Table 1. Genotype and allele frequencies of *NCF2, NCF4, CYBA* genes polymorphisms in RA patients and controls [n(%)]

SNP	Analyze model		RA (N = 593)	Control (N = 596)	*P value*
NCF2					
rs10911363	Genetypes	GG	125	144	0.371
		GT	304	289	0.747
		TT	164	163	
	Alleles	G	554	577	0.408
		T	632	615	
NCF4					
rs1883112	Genetypes	GG	57	56	0.972
		GA	248	255	0.754
		AA	288	285	
	Alleles	G	362	367	0.888
		A	824	825	
rs4821544	Genetypes	CC	4	7	0.323
		CT	117	146	0.043
		TT	472	443	
	Alleles	C	125	160	0.031
		T	1061	1032	
	Dominant model	TT	472	443	0.031
		CT+CC	121	153	
rs729749	Genetypes	TT	104	102	0.445
		CT	266	302	0.033
		CC	223	192	
	Alleles	T	474	506	0.219
		C	712	686	
CYBA					
rs3794624	Genetypes	AA	14	15	0.929
		GA	160	147	0.368
		GG	419	43	
	Alleles	A	188	177	0.498
		G	998	1015	
rs4673	Genetypes	AA	1	5	0.140
		GA	85	90	0.673
		GG	507	501	
	Alleles	A	87	100	0.34
		G	1099	1092	

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AB0024

ASSOCIATION OF IL6 RS1800795 BUT NOT IL6R RS2228145, RS4845618 AND STAT4 RS7574865 POLYMORPHISMS WITH CHLAMYDIA-ASSOCIATED RHEUMATOID ARTHRITIS

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Background: Rheumatoid arthritis (RA), associated with Chlamydial Infection, has some clinical and immunological particulars that interfere with the early diagnosis and require significant changes in treatment strategy [1].
Objectives: To estimate the distribution of some non-HLA genetic markers such as STAT4 rs7574865, IL6 rs1800795, IL6R rs2228145 and rs4845618 in Chlamydia positive and negative RA patients and healthy controls.
Methods: We examined 380 healthy blood donors and 187 RA patients classified according to the ACR/EULAR 2010 criteria for RA [2]. Twenty-three of the RA patients were positive for Chlamidia trachomatis (n=17) or Chlamidia pneumonia (n=6) persistence. DNA from peripheral blood samples was extracted by phenol-chloroform method. SNPs were genotyped by the real-time PCR with fluorescent probes. Statistical significance of SNPs' frequency was estimated by two-way Fisher exact test (F, $p_{2\text{-}t}$) with Bonferroni correction for multiple comparisons (p_{cor}). Moreover, diagnostic odds ratio (dOR), the likelihood ratio of positive (LR^+) and negative (LR^-) tests and corresponding confidence intervals (CI) were calculated.
Results: We revealed statistically significant increase of genotype CC frequency (IL6 rs1800795) in Chlamydia-associated RA (60.9%) vs healthy donors (20.7%): $p_{2\text{-}t}$=0.000065; p_{cor}=0.00026; dOR=5.95 ($CI_{95\%}$ 2.53-13.94); LR^+=2.94 ($CI_{95\%}$ 1.90-3.29); LR^-=0.49 ($CI_{95\%}$ 0.28-0.75) as well as in Chlamydia-associated RA (60.9%) vs Chlamydia-negative RA (23.9%): $p_{2\text{-}t}$=0.00051; p_{cor}=0.002; dOR=4.99 ($CI_{95\%}$ 2.04-12.16); LR^+=2.56 ($CI_{95\%}$ 1.60-3.57); LR^-=0.51 ($CI_{95\%}$ 0.29-0.78). Significant differences in STAT4 rs7574865, IL6R rs2228145 and IL6R rs4845618 distribution between studied groups were not found.
Conclusion: Our data suggest the association between CC genotype of IL6 rs1800795 and Chlamydia-associated RA.
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Adaptive immunity (T cells and B cells) in rheumatic diseases

AB0025

B-CELL SUBSETS AS ADDITIONAL DIAGNOSTIC TOOL FOR PRIMARY SJOGREN'S SYNDROME AND SYSTEMIC LUPUS ERYTHEMATOSUS

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Background: Systemic lupus erythematosus (SLE) and primary Sjögren's syndrome (pSS) are chronic complex disorders with an autoimmune background, multifactorial etiology, multiple circulating antinuclear antibodies and damage of various organs. SLE and pSS have several similar clinical and serological aspects; likewise, SLE and Sjögren's syndrome may coexist (so-called secondary Sjögren's syndrome). However, applied classification criteria do not differentiate SLE and pSS. It is known that humoral immunity plays significant part in pathogenesis of those diseases; hereby, we can expect imbalances in B cell subset frequencies during SLE and pSS.
Objectives: To investigate clinical utility of B cell subsets in distinguish SLE and pSS during diagnosis.
Methods: A total of 25 SLE patients, 25 SS patients and 49 healthy volunteers (HV) were included in the study. The diagnosis of SLE was performed according to the 2019 EULAR – ACR classification criteria, the diagnosis of pSS - according to the 2016 EULAR – ACR criteria. Phenotyping of blood B cell subsets was done using flow cytometry. Total peripheral blood B cells were identified using CD19 expression, distinct B cell subsets were characterized by IgD, CD38 and CD27 expression. All of the statistical analysis of data was performed with STATISTICA Version 12.0 Inc. (USA).
Results: We evaluated the percentages of circulating B-cell subsets using three major classification schemes based on the relative co-expression of either IgD/CD38 (so-called "Bm1-Bm5" classification), IgD/CD27 and CD38/CD27. A discriminant analysis was performed for all B cell classifications. Analysis of CD38 and CD27 co-expression demonstrated most significant separation between patients with SLE and pSS (fig. 1). Moreover, discriminant analysis carried out by using a forward stepwise model demonstrated that the top significance was documented while assessing the percentage of plasmoblasts (CD27hiCD38hi), resting memory B-cells (CD27dimCD38low), mature active B-cells (CD27dimCD38dim), naive mature B-cells (CD27dimCD38low), as well as counting the absolute numbers of transitional B-cells (CD27lowCD38hi), model percent correct was 78,6% (p <0,05, tab.1).

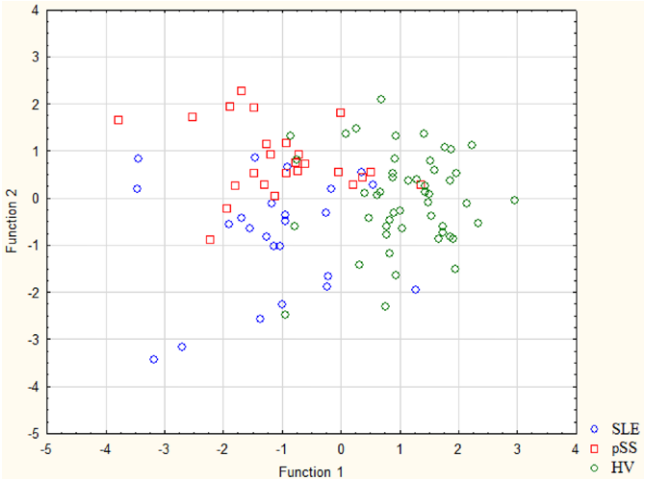

Figure 1. Graphic distribution of SLE and pSS patients as well as HV analyzed by discriminant analysis.

Conclusion: B cell subsets might provide a useful diagnostic tool for distinction SLE and pSS. More research needed to investigate clinical value of B-cell subsets in autoimmune rheumatic diseases.

Table 1. Peripheral B-cell subset composition in SLE and SS patients vs. HV group assessed by discriminant analysis.

Parameter	F-test	p-level
Plasmoblasts (CD27hiCD38hi), %	7,93	<0.001
Resting memory B-cells (CD27dimCD38low), %	13,72	<0.001
Transitional B-cells (CD27lowCD38hi)	29,74	<0.001
Mature active B-cells (CD27dimCD38dim), %	5,20	<0.001
Naive mature B-cells (CD27dimCD38low), %	3,10	0.049
Double negative (CD27lowCD38low), %	1,98	0,14
Resting memory B-cells (CD27dimCD38low)	1,02	0,36
Double negative (CD27lowCD38low)	2,32	0,10
Plasmoblasts (CD27hiCD38hi)	1,02	0,36
Naive mature B-cells (CD27dimCD38low)	1,03	0,36
Mature active B-cells (CD27dimCD38dim)	1,02	0,36
Transitional B-cells (CD27lowCD38hi), %	1,03	0,36

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AB0026 SELECTIVE INHIBITION OF TYROSINE KINASE 2 WITH AN ORAL AGENT, BMS-986165, COMPARED WITH JANUS KINASE INHIBITORS

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Background: BMS-986165 is an oral, selective inhibitor of tyrosine kinase 2 (TYK2) with a unique mode of binding to the pseudokinase domain of the enzyme rather than the active site within the kinase domain. This unique mode of binding provides high functional selectivity for TYK2 versus other tyrosine kinases (TYKs) in cellular and other in vitro assays.[1] This approach may provide robust efficacy with a differentiated safety profile due to decreased off-target activity on other kinases. In a 12-week, placebo-controlled Phase 2 trial in patients with moderate to severe plaque psoriasis,[2] BMS-986165 had a favorable safety profile, and 67%–75% of patients achieved Psoriasis Area and Severity Index 75 (PASI 75) after 12 weeks at doses ≥3 mg twice daily versus 7% with placebo. BMS-986165 is currently under investigation in multiple autoimmune disorders such as psoriatic arthritis, psoriasis, and systemic lupus erythematosus.

Objectives: To understand the selectivity of BMS-986165 compared with JAK inhibitors, such as tofacitinib (Tofa), upadacitinib (Upa), and baricitinib (Bari), at clinically relevant doses and plasma concentrations.

Methods: In vitro whole blood assays were developed to measure the activity of common pairings of JAKs (JAK 1/3, JAK2/2, and TYK2/JAK2) and concentrations providing half-maximal inhibition (IC_{50}) for BMS-986165, Tofa, Upa, and Bari were determined. The whole blood IC_{50} values were plotted against pharmacokinetic profiles of these agents at approved doses and/or doses evaluated in their respective Phase 2/3 trials. The time that concentrations were >IC_{50} and projected average daily inhibition were evaluated.

Results: At clinically relevant doses and exposures, BMS-986165 plasma concentrations were higher than the TYK2 whole blood IC_{50} value for a considerable part of the dosing interval. Additionally, the maximal plasma concentration (C_{max}) of BMS-986165 was approximately >9- to 18-fold lower than the JAK 1/3 whole blood IC_{50} value and >52- to >109-fold lower than JAK2/2 whole blood IC_{50}, indicating lack of meaningful inhibition of the JAK 1-3 pathways by BMS-986165 at therapeutic doses. At clinically relevant doses, projected C_{max} values of Tofa, Upa, and Bari were many-fold lower than TYK2 IC_{50}, indicating minimal or no meaningful inhibition of the TYK2 pathway. As expected, Tofa, Upa, and Bari had varying degrees of inhibition against JAK1/3 (daily average inhibition range: 70%–94%) and JAK2/2 pathways (daily average inhibition range: 24%–67%) at clinically relevant doses and exposures.

Conclusion: These results demonstrate the high TYK2 functional selectivity of BMS-986165 at clinically relevant doses and plasma concentrations compared with Tofa, Upa, and Bari and indicate that BMS-986165 is in a different class compared with JAK 1–3 inhibitors. Ongoing studies in psoriasis and other conditions may confirm the expected safety of BMS-986165 based on the above results. The daily average inhibition of JAK1 and JAK2 likely explains some common laboratory observations and adverse events reported for the JAK1–3 inhibitors.

References:

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AB0027 B CELL SYNOVITIS IN RELATION TO DIAGNOSIS AND CLINICAL PHENOTYPE: COMPARISON BETWEEN RHEUMATOID AND PSORIATIC ARTHRITIS

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Background: Rheumatoid arthritis (RA) and psoriatic arthritis (PsA) are both characterized by significant heterogeneity in terms of clinical presentation and outcomes. Furthermore, RA and PsA may share some overlapping features such as autoantibody-negativity, polyarticular involvement, response to certain therapies and pattern of joint damage. The pathobiological bases underlying the intra-disease heterogeneity and the inter-disease similiarities between RA and PsA are however unkown.

Objectives: Aim of the current study was to investigate the relationship between the synovial immune phenotype and different clinical subsets in patients with RA and PsA.

Methods: The study population included 96 patients undergoing ultrasound-guided synovial biopsy of the knee and serum sampling on the same day. Patients were recruited according to defined clinical subtypes: anti-citrullinated positive (ACPA) RA (n=26), ACPA-negative RA (n=32), polyarticular (≥5 involved joints) PsA (n=15), and oligoarticular PsA (n=23). Patients were compared for: (i) demographic and clinical features; (ii) synovial histopathological characteristics including CD68-positive infiltrating macrophages, CD3-positive T lymphocytes, CD20-positive B lymphocytes (semi-quantitative scores 0-3); (iii) serum levels of the lymphoid chemokine CXCL13 as a marker of germinal centre activity.

Results: Collectively, ACPA-positive RA patients, ACPA-negative RA patients and patients with polyarticular PsA presented comparable demographic and clinical features including gender distribution, age, number of involved joints and levels of acute phase reactants. Patients with oligoarticular PsA were instead younger, more frequently males, and with lower levels of acute phase reactants. The degree of macrophage and T cell infiltration correlated with the erythrocyte sedimentation rate (rho 0.38, p=0.001 and rho 0.24, p=0.04 respectively) and C-reactive protein levels (rho 0.38, p=0.001 and rho 0.28, p=0.01 respectively) irrespective of diagnosis, and was significantly lower in oligoarticular PsA (**Figure 1 A**, **B**). In contrast, the degree of B cell infiltration showed significant differences in relation to the disease subtype: the lowest levels were found in oligoarticular PsA, the highest levels in ACPA-positive RA, whilst ACPA-negative RA and polyarticular PsA presented with intermediate and comparable levels between the two extremes (**Figure 1 C**). Serum levels of CXCL13 correlated with the synovial B cell score (rho 0.30, p=0.03) and, similarly to synovial B cell infiltration, were differentially increased according to the clinical phenotype, with again similarities between ACPA-negative RA and polyarticular PsA (**Figure 1 D**).