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AB0058 IL2 DECREASE AND INCREASE OF IL10 AND INF1A ARE ASSOCIATED TO CLINICAL ACTIVITY IN SYSTEMIC LUPUS ERYTHEMATOUS PATIENTS

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Background: Systemic lupus erythematosus (SLE) is an autoimmune disease characterised by deregulation of cytokine production. INF1A is a proinflammatory cytokine considered as a key molecule in the SLE etiopathogenesis, being responsible indirectly of IL10 upregulation. BLYS is involved in autoantibodies production and clinical activity in SLE, and its expression is regulated by other cytokines as IL10 and INF1A. IL2 is an anti-inflammatory cytokine in SLE, but its loss leads to the production of Th2 proinflammatory cytokines as IL4, IL5 and IL13.

Objectives: To analyse the association among inflammatory cytokine levels and clinical activity, as well as to identify a cytokine profile related to disease activity in SLE.

Methods: A cross-sectional, observational study of 142 patients diagnosed of SLE^{SLECC 2012} criteria), and 35 healthy controls, was performed. A complete blood-test and an interview were carried out to collect their clinical data. We analysed inflammatory cytokines serum levels by colorimetric methods. Biostatistical analysis with R was performed.

Results: Mean cytokine levels for the SLE patients and healthy controls are shown in the table 1.

Abstract AB0058 – Table 1

	SLE patients (pg/ mL)	Healthy controls (pg/ mL)
	Mean (SD)	Mean (SD)
IL2	4.34 (12.2)	4.96 ^{4,5}
IL4	58.65 (64.6)	89.05 ^{70,18}
IL5	18 (5.71)	7.33 ^{8,59}
IL10	12.29 (32.82)	1.92 ^{3,67}
IL13	44.97 (273.78)	42.85 ^{93,05}
IL21	3.18 (5.61)	2.82 ^{3,35}
INF1A	15.69 (24.59)	4.84 ^{1,91}
BLYS	2293.82 (6948.46)	1181.15 ^{260,04}

The mean clinical activity measured by SLEDAI was 5.91±5.06, and we observed a statistically significant association between high levels of IL10 and high clinical activity (p=0.001).

Statistical analysis indicates that complement consumption is associated with increased levels of IL10 (p=0.029), INF1A (p<0.001), IL4 (p=0.004), IL5 (p=0.009) and decreased levels of IL2 (p=0.045); or anti-DNA positivity is associated with increased levels of INF1A (p=0.002) and decreased levels of IL2 (p=0.045), IL4 (p=0.034) and IL5 (p=0.007).

Moreover, BLYS seems to have increased in patients with positive antiphospholipid antibodies and anti-DNA. IL10 is associated with ENAs positivity (p=0.022). In patients with other autoimmune disease associated with SLE, an increase of INF1A (p=0.008) and IL5 (p=0.044) is observed.

SLE patients were categorised by normal, low or high level of the eight cytokines. Despite the fact that no specific cytokine profile associated with clinical activity was observed, those patients with high SLEDAI score had increased levels of IL10 and INF1A and decreased levels of IL2 and IL21.

Conclusions: Our SLE patients displayed mainly IL10, INF1A and BLYS increased, and IL2 decreased. Although IL10 seems to be the cytokine which best fits to clinical activity in SLE, altered levels of INF1A, IL2, IL4, and IL5 are associated with complement consumption or anti-DNA positivity.

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AB0059 FETUIN-A: CLINICAL AND LABORATORY ASSOCIATIONS IN WOMEN WITH RHEUMATOID ARTHRITIS

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Background: Fetuin-A is an acute-phase protein with contradictory effects. It is well known that fetuin-A low levels are associated with calcification and higher risk of cardiovascular diseases and its level is downregulated by pro-inflammatory cytokines.¹ Nevertheless, it was shown, that fetuin-A induces synthesis of pro-inflammatory cytokines in adipocytes and macrophages.²

Objectives: To investigate the level of fetuin-A in women with rheumatoid arthritis (RA).

Methods: At baseline we measured fetuin-A level, femoral neck, total hip and L₁₋₄ BMD by DXA in 110 women with RA (mean age 54.5±12.6; hereinafter M±Std. dev.) and 30 healthy controls. Serum CRP and ESR were measured to assess inflammation. DAS28 was calculated to determine RA activity. The diagnosis of osteoporosis was set according to the recommendations of world health organisation – T-scores≤-2.5 for patients without glucocorticoid therapy in anamnesis, T-scores≤-1.5 for patients treated with glucocorticoid for 3 months in anamnesis or with an osteoporotic fracture in anamnesis. Fetuin-A in serum was determined by enzyme-linked immunosorbent assay.

Results: Mean concentration of fetuin-A in group with RA was 765,69 ±120,64 ug/ml, which was lower than of healthy controls – 812,95 ug/ml (p=0,0438). Secondary osteoporosis was revealed in 52 patients (47%) with RA with mean level of fetuin-A at 733,7±18,83 ug/ml vs. 794,36±12,83 ug/ml (p=0,0078) of 58 (53%) non-osteoporotic patients. Moderate negative correlations were observed between fetuin-A and DAS28 (r=-0,4334; p<0,001), fetuin-A and CRP (r=-0,3148; p<0,001), fetuin-A and ESR (p=-0,344; p<0,001). Mean concentrations of fetuin-A were significantly different between the subgroups with moderate (3,2≤DAS28<5,1) and high disease activity (5,1≤DAS28) of RA patients and healthy controls: 742,41±12,07 ug/ml vs. 812,95 ug/ml (p=0,0021) and 663,9 ±39,14 ug/ml vs. 812,95 ug/ml (p<0,001).

Conclusions: Our study confirms that lower levels of fetuin-A are associated with higher activity of RA and with the loss of bone mineral density.

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AB0060 MECHANISMS OF ACTION OF CHONDROITIN SULFATE AND GLUCOSAMINE IN MUSCLE TISSUE: IN VITRO AND IN VIVO RESULTS. A NEW POTENTIAL TREATMENT FOR MUSCLE INJURIES?

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Background: Musculoskeletal injuries are the most common cause for severe, chronic pain and physical disability affecting hundreds of millions of people around the world and represent a major concern also in sports medicine. A preclinical study evaluated the impact of chondroitin sulfate (CS) and glucosamine (GLU) combination (both compounds used in the treatment of osteoarthritis) on muscle healing and force recovery. Although the mechanisms of action of the combination CS +GLU have been largely studied in articular tissue, its potential therapeutic effects for muscle healing remain still unknown.

Objectives: The aim of the present study is to elucidate the mechanisms of action responsible for this interesting benefit.

Methods: Human skeletal muscle biopsies were digested with Protease type XIV and the resulting tissue suspension were collected by centrifugation. The digested muscle pellet was then triturated to liberate the human satellite cells. Differential centrifugations were used to enrich the cell fraction. Cell suspension was then transferred onto cell-culture dishes in Growth media (DMEM/M-199 medium (3:1) with 10% FBS, 10 µg/ml insulin, 2 mM glutamine, 25 ng/ml fibroblast growth factor, and 10 ng/ml epidermal growth factor) and cells were expanded in a growing monolayer. The effect of CS+GLU treatment in primary human skeletal muscle

cells was evaluated in a cell proliferation assay. NF- κ B intracellular levels were determined by Western Blot. TNF- α production was measured in culture medium supernatants by ELISA.

Results: An enhancement in cell proliferation was found in CS+GLU treatments at a concentrations of 100 and 200 μ g/ml, increasing 1,60-fold ($p<0.01$) and 2,04-fold ($p<0.001$), respectively, compared to untreated cells. In addition, myoblasts were then incubated with IL-6 (50 ng/ml) for 72 hour in order to induce an inflammatory environment. The results showed an IL-6 induced-reduction on cell proliferation in all groups, although the data did not reach statistical significance. Therefore, an IL-6 inhibitory effect on cell proliferation in human muscle cannot be ensured. We also measured the effect of the combined treatment CS+GLU on NF- κ B activation and TNF- α production in human skeletal muscle cells in primary culture. Despite of TNF- α levels were undetectable in cell supernatants, preliminary data showed a slight reduction on NF- κ B signalling pathway. Global gene expression profiles, measured by microarrays and GeneChip Human Gene 1.0 ST Arrays (Affymetrix), will also be analysed.

Conclusions: The mechanisms of action involved in the potential therapeutic effect described in an *in vivo* injured muscle model seem to be related with an increase in muscle cell proliferation, together with blocking NF- κ B nuclear translocation and TNF α production. Although further investigation is required, these pre-clinical data suggests potentially positive effects of CS and GLU administration for the treatment of skeletal muscle injuries in sports medicine.

Disclosure of Interest: None declared

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AB0061

SERUM IL-37 AS AN EFFICIENT BIOMARKER OF DISEASE ACTIVITY IN PATIENTS WITH ANKYLOSING SPONDYLITIS: POST-HOC ANALYSIS OF PLANETAS STUDY

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Background: IL-37 is an anti-inflammatory cytokine which belongs to IL-1 cytokine superfamily. Patients with ankylosing spondylitis (AS) also had a higher serum IL-37 concentration than controls, and were also associated with other inflammatory markers such as CRP, ESR, and BASDAI levels.¹ However, the relationship between serum IL-37 and disease activity after anti-TNF treatment has not been reported.

Objectives: To investigate the association of serum IL-37 level with disease activity in AS patients who were treated with infliximab.

Methods: Patients were recruited from the PLANETAS study (NCT01220518). Patients with active AS were treated with CT-P13 or infliximab originator. The serum levels of IL-37 were measured at week 0 and week 30 with specific ELISA. Other demographic, laboratory and clinical variables were evaluated simultaneously.

Results: Fifty patients with active AS (BASDAI >4) were analysed. The median age of patients was 40 years old [Interquartile range (IQR), 33.8–49.5], and the median BASDAI score was 6.7 (IQR 5.3–7.9). Compared to baseline, all measured clinical and laboratory parameters and serum IL-37 were significantly reduced. There was a statistically significant correlation between IL-37 and CRP, BASDAI at baseline, but not at week 30. Additionally, the differences (Δ) of parameters at baseline and at week 30 were assessed on their associations with other disease activity parameters. Delta IL-37 was significantly correlated with Δ CRP, Δ BASFI and Δ BASDAI. The ROC curves of serum biomarkers for ASAS 20 achievement revealed that AUC value for Δ IL-37 (AUC=0.74) was similar with Δ ESR (AUC=0.71, $p=0.64$) and superior than Δ CRP (AUC=0.54, $p<0.01$). AUC value for Δ IL-37 of ASAS 40 achievement was 0.66, which was similar with Δ ESR (AUC=0.60, $p=0.38$) and superior than Δ CRP (0.46, $p<0.01$).

Abstract AB0061 – Table 1. Demographic & Clinical characteristics of analysed patients, comparing at baseline and at week 30.

Variables	At baseline	At week 30	P
Age	40.0 (33.8–49.5)	-	N/A
Female sex	7 (14%)	-	N/A
IL-37	105.1 (25.9–286.9)	44.5 (18.2–153.9)	<0.01
ESR	35.0 (28.0–41.3)	7.5 (5.0–16.0)	<0.01
CRP	158.1 (53.4–291.4)	20.0 (7.4–73.1)	<0.01
BASDAI	6.7 (5.3–7.9)	3.3 (1.9–4.5)	<0.01
BASMI	4.0 (3.0–5.0)	3.0 (2.0–4.0)	<0.01
BASFI	6.6 (5.3–8.1)	3.3 (1.6–5.9)	<0.01
PGD	70.5 (57.3–80.8)	33.0 (14.8–53.3)	<0.01

Abstract AB0061 – Table 2. Correlations between IL-37 and other disease activity markers; at baseline and the differences between baseline and at week 30.

	At baseline			Difference between baseline and week 30		
	IL-37	ESR	CRP	Δ IL-37	Δ ESR	Δ CRP
IL-37		0.14	0.39**	Δ IL-37	0.24	0.36*
ESR	0.14		0.57**	Δ ESR		0.50**
CRP	0.39**	0.57**		Δ CRP	0.36*	0.50**
BASDAI	0.31*	0.31*	0.23	Δ BASDAI	0.32*	0.25
BASMI	0.05	0.09	0.16	Δ BASMI	-0.05	0.06
BASFI	0.20	0.36**	0.25	Δ BASFI	0.34*	0.35*
PGD	0.25	0.10	0.06	Δ PGD	0.16	0.28
						-0.06

Abstract AB0061 – Figure 1. Figure 1 ROC Curves of disease activity markers of ASAS 20 and ASAS 40 achievement.

Conclusions: Serum IL-37 levels are associated with BASDAI, patient's pain score, and CRP in active AS patients. Change in serum IL-37 level may serve as an efficient biomarker predicting the improvement of BASDAI and the achievement of ASAS 20 and 40 after anti-TNF treatment in AS patients.

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AB0062

RECIPROCAL INTERACTION BETWEEN MACROPHAGE MIGRATION INHIBITORY FACTOR AND INTERLEUKIN-8 IN GOUT

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Background: Macrophage migration inhibitory factor is a proinflammatory, chemotactic, and tissue destructive cytokine.

Objectives: This study determined monosodium urate crystal-induced macrophage migration inhibitory factor production and its interaction with interleukin-8 in gout.

Methods: Peripheral blood, synovial fluid, and clinical data were obtained from 98 patients with gout. Synovial fluid and serum concentrations of macrophage migration inhibitory factor and interleukin-8 were measured. Synovial fluid monocytes and neutrophils were cultured with monosodium urate crystals and the cytokine production was determined. The signalling pathways involved were determined using signal inhibitors. The interaction between macrophage migration inhibitory factor and interleukin-8 was investigated.

Results: Synovial fluid macrophage migration inhibitory factor was higher in acute gout and that in serum was higher in patients with intercritical gout compared with controls. Synovial fluid macrophage migration inhibitory factor was positively correlated with synovial fluid leukocyte and neutrophil counts and interleukin-8. The expression of macrophage migration inhibitory factor was similar in synovial fluid neutrophils and monocytes, while interleukin-8 was higher in monocytes. Monosodium urate crystals induced macrophage migration inhibitory factor production in monocytes and interleukin-8 production in neutrophils. This effect was decreased by inhibiting Fc-gamma receptor 1 and toll-like receptor 4. Interleukin-8 increased macrophage migration inhibitory factor production in monocytes while macrophage migration inhibitory factor increased interleukin-8 production in neutrophils.