FRI0333

B-CELLS DEPLETION AS RESCUE THERAPY FOR EXTRA-CRITERIA MANIFESTATIONS OF PRIMARY ANTIPHOSPHOLIPID SYNDROME

S. Sciascia¹, M. Radin¹, I. Cecchi¹, E. Rubini¹, D. Rossi², M. Bazzan³, D. Roccatello¹. ¹Department of Clinical and Biological Sciences, Università Degli Studi Di Torino; ²Ospedale S. Giovanni Bosco, Turin, Italy; ³UOSD Hematology and Thrombosis Unit, Ospedale S. Giovanni Bosco, Turin, Italy

Background: While immunosuppressive drugs may be helpful in patients with active systemic autoimmune diseases, their use in antiphospholipid syndrome (APS) is still controversial, and mainly limited to very selected cases of catastrophic APS or in severe cases refractory to standard therapy.¹ B-cells are likely to play a central role in the generation of the aPL-induced clinical manifestations of the disease, so they might constitute a logical therapeutic target in APS.

Objectives: To investigate PAPS patients with extra-criteria manifestations of APS treated with Rituximab (RTX) as a rescue therapy.

Methods: We retrospectively retrieved data from patients who attended the S. Giovanni Bosco Hospital, Turin, Italy, who met the following inclusion criteria: a) persistent aPL positivity and fulfilled the Sydney criteria for PAPS² b) presented with at least 1 extra-criteria manifestation; c) were treated with RTX as a rescue therapy (e.g. because they were refractory/intolerant/contraindicated to standard therapy) for the management of extra-criteria manifestations of APS.

Results: This retrospective study included 7 consecutive PAPS patients [median age 53 (range 38–66), female 6:1]. Table 1 resumes the characteristics of the PAPS patients included in the study. Six patients presented with severe thrombocytopenia (plts <50.000/mm³) and 1 patient presented with recurrent superficial venous thrombosis (3 events in 6 months despite ongoing anticoagulation therapy with VKA). Previous therapies included intravenous immunoglobulins (5 patients) and high doses of steroids (3 patients). One patient received RTX as rescue therapy as a steroid-sparing agent because of the high cardiovascular risk (high body mass index, uncontrolled arterial hypertension, and diabetes). We observed a full response after treatment with RTX in 6 out of 7 patients (86%, 5 with thrombocytopenia and 1 with recurrent superficial thrombosis). One patient who did not respond to the B-cell depletion therapy, and was treated with a splenectomy 1 month after RTX therapy and platelets levels normalised 3 months after the procedure. Overall, median time free from relapse was 27.5 months (range 4–97), no adverse events were reported, no patients developed infections.

Abstract FRI0333 – Table 1. Patients with PAPS with extra-criteria manifestations that followed a B-cells depleting protocol from the experience of our centre

	Age	aPL profile	Clinical manifestations of APS	Extra-criteria manifestations	RTX Protocol	Adverse events	Previous Immuno modulator Therapy	Anticoagulation therapy	Time free from relapse (months)
Patient 1 (male)	45	Triple positivity	1 episode of TVP and PE, 1 episode of retinal thrombosis	Recurrent superficial venous thrombosis	CYC 750mg/weekly for 2 weeks and RTX 375 mg/m ² weekly for 4 weeks + 2 monthly infusions	None	IVIg	Warfarin, target INR 2.5-3.5	10-ongoing
Patient 2 (female)	38	Triple positivity	1 episode of stroke	Severe thrombocytopenia	RTX 375 mg/m ² weekly for 4 weeks + 2 monthly infusions	None	IVIg	Warfarin, target INR 2-3	94-ongoing
Patient 3 (female)	46	Triple positivity	1 retinal haemorrhage, 1 thrombosis of dural venous sinuses, 1 thrombosis of the jugular vein	Severe thrombocytopenia	RTX 1g/15 days, 2 infusions in total	None	IVIg, high doses of steroids	Warfarin 2.5-3.5, then Fondaparinux	12
Patient 4 (female)	53	1A positive	Recurrent miscarriages, Thrombosis of the Abdominal aorta	Severe thrombocytopenia	RTX 1g/15 days, 2 infusions in total	None	IVIg, high doses of steroids	Warfarin, target INR 2-3	4-ongoing
Patient 5 (female)	58	Triple positivity	1 episode of TVP and PE, 1 recurrence of TVP	Severe thrombocytopenia	RTX 375 mg/m ² weekly for 4 weeks + 2 monthly infusions	None	None	Warfarin, target INR 2-3	43-ongoing
Patient 6 (female)	60	Triple positivity	1 episode of stroke	Severe thrombocytopenia	RTX 375 mg/m ² weekly for 4 weeks + 2 monthly infusions	None	IVIg	Warfarin, target INR 2-3	97-ongoing
Patient 7 (female)	66	Triple positivity	1 episode of TVP	Severe thrombocytopenia	RTX 375 mg/m ² weekly for 4 weeks	None	High doses of steroids	Warfarin, target INR 2-3	0

APS Antiphospholipid Syndrome, UC undifferentiated connective tissue disease, CYC cyclophosphamide, RTX rituximab, AZA azathioprine, MTX methotrexate, DVT deep vein thrombosis, PE pulmonary embolism

Conclusions: In selected case of patients with PAPS, RTX can represent a safe and efficacious therapeutic tool to manage the extra-criteria manifestations of the syndrome, especially when standard approaches have failed or cannot be pursued.

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FRI0334

COMPARISON OF DIFFERENT DEFINITIONS OF REMISSION IN SYSTEMIC LUPUS ERYTHEMATOSUS (SLE) – A STUDY BASED ON THE BLISS-76 CLINICAL TRIAL

S. Emamikia¹, C. Gentile¹, E. Arkema², L. Arnaud³, K. Chatzidionysiou¹, R. van Vollenhoven^{1,4}. ¹Department of Medicine; ²Clinical Epidemiology Unit, Karolinska Institute, Stockholm, Sweden; ³Department of Rheumatology, Université de Strasbourg, Strasbourg, France; ⁴Amsterdam Rheumatology and Immunology Center, Amsterdam, Netherlands

Background: Standardisation of a definition of disease remission in SLE is one of the most important unmet needs in rheumatology and up to today there is no gold standard for the definition of remission.¹

Objectives: An international task force consisting of 60 rheumatologists, nephrologists, dermatologists, clinical immunologists and patient representatives agreed on various definitions of remission in SLE (DORIS).² Our aim was to apply these definitions on a clinical trial.

Methods: This is a post-hoc analysis of a prospective randomised controlled trial (RCT) in SLE, the BLISS-76 clinical trial.³ We have applied two DORIS definitions (table 1) at three time points, week (wk) 24, 52 and 76. The patient could be in remission *on* or *off* treatment. Remission *on* treatment allowed maintenance anti-malarials, low dose glucocorticoids (GCs) (prednisone ≤5 mg/day or equivalent), maintenance immunosuppressives and maintenance biologics. Remission *off* treatment allowed maintenance anti-malarials only. Additionally, we applied each definition where the remission *on* treatment allowed a GC dose ≤10 mg/day (not a part of the original DORIS-definitions).

Abstract FRI0334 – Table 1. DORIS definitions of remission in SLE

Definition	1a	1b	3a	3b
cSLEDAI=0	✓	✓	-	-
PhGA<0.5	✓	✓	✓	✓
Serology	Regardless	Normal	Regardless	Normal
BILAG D/E only	-	-	✓	✓

cSLEDAI: clinical Systemic Lupus Erythematosus Disease Activity Index;

PhGA: Physician Global Assessment;

BILAG: British Isles Lupus Assessment Group

Note: Anti-double stranded DNA and complement (C3 and C4) is included in serology. These definitions were first tested (a) regardless of serology and then (b) normal serology (negative anti-dsDNA antibodies AND normal complement).

Abstract FRI0334 – Table 2. Percent of Patients who started the BLISS-76 trial (n=819) who were in remission at week 24, week 52, and week 76 using different definitions

	Definition 1a, On treatment (GCs ≤5 mg allowed)	Definition 1a, On treatment (GCs ≤10 mg allowed)	Definition 1a, Off treatment	Definition 1b, On treatment (GCs ≤5 mg allowed)	Definition 1b, On treatment (GCs ≤10 mg allowed)	Definition 1b, Off treatment
% (n) in remission W24	4.2 (34)	7.3 (60)	0.4 (3)	1.0 (8)	1.7 (14)	0.1 (1)
% (n) in remission W52	7.4 (61)	11.8 (97)	0.7 (6)	2.6 (21)	3.2 (26)	0.5 (4)
% (n) in remission W76	9.5 (78)	13.8 (113)	1.0 (8)	3.2 (26)	4.4 (36)	0.4 (3)
	Definition 3a, On treatment (GCs ≤5 mg allowed)	Definition 3a, On treatment (GCs ≤10 mg allowed)	Definition 3a, Off treatment	Definition 3b, On treatment (GCs ≤5 mg allowed)	Definition 3b, On treatment (GCs ≤10 mg allowed)	Definition 3b, Off treatment
% (n) in remission W24	0.9 (7)	2.2 (18)	0	0.5 (4)	0.6 (5)	0
% (n) in remission W52	1.3 (11)	2.8 (23)	0.1 (1)	0.7 (6)	1.1 (9)	0.1 (1)
% (n) in remission W76	2.9 (24)	4.5 (37)	0.1 (1)	1.6 (13)	2.3 (19)	0.1 (1)

Def1a:cSLEDAI=0, PhGA<0.5 and normal serology

Def 1b: cSLEDAI=0, PhGA<0.5 and regardless of serology

Def3a:BILAG D/E only, PhGA<0.5 and normal serology

Def 3b: BILAG D/E only, PhGA<0.5 and regardless of serology

GCs: Glucocorticoids

On treatment: maintenance anti-malarials, low dose glucocorticoids (prednisone ≤ 5 mg/day or equivalent), maintenance immunosuppressives, and maintenance biologics are allowed.

Off treatment: maintenance anti-malarials only is allowed.

Results: There were 819 patients enrolled in BLISS-76. The proportions of patients that fulfilled remission according to the above definitions are shown in table 2. The highest point prevalence (9.5%) was when definition 1a *on* treatment was applied at wk 76. As expected, even more patients fulfilled definition 1a when a GC dose ≤10 mg/day was allowed at wk 76 (13.8%). More patients fulfilled the

remission criteria when clinical SLEDAI was used compared to when BILAG was used. When serology (anti-DNA antibodies and complement) was taken into consideration (definitions 1b and 3b), less patients fulfilled remission. Very low numbers of patients ($\leq 1\%$) fulfilled remission off treatment.

Conclusions: Overall, few patients fulfilled remission according to these definitions. More patients fulfilled the definitions when serology was excluded and when a higher dose of GCs was allowed.

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FRI0335 HEMATOPOIETIC STEM CELL TRANSPLANTATION FOR AUTOIMMUNE DISEASES – A 20 YEARS SINGLE CENTRE EXPERIENCE

T. Alexander¹, L. Templin¹, A. Grützkau², H. Hirsland², A. Thiel³, G. Burmester¹, A. Radbruch², R. Arnold⁴, F. Hiepe¹. ¹Rheumatology and Clinical Immunology, Charité – University Medicine Berlin; ²German Rheumatism Research Center; ³Center Research Translation Education Berlin-Brandenburg Center for Regenerative Therapies; ⁴Hematology, Oncology and Tumor Immunology, Charité – University Medicine Berlin, Berlin, Germany

Background: Over the past 20 years, hematopoietic stem cell transplantation (HSCT) has been emerging as a promising treatment option for severe cases of autoimmune diseases (ADs). Meanwhile, positive results have been obtained in 3 randomised clinical trials for systemic sclerosis. The goal of this therapy is to induce medication-free remissions by ablating the pathologic autoreactive memory and restoring of self-tolerance.

Objectives: Here, we summarise the clinical outcomes of AD patients receiving HSCT at the Charité – University Medicine.

Methods: In this prospective study, the outcome of 22 patients been analysed after receiving a CD34⁺-selected autologous HSCT after immunoablation with ATG and cyclophosphamide for different ADs (10 SLE, 4 SSC, 3 vasculitis, 2 multiple sclerosis, 1 polychondritis, 1 inflammatory polyneuropathy, 1 autoimmune haemolytic anaemia) between 1998 and 2015. Multiparametric flow cytometry was applied to characterise peripheral blood lymphocytes subsets including analysis of the TCR-Vbeta repertoire on CD4⁺ T cells, CD31 expression as marker for thymic output of CD4⁺ T cells, including Foxp3⁺ Tregs. In SLE, Siglec-1 on monocytes as surrogate for interferon activity and RNA expression profiling by microarray of FACS-sorted CD14⁺ monocytes was performed (Affymetrix). Autoantibodies were investigated with ELISA.

Results: With a median follow-up of 135 months, the overall survival was 76.5% and progression-free survival 67.9%, respectively. 3 deaths were regarded treatment related, 1 patient had persisting disease (haemolytic anaemia) and 4 relapses occurred in SLE at 1, 18, 36 and 80 months, respectively. Remaining patients are in stable clinical remissions despite discontinuation of immunosuppressive therapy. HSCT was associated with significant reduction or normalisation of auto-antibody levels and a profound reconfiguration of the adaptive immune system, the latter characterised by a re-emergence of naïve T cells with markers of recent thymic emigrants and renewed TCR repertoire, including Foxp3⁺ Tregs and regeneration of naïve B cells. In SLE patients, Siglec-1 expression on monocytes completely normalised and transcriptome analysis revealed an abrogation of type I interferon signalling in responding patients.

Conclusions: Our data provide the "...proof-of-concept" that a chronic autoimmune system can be reset into a naïve and self-tolerant state by HSCT, potentially providing cure in AD. Although applied as salvage therapy in severely affected patients with poor outcomes, TRM gradually improved due to accumulating centre experience and better patient selection and supportive care. Based on positive results from RCT in the major indications, HSCT should be placed earlier in the

treatment algorithm, especially in systemic sclerosis with rapid progress and lung involvement.

Disclosure of Interest: None declared

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FRI0336 BELIEF ABOUT MEDICINE QUESTIONNAIRE PREDICTS THERAPEUTIC ADHERENCE TO HYDROXYCHLOROQUINE DURING SYSTEMIC LUPUS ERYTHEMATOSUS

Y. Rozban¹, H. Devilliers², M. Hié¹, P. Micheline¹, A. Mathian¹, F. Cohen-Aubart¹, H. Julien¹, N. Zahr³, Z. Amoura¹. ¹French National Referral Center for Systemic Lupus Erythematosus, Antiphospholipid Antibody Syndrome and Other Autoimmune Disorders, Service de Médecine Interne 2, Institut E3M, Assistance Publique-Hôpitaux de Paris (APHP), Groupement Hospitalier Pitié-Salpêtrière, Paris; ²Médecine Interne et Maladies Systémiques – Médecine 2, CHU Dijon Bourgogne, Dijon; ³Service de pharmacologie biologique, Assistance Publique-Hôpitaux de Paris (APHP), Groupement Hospitalier Pitié-Salpêtrière, Paris, France

Background: Therapeutic adherence is a key element of chronic disease management and one of the most difficult to assess. The Belief about Medicines Questionnaire (BMQ) evaluates patients' own beliefs related to medication. It is available in two sections: the BMQ-General and the BMQ-Specific. The BMQ-Specific focuses on the representations of medication prescribed for personal use. It was set up as a screening test for poor therapeutic adherence during certain chronic diseases. Early detection of lupus patients at risk of poor therapeutic adherence could lead to preventive actions.

Objectives: To assess the BMQ-Specific as a predictive test of adherence to hydroxychloroquine in SLE.

Methods: Case-control, retrospective and monocentric study. Cases were enrolled according to the following criteria: systemic lupus erythematosus (SLE) according to the ACR classification criteria and HCQ dosage <100 ng/ml after a minimum of 2 months of treatment. The matched control was a lupus patient, enlisted within the centre the same week, with a HCQ dosage ≥ 800 ng/ml. Each patient answered the BMQ-Specific through a telephone interview. The BMQ-Specific comprises two 5-item factors assessing beliefs about the necessity of prescribed medication (*Specific-Necessity*) and concerns about the danger of dependence and long-term toxicity of medication (*Specific-Concerns*). Responses to each statement were scored on a five-point Likert scale (1=strongly disagree and 5=strongly agree). Scores obtained for the individual items within both scales were summed to give total scores for the Specific-Necessity and Concerns scales range from 5 to 25. A Necessity-Concerns (N-C) differential was calculated (range from -20 to +20). It expresses the cost-benefit perceived by the patient for taking the medication. Case and control characteristics were compared using usual tests. Diagnosis performance of each BMQ score and necessity-concern differential were studied by the mean of ROC curves.

Results: The BMQ-Specific questionnaire was submitted to 118 patients: 59 cases and 59 matched controls. The concern score was significantly higher in cases (mean 16.8 vs. 12.7, $p < 0.0001$). The necessity score was significantly higher in control (mean 18.4 vs 15, respectively, $p < 0.0004$). ROC curves show a better area under the curve (AUC) with the N-C differential compared to the AUC of separate scores (respectively 0.8 vs 0.7). The sensitivity and specificity are optimal for a N-C differential of 3.

Conclusions: During SLE, nonadherent patients are primarily concerned about the risks inherent to treatment, rather than its effectiveness. To date, we are the only study to show that specific BMQ is an efficient tool for detecting patients at risk of poor therapeutic adherence to HCQ during SLE. The necessity-concerns differential score must be preferred to the scores taken separately. Thus, targeted educational actions can be provided as soon as the patients are taken in charge, in order to improve their adherence to treatment.

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FRI0337 FACTORS ASSOCIATED WITH POOR THERAPEUTIC ADHERENCE TO HYDROXYCHLOROQUINE DURING SYSTEMIC LUPUS

Y. Rozban¹, H. Devilliers², M. Hié¹, M. Pha¹, A. Mathian¹, F. Cohen-Aubart¹, J. Haroche¹, J.-S. Hulot³, N. Zahr³, Z. Amoura¹. ¹French National Referral Center for Systemic Lupus Erythematosus, Antiphospholipid Antibody Syndrome and Other Autoimmune Disorders, Service de Médecine Interne 2, Institut E3M, Assistance Publique-Hôpitaux de Paris (APHP), Groupement Hospitalier Pitié-Salpêtrière, Paris; ²Médecine Interne et Maladies Systémiques – Médecine 2, CHU Dijon, Dijon; ³Pharmacologie biologique, Hôpital universitaire Pitié-Salpêtrière, PARIS, France

Background: Poor adherence to medication regimens is a major cause of relapse during systemic lupus erythematosus (SLE). Hydroxychloroquine (HCQ),