Conclusion: Enhanced expression of STAT1 by B-cells candidates as key node of two immunopathogenic signatures (type I IFN and B-cells) related to important immunopathogenic pathways and lupus activity. We show that STAT1 is activated upon IFN α exposure in SLE plasmablasts. Thus, Jak inhibitors, targeting JAK-STAT pathways, hold promise to block STAT1 expression and control plasmablast induction in SLE.

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Metabolic pathways during the regulation of inflammation and immunity

OP0006

ABNORMAL IRON METABOLISM AND MITOCHONDRIAL DYSFUNCTION: INVESTIGATING A NOVEL PATHOLOGICAL MECHANISM IN SYSTEMIC LUPUS ERYTHEMATOSUS

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Background: Iron is vital for numerous essential physiological processes including erythropoiesis and energy metabolism (as iron is found in the mitochondrial electron transport chain, the central site of ATP production). Iron homeostasis is tightly controlled by a number of regulators including; 1. Hepcidin, which prevents iron release from stores (under the influence of IL6 and IL1 β); 2. Ferritin, an iron storage protein; 3. Lipocalin-2 (LCN2), which is released upon innate immune activation that induces iron sequestration; 4. Transferrin, which binds circulating iron and enables its transport to effector cell targets; 5. Haptoglobin, which binds free haemoglobin and assisting iron recycling; 6. Erythropoietin (EPO), which stimulates erythropoiesis as a result of hypoxia.

Chronic inflammation may result in dysregulation of iron metabolism and in turn impair mitochondrial function yet little is known regarding how these processes change in systemic lupus erythematosus (SLE).

Objectives: In this study, we investigated how dysregulation of iron metabolism may occur in SLE and subsequently sought to identify how a lack of iron may ultimately induce abnormal mitochondrial function.

Methods: 1. *Investigating abnormal iron metabolism in SLE.* Serum samples from patients with SLE (n=39) and healthy controls (HC, n=17) were assessed hepcidin, IL-1 β , IL-6, ferritin, LCN2, EPO, haptoglobin and transferrin levels by ELISA. Hierarchical cluster analysis of normalised data (converted to Z-scores) was performed using MeV software in order to characterise patient groups based upon iron metabolism profile. Anti-dsDNA antibody titres, complement C3 levels and SLEDAI-2K were excluded to limit the influence of these variables on cluster analysis. Results were presented as a heatmap.

2. *Studying mitochondrial function in iron deficiency and SLE.* Peripheral blood mononuclear cells (PBMCs) from HCs and patients with SLE were analysed using Seahorse Respirometry, which measures mitochondrial oxygen consumption rate (a measure of energy metabolism dependent upon oxidative phosphorylation). To assess differences between health, iron deficiency and SLE 3 groups were assessed; 1. PBMCs derived from HCs; 2. PBMCs from patients with SLE; 3. Healthy PBMCs cultured in iron deficient condition, in which cells were treated with the potent iron chelator, Deferiprone.

Results: Figure 1a demonstrates that four groups were identified following cluster analysis. In spite of excluding markers of disease activity, these groups

showed significant differences in SLEDAI-2K (shown in Figure 1b). In summary, patients with more active disease (Groups C and D) showed higher levels of hepcidin (which prevents the release of iron from stores, under the influence of IL-1 β and IL-6) and reduced transferrin thus suggesting that iron is inefficiently transported when compared with those with less active disease (in Groups A and B).

Figure 1a: Results of hierarchical clustering identified four patient groups (A-D) based upon key regulators of iron metabolism
Figure 1b: Differences in disease activity (SLEDAI-2K) between each group produced from hierarchical cluster analysis (A-D)

Figure 2a demonstrates that basal mitochondrial respiration is significantly reduced in PBMCs derived from healthy controls when grown in iron deficiency conditions (following treatment with Deferiprone and is lower still in those with SLE. Figure 2b shows that PBMCs from patients with SLE have reduced maximal mitochondrial respiration capacity that is comparable to the levels seen in iron deficient healthy PBMCs.

Figure 2

Conclusion: Patients with SLE demonstrate abnormalities in iron metabolism that results in cellular iron deficiency as iron is not released from stores, nor adequately transported at the rate required to meet physiological demands. Furthermore, PBMCs derived from patients with SLE who impaired basal and maximal respiration that is comparable with healthy PBMCs treated potent iron chelation. This suggests that abnormal iron metabolism may in turn limit mitochondrial energy metabolism in SLE and represents a potential future therapeutic target.

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OP0007-PARE

CAMPAIGN TO PROMOTE PHYSICAL ACTIVITY & EXERCISE TO RMD PATIENTS THROUGH EDUCATION AND PRACTICE

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Background: Euler give's a lot of attention to outline the need of a change in RMD patients life style that is very well outlined into the 2018 Euler recommendations for Physical Activity (PA).

Objectives: Driven by those recommendations that says that "PA should be an integral part of standard care throughout the course of disease," CypLAR decided to create a campaign to promote PA through educating RMD patients on the PA benefits, make them to change their life style and enroll them to PA programs. More over we want to inform Rheumatologist and HPR's on that effort and enroll them to that campaign. The CypLAR's goal through that campaign is to manage and enroll as much as possible patients to PA Programs for a continual period of about 10 months.

Methods: To achieve all the above we decided to move to the following steps:

- Offer PA Programs organized by CypLAR or HPR associates
- Increase awareness regarding the benefits of the PA (Land based & Aquatic) programs to Rheumatologists, HPR's and RMD patients
- Integrate PA into National Health System and procedures
- Offer incentives

Results:

- We managed to increase the PA programs that we used to offer from 1 to 3 in every major cities with also some more opportunities ahead. That also increases the number of participants attracting around 100 participants instead of 20 that we used to before.
- Towards awareness, we presented Exercise rehabilitation in conferences around Europe (Agora 2017,2018,2019, Eular 2018, Cyprus – Crete Conference 2017, 2019, Enfa 2019, Pain Conference, Athens 2019) and also published related articles on CypLAR's magazine that is published twice a year that is distributed to more than 5000 members.
- We managed to include the Aquatic Exercise Rehabilitation to the new National Strategic plan for Rheumatic Diseases.
- As incentives, we created a fund that is addressed to partially support low income patients. Furthermore we acquire special discount membership fees to our members on PA programs that are offered by associates.
- We organize our own sport related fund events and also participate in others sport funding events. Especially the Charity Swimming Event "Swim for my fellow" which is co-organized by the Iacovou Swimming Centre and CypLAR for the last 5 years is also under the Limassol Municipality Annual Sport Events called "Lemesia" which this year will have an International promotion due Limassol's Award as the "European City of Sports" for 2020.
- We are in the process and in contact with big companies in order to become our campaign Sponsors

We attracted a fund of €2000 from Cyprus Sport Organization that offered a partial financial support to 30 patients for their participation in PA programs for 3 months.

Conclusion: We all believe that the success on that campaign is based on Education (articles, presentations), the available options (programs/positions to participate) and Incentives (financial) that all of them needs further development.

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How to build and choose an appropriate outcome measure

OP0008

DEVELOPMENT AND VALIDATION OF AN ALTERNATIVE ANKYLOSING SPONDYLITIS DISEASE ACTIVITY SCORE WHEN PATIENT GLOBAL ASSESSMENT IS UNAVAILABLE

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United Kingdom; ⁸Purpan Teaching Hospital, Toulouse, France; ⁹MUMC, Maastricht, Netherlands; ¹⁰Maastricht University, Maastricht, Netherlands

Background: Ankylosing Spondylitis Disease Activity Score (ASDAS) is a composite index measuring disease activity in axial spondyloarthritis (axSpA). It includes questions from the Bath Ankylosing Spondylitis Disease Activity Index (BASDAI), Patient Global Assessment (PGA), and inflammation biomarkers. However, ASDAS calculation is not always possible because PGA is sometimes not collected.

Objectives: To develop an alternative ASDAS to be used in research settings when PGA is unavailable.

Methods: Longitudinal data from 4 axSpA cohorts and 2 RCTs were combined. Observations were randomly split in a development (N=1026) and a validation cohort (N=1059). Substitutes of PGA by BASDAI total score, single or combined individual BASDAI questions, and a constant value, were considered. In the development cohort, conversion factors for each substitute were defined by Generalized Estimating Equations. Validation was performed in the validation cohort according to the OMERACT filter, taking into consideration: 1) Truth (agreement with original-ASDAS in the continuous score, by intraclass correlation coefficient -ICC- and in disease activity states, by weighted kappa) 2) Discrimination (standardized mean difference -SMD- of ASDAS scores between high/low disease activity states defined by external anchors e.g Patient Acceptable Symptom State -PASS-; agreement -kappa- in the % of patients reaching ASDAS improvement criteria according to alternative vs. original formulae) 3) Feasibility.

Results: Taking all psychometric properties into account and comparing the different formulae (Table), alternative-ASDAS using BASDAI total as PGA replacement proved to be: 1) truthful (agreement with original-ASDAS: ICC=0.98, kappa=0.90); 2) discriminative: it could discriminate between high/low disease activity states (e.g. scores between PASS no/yes: SMD=1.37 versus original-ASDAS SMD=1.43) and was sensitive to change (agreement with original-ASDAS in major improvement/clinically important improvement criteria: kappa=0.93/0.88; 3) feasible (BASDAI total often available; conversion coefficient≈1).

Conclusion: Alternative-ASDAS using BASDAI total score as PGA replacement is the most truthful, discriminative and feasible instrument. This index enables ASDAS calculation in existing cohorts without PGA.

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Table. Psychometric properties of alternative ASDAS formulae

	Truth N= 823		Discrimination (disease activity states) N=381		Discrimination (sensitivity to change) N=375	
	Agreement with original-ASDAS		Patient Acceptable Symptom State (PASS)		Agreement with:	
	ICC	Weighted Kappa	PASS =no	PASS=yes	major improvement	clinically important improvement
			Mean ASDAS, SD	SMD		Kappa
Original-ASDAS	-	-	3.19, 0.97	1.86, 0.88	1.43	-
ASDAS-Q1	0.97	0.86	3.02,0.90	1.80,0.87	1.37	0.90
ASDAS-Q14	0.98	0.88	3.08,0.94	1.80,0.89	1.39	0.92
ASDAS-Q145	0.98	0.89	3.13,0.96	1.82,0.91	1.40	0.92
ASDAS-BT	0.98	0.90	3.15,0.99	1.83,0.93	1.37	0.93
ASDAS-C3	0.97	0.84	3.02,0.98	1.71,0.94	1.36	0.87

Legend. The alternative Ankylosing Spondylitis Disease Activity Scores (ASDAS) formulae were calculated using as PGA replacement: question 1 (Q1), average of questions 1 and 4 (Q14), average of questions 1,4,5 (Q145) and total score (BT) of the Bath Ankylosing spondylitis Disease Activity Score (BASDAI) or a constant value (ASDAS-C3); original-ASDAS= ASDAS according to the usual formula; ICC =Intraclass Correlation Coefficient; SD= Standard Deviation; SMD=Standardized mean difference