts randomised, n	42	60
SRI-4 response, n (%)	13 (31.0)	36 (60.0)
P value		0.005 ^a
Change from baseline SLEDAI-2K, median (range)	–2.0 (–20; 10)	–6.0 (–10; 3)
P value		0.026 ^{a,b}
Change from baseline PGA, median (range)	–1.6 (–5.6; 2.7)	–2.5 (–6.6; 2.8)
P value		0.211 ^{a,b}
BICLA response, n (%)	14 (33.3)	21 (35.0)
P value		0.994 ^a
Pts with no BILAG worsening, n/N (%)	11 (26.2)	29 (48.3)
P value		0.028
Pts with ≥50% improvement from baseline in joint activity ^c , % (95% CI)	63.2 (61.7–64.6)	87.7 (86.8–88.6)
P value		0.021 ^d
Pts with ≥50% improvement from baseline in CLASI activity score ^e , % (95% CI)	25.2 (23.1–27.4)	58.7 (57.4–60.1)
P value		0.043 ^e

^aPrespecified analyses; all other analyses were post-hoc.

^bOne-sided test for no difference between treatment groups using a Wilcoxon non-parametric median test for difference of location

^cPt subpopulation (67% of total) with ≥4 active joints at baseline

^dPt subpopulation (58% of total) with baseline CLASI activity score ≥4

^eProportion of responders and p values based on mITT analysis using a multiple imputation model for missing data from wks 16 to 24

BICLA, BILAG-based Combined Lupus Assessment; BILAG, British Isles Lupus Assessment Group; CLASI, Cutaneous Lupus Erythematosus Disease Area and Severity Index; SLEDAI-2K, Systemic Lupus Erythematosus Disease Activity Index 2000 PGA, physician's global assessment

Conclusions: UST treatment showed efficacy in pts with active SLE and was well-tolerated. UST may work via a novel mechanism of action in SLE.

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FRI0304 LONG-TERM AND LOW-DOSE IL-2 THERAPY MAINTAINS THE TH17/TREG BALANCE IN PERIPHERAL BLOOD OF PATIENTS WITH PRIMARY SJÖGREN'S SYNDROME

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Background: Primary Sjögren's syndrome (pSS) is a chronic autoimmune disease mainly affecting exocrine glands. To date, evidence-based guidelines for the management of pSS are lacking. Regulatory T cells (Tregs) are crucial in maintaining immune tolerance and immune homeostasis, but their role in pSS is unclear. Furthermore, low-dose Interleukin-2 (IL-2) has been shown considerable curative effect on expansion of (Tregs) in patients with GVHD. However, the effects of low-dose IL-2 on Tregs and Th17 cells in pSS are not fully elucidated.

Objectives: To explore the long-term effects of low dose IL-2 on Treg cells, Th17 cells and the ratio of them in peripheral blood of Chinese Han patients with primary Sjögren's syndrome.

Methods: A total of 190 pSS patients consented at enrollment to donate PB samples for comprehensive immune-phenotyping. In the study, BD Trucount tubes with the lyophilized pellet of a known number of internal counting beads were used for determining absolute counts of total CD4⁺ T cells in PB and then calculating the absolute number of Th17 cells and CD4⁺Tregs. Eighty eight in 190 were given low-dose recombination human IL-2 (rhIL-2, 2.50 WIU/day for 5 days and then 50WIU/w for several months) by hypodermic injection combined with standard therapy, which includes glucocorticoid, immune-suppressants, biological agents or combination of them, while others (12 in 69) were given standard therapy only.

Results: (¹The absolute number of Treg cells decreased significantly in peripheral blood of pSS patients compared with that of healthy control.²After short period therapy of low dose rhIL-2, Treg cells increased rapidly in one week but decreased to a lower level after one month[20.91 (9, 31.75) vs. 130.31 (65.18, 170.12) vs. 30.37(, ^{16, 44} p<0.01]. At the same time the ratio of Th17/Treg cells decreased rapidly in one week but increased to a higher level after one month[0.23 (0.19, 0.33) vs. 0.09 (0.04, 0.18) vs. 0.18 (0.14, 0.69), p<0.1].³Long-term IL-2 could maintain the higher level of CD4⁺Treg cells and the balance of Th17/Treg.⁴Patients with balanced Th17/Treg have more obvious improvement of symptoms and more significantly decreased dose of glucocorticoid and HCQ compared with standard therapy group.

Abstract FRI0304 – Figure 1. The change of absolute numbers of Treg cells (A) and the ratio of Th17/Treg (B) after short-term and low-dose IL-2 therapy. (A) Absolute number (cells/μl) of Treg cells increased rapidly 7 days after IL-2 therapy but decreased to a lower level after 30 days. (B) Ratio of Treg cells decreased rapidly 7 days after IL-2 therapy but increased to a higher level after 30 days. Data are presented as median (Q1, Q3). Statistical analysis was performed using the Related Samples Friedman's Two-Way Analysis of Variance by Ranks. * P<0.05, ** P<0.01, *** P<0.001 vs. Healthy controls. Asymptotic significances (2-sided tests) are displayed. The significance level is p<0.05.

Conclusions: Therapy of low dose rhIL-2 could promote the proliferation of Treg cells and rebuild the balance of Th17/Treg for both short and long term. To rebuild