

Possible interplay between interleukin-15 and interleukin-17 into the pathogenesis of idiopathic inflammatory myopathies

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The aim of this study was to assess the serum levels of interleukin (IL)-15 and IL-17 in patients with idiopathic inflammatory myopathies (IIM) and correlate them with IL-6, IL-10, monocyte chemoattractant protein-1 (MCP-1), macrophage inflammatory protein-1 α (MIP-1 α), MIP-1 β levels. Possible correlations with disease activity parameters were also evaluated.

Sera from 14 polymyositis (PM), 10 dermatomyositis (DM), 7 anti-synthetase syndrome new onset patients and 19 healthy controls (HCs) were analyzed by multiplex immunoassay. Sera from 19 patients were analyzed after 5 months median follow-up. All patients underwent physical examination, the 5-points manual muscle test (MMT), the health assessment questionnaire and serum creatine kinase measurement. All patients received glucocorticoids, and 13 were taking also immunosuppressive therapy.

At baseline, serum levels of IL-15, IL-17, MCP-1 and MIP-1 β were significantly higher in IIM patients than in HCs. IL-17 serum levels were directly correlated with disease duration ($r=0.39$, $P=0.02$), while a significant inverse correlation was detected between IL-17 levels and MMT scores ($r=-0.4$, $P=0.02$). The highest IL-15 levels were present in DM patients ($P=0.02$ vs PM). The most striking finding was the strong correlation between IL-15 and IL-17 levels ($r=0.60$, $P=0.0001$), and this correlation was even stronger in DM patients ($r=0.82$, $P=0.006$).

The strong correlation between IL-15 and IL-17 in IIM patients, and especially in DM, suggests that there may be an interplay between the two cytokines in the pathogenesis of myositis. Further studies of larger patient cohorts and muscle biopsies are needed to confirm these preliminary data.

Key words: Interleukin (IL)-15, IL-17 isoform A, IL-6, IL-10, Monocyte chemoattractant protein-1, Macrophage inflammatory protein (MIP)-1 α , MIP-1 β , Idiopathic inflammatory myopathies.

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INTRODUCTION

Idiopathic inflammatory myopathies (IIM), including polymyositis (PM) and dermatomyositis (DM), are heterogeneous diseases occurring with proximal symmetrical muscle weakness, increased serum muscle enzymes, inflammatory infiltrates on muscle biopsy and specific skin lesions (1, 2). IIM can also be sub-classified on the basis of the auto-antibody profile. Among myositis-specific auto-antibodies, those targeting aminoacyl-tRNA synthetases have been associated with a specific clinical phenotype, the so-called anti-synthetase syndrome (ASS), anti-Jo-1 being the most frequent antibody (3-5).

Even if the pathogenesis of IIM is not yet

fully understood, many authors suggest that an active role may be played by cytokines found both in muscle tissue and peripheral blood, including interleukin (IL)-15, IL-17, IL-6, IL-10, monocyte chemoattractant protein-1 (MCP-1), macrophage inflammatory protein-1 α (MIP-1 α), and MIP-1 β (6-19). Recently, IL-15 and IL-17 have emerged as candidate mediators of induction/expansion of the pro-inflammatory cytokine cascade in IIM, and systemic or muscle production of IL-15 and IL-17 has been demonstrated in patients affected by IIM (20-22). IL-15, originally identified as T cell activating factor, is widely expressed in human tissues including skeletal muscle, but it is rarely detected in healthy conditions. It participates in the development

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of natural killer cells, binding its unique receptor shared with IL-2. IL-15 has been reported to be increased in autoimmune or inflammatory diseases, such as in the synovial fluid or membrane of rheumatoid arthritis (RA) patients (23-25). In PM and DM, IL-15 and its receptor have been found in muscle tissue, and high serum levels have also been detected (11, 20, 22). It is well known that the T helper 17 pathway is one of the most important mechanisms inducing and maintaining chronic inflammation (26). In IIM, IL-23 and IL-17 amplify the immune response by activating monocytes and innate immunity, ultimately leading to muscle destruction (21, 27). In RA, a strong correlation between IL-15 and IL-17 has been found, as IL-15 induces the T cells to produce IL-17 which stimulates synoviocytes to release pro-inflammatory mediators (28). To our knowledge, in IIM a possible interaction between IL-15 and IL-17 has not previously been explored.

In this study we aimed at evaluating the behavior of IL-15 and IL-17 serum levels and correlating them with the other cytokines involved in the pathogenesis of muscle damage in PM, DM and ASS patients at baseline and follow-up. In addition, possible correlations with scores of the 5 points-manual muscle test (5-MMT), health assessment questionnaire (HAQ) and creatine kinase (CK) were assessed.

■ MATERIALS AND METHODS

Patients

The study included 31 consecutively enrolled Caucasian patients affected by IIM [26 women, 5 men (mean age \pm standard deviation, SD) 58.8 years \pm 2.1]. According to Bohan and Peter criteria (29, 30), definite PM was diagnosed in 14, definite DM in 10, and 7 patients were classified as having ASS anti-Jo-1 positive (ASS anti-Jo-1+ve) (31). Only three of the 7 ASS anti-Jo-1+ve patients had myositis, 2 PM and 1 DM. The control group included 19 healthy controls (HCs) (16 women, 3 men, mean age \pm SD of 45.8 years \pm 1.8). We defined as baseline the time the patient was enrolled in

the study. At baseline the median disease duration was 12 months, and the patients were longitudinally followed with regular check-ups. Prior approval of the study was obtained from the local ethics committee and patients were enrolled after giving written informed consent in accordance with the Helsinki declaration.

All patients underwent physical examination, the total MMT (group of 24 proximal, distal, and axial muscles assessed bilaterally) scored by the 5-points Medical Research Council scale (32) generated a final score as a result of the average of all muscles tested scores, HAQ (33) and routine blood tests including CK assessed by ELISA (normal values 84-199 U/L). At baseline, serum was obtained from each patient, and frozen at -80°C until use. A second sample was obtained after a median follow-up of 5 months in 19 patients. Patients demographic, clinical and laboratory data are summarized in Table I.

At baseline, all patients were taking low doses of glucocorticoids [median 5 mg daily, inter-quartile range (IQR) 5.6]. 13 patients were also treated with disease modifying anti-rheumatic drugs (DMARDs), 5 with azathioprine (AZA), 3 with methotrexate (MTX), 1 with cyclosporine A (CYC), 3 with a combination of MTX-AZA and 1 with a combination of CYC-MTX. The other 18 were DMARDs-free.

Serum cytokines measurement

Multiplex immunoassay (Bioplex 200 System, Bio-Rad Lab., Hercules, CA, USA) was used to simultaneously measure the serum levels of IL-6, IL-10, IL-15, IL-17 isoform A, MCP-1, MIP-1 α and MIP-1 β in all patients and HCs. We used the commercial human antibodies kit produced by Bio-Rad (Bioplex Pro™ Cytokine Assay, 1 x 96 well 9-plex Group I, Bio-Rad). The assay was performed according to the manufacturer's instructions. The ranges of measurability of the standard curve were 0.07-19,147 pg/mL for IL-6, 0.11-28,093 pg/mL for IL-10, 0.1-24,906 pg/mL for IL-15, 0.08-21,505 pg/mL for IL-17, 0.09-23,735 pg/mL for MCP-1, 0.08-21,778 pg/mL for MIP-1 α and 0.08-20,198 pg/mL for MIP-1 β .

Table 1 - Disease characteristics of the patients at baseline and follow-up.

Pt	Age At onset	Gender	Ethnicity	Dg	AutoAb	Skin	Arthritis	ILD	Dysphagia	Cancer	Dis. Durat.	Steroid	DMARDs	CK 1th	MMT1th	HAQ 1th	Follow up (months)	CK 2nd	MMT 2nd	HAQ 2nd
1	50	F	Caucasian	ASS Jo-1+	ANA+, anti SSA+, anti Jo1+	yes	yes	yes	yes	no	132	7.5	MTX-AZA-Ig	389	4.24	1.75				
2	56	F	Caucasian	ASS Jo-1+	ANA+, anti Jo1+	no	no	yes	yes	no	60	5		151	4.71	1.12				
3	48	F	Caucasian	ASS Jo-1+	anti SSA+, anti Jo-1+	no	no	yes	no	no	12	10		533	4.69	2.12				
4	70	F	Caucasian	ASS Jo-1+	ANA+, anti Jo-1+	no	yes	yes	no	no	4	10		68	4.83	0.37	11	87	4.65	0.37
5	51	F	Caucasian	ASS Jo-1+	ANA+, anti Jo-1+	yes	no	yes	no	no	12	5		83	4.36	2.37	5	51	4.36	1.37
6	50	F	Caucasian	ASS Jo-1+	ANA+, anti SSA+, anti Jo-1+	yes	yes	yes	no	no	6	10	CYC-MTX	58	4.9	0.25	6	31	5	1.75
7	66	F	Caucasian	ASS Jo-1+	ANA+, anti SSA+, anti Jo-1+	yes	yes	yes	no	no	17	25		712	4.73	1.37	5	301	4.73	1.12
8	58	F	Caucasian	DM	ANA+, anti TIF1 γ +	no	yes	no	yes	yes	2	10								
9	48	F	Caucasian	DM	ANA+, anti Mi-2+	no	yes	yes	no	no	36	25	MTX	186	4.87	0.87				
10	84	F	Caucasian	DM	ANA+, anti SAE1-2+	no	yes	yes	no	no	1	25		58	4.24	1.75				
11	72	F	Caucasian	DM	ANA+, anti SSA+, anti SAE1-2+	no	yes	yes	no	no	8	10	CYC	21	4.29	1.75				
12	66	F	Caucasian	DM	ANA+	no	yes	yes	no	no	1	5		59	4.35	2.12	9	85	4.5	1.75
13	65	F	Caucasian	DM	ANA+	no	yes	no	yes	no	9	25	MTX-AZA	201	3.6	N.A.				
14	41	F	Caucasian	DM	ANA+, anti SAE2+	no	yes	no	yes	no	3	5		170	3.85	N.A.	5	110	3.85	N.A.
15	49	F	Caucasian	DM	None	no	yes	no	no	no	15	2.5	AZA	74	4.65	1.12	5	84	5	1.12
16	60	M	Caucasian	DM	None	no	yes	yes	yes	no	15	5		18	4.7	0.62	4	94	4.75	0.62
17	45	F	Caucasian	DM	None	no	yes	no	yes	yes	4	25		151	3.46	2.75	4	127	4.5	0.87
18	69	F	Caucasian	PM	ANA+	yes	no	yes	yes	no	1	5		205	3.33	2.87				
19	33	M	Caucasian	PM	ANA+, anti Pm-Scl+, anti Scl70+	no	yes	yes	no	no	7	12.5	MTX-AZA	574	5	0.62	16	105	4	N.A.
20	46	F	Caucasian	PM	ANA+	yes	no	yes	yes	no	36	2.5		385	2.72	3				
21	67	F	Caucasian	PM	ANA+, anti Pm-Scl+, anti Scl70+	no	no	yes	yes	no	11	25	MTX-AZA	881	4.5	N.A.	16	191	5	N.A.
22	56	M	Caucasian	PM	ANA+, anti SSA+, anti Pm-Scl+	no	no	no	yes	no	4	25		3210	3	N.A.	1	122	3.9	N.A.
23	58	F	Caucasian	PM	ANA+, anti SSA+	no	no	yes	yes	no	108	5	AZA	250	3.86	2.25				
24	44	F	Caucasian	PM	None	yes	no	no	no	yes	1	5		11706	4.87	1.12	12	70	4.9	0.75
25	40	F	Caucasian	PM	ANA+	no	no	yes	yes	no	84	5	AZA	98	4.69	2.5				
26	36	F	Caucasian	PM	ANA+, anti SSA+	yes	no	yes	yes	no	72	2.5	MTX	582	4.8	1.2	20	138	4.83	1.5
27	67	M	Caucasian	PM	None	no	no	no	yes	no	14	5	MTX	324	4.44	1.5	20	143	4.68	0.75
28	64	F	Caucasian	PM	None	no	no	no	no	no	12	5	AZA	438	4.31	0.12	21	288	4.9	0.25
29	52	F	Caucasian	PM	None	no	no	no	yes	no	36	5		327	4.37	1.75	5	228	4.71	1.75
30	76	F	Caucasian	PM	ANA+, anti SSA+	no	no	yes	no	no	1	10		1161	4.86	2.75	4	106	4.95	0.87
31	78	M	Caucasian	PM	None	no	no	no	no	no	1	5		918	4.86	1.12	4	378	4.5	1.12

Pt, patient; Dg, diagnosis; AutoAb, autoantibodies; Skin involv., skin involvement; ILD, interstitial lung disease; Dis. Durat., disease duration (months); DMARDs, disease modified anti rheumatic drugs; CK 1th, creatine kinase first sample; MMT 1th, manual muscle test first sample; HAQ 1th, health assessment questionnaire first sample; CK 2nd, CK second sample; MMT 2nd, MMT second sample; HAQ 2nd, HAQ second sample; PM, polymyositis; DM, dermatomyositis; ASS Jo1+, anti synthetase syndrome Jo1 positive; Steroid, prednisone (mg/day); AZA, azathioprine; MTX, methotrexate; CYC, cyclosporine; N.A., not available.

Statistical analysis

A normal distribution of continuous variables was estimated by Kolmogorov-Smirnov test. Continuous variables were calculated as means plus 1 SD if normally distributed, whereas medians and IQR range were calculated for not normally-distributed continuous variables. For categorical variables, counts and percentages were calculated. Differences in means for normally distributed continuous variables were compared by analysis of variance (ANOVA), while the Kruskal-Wallis test was used to compare not normally-distributed continuous variables. Within-group comparisons between baseline and follow-up results were evaluated by the Wilcoxon signed-rank test. Spearman's rank correlation test was used to correlate not normally-distributed variables, and the Pearson correlation test for normally-distributed variables. Partial correlation analysis was carried out to study the relationship between two variables after excluding the effect of one or more independent factors. Statistical analyses were done using the SPSS (version 20) statistical software; P values <0.05 were considered statistically significant.

RESULTS

Clinical assessment

With respect to the group of patients, at baseline (Tab. I), the median CK level was 325.5 U/L (IQR 691), the median MMT and HAQ scores were 4.67 (IQR 0.4) and

1.28 (IQR 1.1), respectively. CK levels dropped significantly from baseline (median 325.5 U/L, IQR 691) to follow-up (median 116.5 U/L, IQR 158, P=0.001). Neither MMT nor HAQ were significantly different between baseline and follow-up. Furthermore, CK levels did not correlate with MMT (r=0.10, P=0.4) and an inverse correlation was also detected between MMT and HAQ (r=-0.65, P=0.0001).

Cytokines measurement

At baseline (Tab. II), IL-15 serum levels were significantly higher in IIM patients (median 1.12 pg/mL, IQR 5.6) than in HCs (median 0.41 pg/mL, IQR 1.5, P=0.01). IL-17 levels were also significantly higher in patients (median 4.23 pg/mL, IQR 5.5) than in HCs (median 1.44 pg/mL, IQR 1.3, P=0.009). Higher serum levels of MCP-1 and MIP-1 β were detected in IIM patients (median 82.81 pg/mL, IQR 79.4 and median 120.03 pg/mL, IQR 57, respectively) than in HCs (median 35.53 pg/mL, IQR 26.4 and median 83.01 pg/mL, IQR 43.9, respectively), and this difference was statistically significant (P=0.001 and P=0.03, respectively).

Concerning IL-6 and IL-10, no statistically significant differences between IIM patients and HCs have been found. Comparing cytokines serum levels of IIM patients at baseline and follow-up, no significant differences were found.

We assessed whether the serum levels of all cytokines were influenced by glucocorticoids and the clinical parameters at baseline (Tab. III). We found a direct corre-

Table II - Cytokines serum levels at baseline and follow-up.

	Patients (baseline) Median (IQR)	Patients (follow-up) Median (IQR)	P (baseline vs follow-up)	HC Median (IQR)	P (baseline vs HC)
IL-6	3.40 (8.8)	3.17 (3.9)	0.23	1.24 (2.1)	0.051
IL-10	1.94 (1.3)	1.5 (1.7)	0.31	1.35 (3.3)	0.47
IL-15	1.12 (5.6)	1.12 (0.7)	0.72	0.41 (1.5)	0.01
IL-17	4.23 (5.5)	1.44 (0.4)	0.48	1.44 (1.3)	0.009
MCP-1	82.81 (79.4)	62.29 (106.1)	0.06	35.53 (26.4)	0.001
MIP-1a	0.35 (0.8)	0.35 (0.6)	0.20	0.35 (0)	0.46
MIP-1b	120.03 (57)	122.14 (85)	0.15	83.01 (43.9)	0.03

HC, healthy control; IQR, inter-quartile range; IL-6, -10, -15, -17, interleukin-6, -10, -15, -17; MCP-1, monocyte chemoattractant protein-1; MIP-1 α , -1 β , macrophage inflammatory protein-1 α , -1 β .

Table III - Correlation coefficients (r) and significance values (P) between cytokines serum levels and clinical parameters at baseline.

	Steroid dosage		CK		MMT		HAQ		Disease duration	
	r	P	r	P	r	P	r	P	r	P
IL-6	0.33	0.07	-0.04	0.81	0.023	0.90	-0.04	0.84	-0.11	0.45
IL-10	0.43	0.01	-0.07	0.69	0.03	0.86	0.1	0.62	-0.27	0.14
IL-15	0.27	0.13	-0.10	0.56	-0.27	0.13	0.32	0.11	-0.22	0.22
IL-17	0.24	0.17	0.03	0.84	-0.40	0.02	0.19	0.33	0.39	0.02
MCP-1	0.22	0.26	-0.24	0.22	0.12	0.54	0.16	0.44	-0.12	0.53
MIP-1 α	0.39	0.02	0.01	0.92	-0.25	0.16	-0.18	0.37	-0.29	0.10
MIP-1 β	0.02	0.89	0.17	0.36	-0.29	0.12	0.30	0.14	0.42	0.02

CK, creatine kinase; MMT, manual muscle test; HAQ, health assessment questionnaire; IL-6, -10, -15, -17, interleukin-6, -10, -15, -17; MCP-1, monocyte chemoattractant protein-1; MIP-1 α , -1 β , macrophage inflammatory protein-1 α , -1 β .

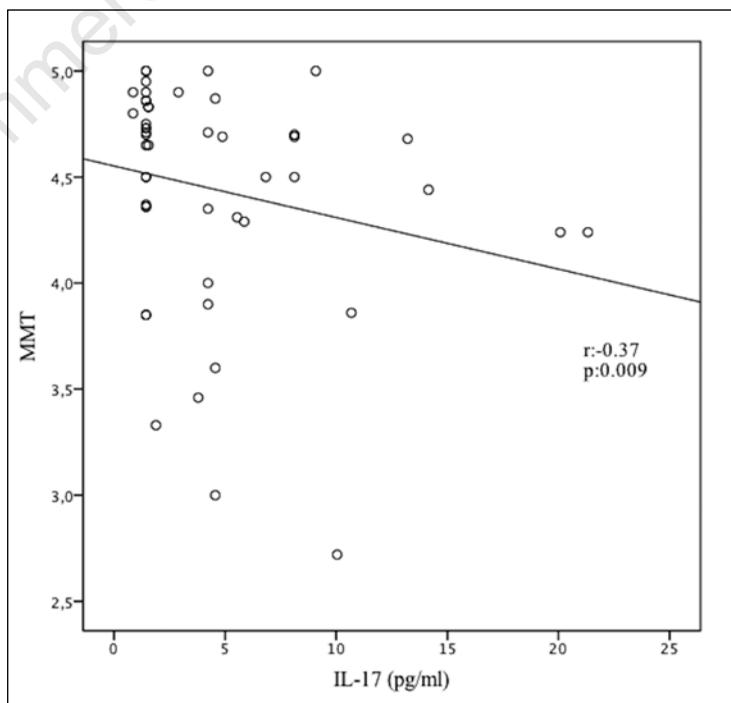
lation between IL-17 and disease duration ($P=0.02$), and an inverse correlation between IL-17 and MMT ($r=-0.40$, $P=0.02$). No correlation between cytokine serum levels and Jo-1 positivity has been found. All patients were receiving glucocorticoids and a direct correlation between the daily dosage of prednisone and IL-10 ($r=0.43$, $P=0.01$), and MIP-1 α ($r=0.39$, $P=0.02$) levels was detected. No correlations between DMARDs intake and the serum levels of all cytokines were found.

At entry, IL-17 was the only cytokine found to correlate with disease activity as MMT score was inversely correlated to IL-17 serum levels ($r=-0.40$, $P=0.02$). To assess whether IL-17 varied depending on the MMT over time, we pooled baseline and follow-up cytokine values and correlated them with MMT scores. Notably, a significant inverse correlation (Fig. 1) was found between IL-17 levels and MMT scores ($r=-0.36$, $P=0.009$).

We also looked for possible different patterns of cytokines among the three subsets of myositis. IL-17 levels did not differ among PM, DM and ASS Jo-1+ve patients. The median IL-15 concentration was 8.8 pg/mL (IQR 12.2) in DM, 1.12 pg/mL (IQR 0.7) in PM, and 1.12 pg/mL (IQR 5.8) in ASS Jo-1+ve, but the difference was statistically significant only between DM and PM ($P=0.02$) (Fig. 2).

Finally, we searched for possible relationships among cytokines in all IIM patients at baseline. Because of the correlation of IL-17 with disease duration, the latter con-

founder was removed by applying partial correlation analysis. The most striking finding was the strong correlation between IL-15 and IL-17 levels ($r=0.60$, $P=0.0001$). In patients affected by DM, the correlation between IL-15 and IL-17 was found to be even stronger ($r=0.82$, $P=0.006$), as shown in Figure 3. No correlation between IL-15 and IL-17 in HCs was found

**Figure 1** - Correlation analysis between the manual muscle test (MMT) score and interleukin (IL)-17 serum levels of idiopathic inflammatory myopathies patients. Baseline and follow-up data were pooled.

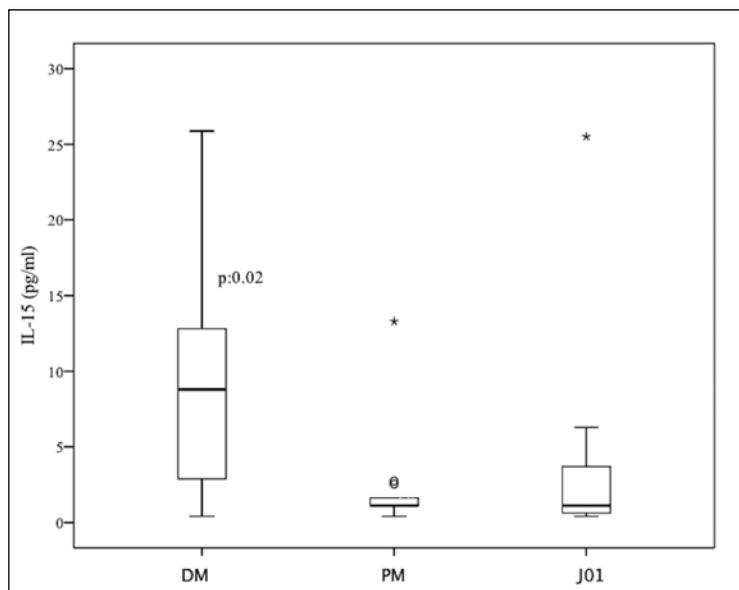


Figure 2 - Comparison of interleukin (IL)-15 serum levels among dermatomyositis (DM), polymyositis (PM), and Jo-1 anti-synthetase syndrome (ASS anti-Jo-1+ve) patients at baseline. Box plots represent medians, 25th and 75th percentiles, and whiskers 10th and 90th percentiles.

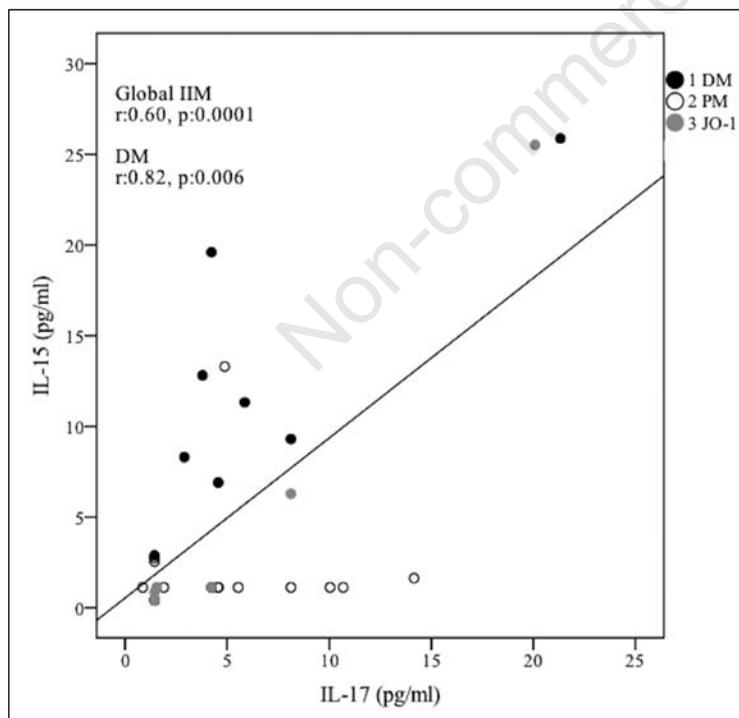


Figure 3 - Correlation analysis between interleukin (IL)-17 and IL-15 serum levels at baseline in all idiopathic inflammatory myopathies (IIM), dermatomyositis (DM) (black close circle), polymyositis (PM) (open circle), and and Jo-1 anti-synthetase syndrome (grey close circle) patients.

($r=0.30$, $P=0.20$). In all IIM, IL-15 levels were also correlated with MCP-1 ($r=0.45$, $P=0.001$), and MIP-1 α ($r=0.30$, $P=0.03$). IL-17 also correlated with MIP-1 β ($r=0.55$, $P=0.0001$).

DISCUSSION

In this study we aimed at evaluating the serum levels of IL-15 and IL-17 in 14 PM, 10 DM and 7 ASS Jo1+ve patients treated in a standard care rheumatology setting, at baseline and after a median follow-up period of 5 months. IL-15 and IL-17 serum levels were also correlated with IL-6, IL-10, MCP-1, MIP-1 α , MIP-1 β serum levels. In addition, we assessed possible correlations between all cytokines serum levels and 5-MMT, HAQ scores and CK concentration.

In agreement with the literature, IIM patients showed higher levels of MCP-1, MIP-1 β , IL-15 and IL-17 than HC (6, 11, 21, 27, 34-39). MCP-1 has already been detected either in sera or in muscle tissue (6, 35-37). While DMARDs did not affect cytokines levels, we found a direct correlation between glucocorticoid dosage and IL-10 or MIP-1 α levels.

In agreement with many reports, high levels of IL-15 and IL-17 were detected in IIM patients (11, 16, 20-22, 27, 39). Unlike a previous study that reported high IL-17 serum levels in early stage disease (27), we found a direct correlation between IL-17 and disease duration. However, differences in serum sampling can account for this discrepancy. We observed, for the first time in IIM patients, that IL-15 and IL-17 serum levels were strongly correlated and that this correlation was not affected by disease duration and therapy.

To date, few and discordant reports concerning comparisons between cytokine serum levels among the different subsets of IIM have been published (16, 40). Instead, our study clearly showed that IL-15 serum levels differed significantly among the clinical subsets, being higher in adult DM than PM. In DM the degree of association between IL-15 and IL-17 was even stronger.

The role of IL-15 and IL-17 in the pathogenesis of IIM is largely unknown, but an interaction between the two cytokines has been demonstrated in RA. IL-17 is strongly expressed in synovial membrane of RA patients (41) and IL-15 is able to stimulate the production of IL-17 by T cells (28). In RA, the uncontrolled release of IL-15, together with the induction of anti-apoptotic signals by Th17 cells, leads to a chronic activation of synoviocytes and progression of the joint damage (42).

Even if RA and IIM are different diseases, IL-15 and IL-17 may also be speculated to have a role in the pathogenesis of IIM. We could envisage that IL-15 and IL-17 mediate the interaction between muscle cells and inflammatory cells.

IL-15 was initially described as an anabolic factor for skeletal muscle, inducing myocyte differentiation and an accumulation of contractile proteins in muscle fibers (43). In IIM muscle, IL-15 is secreted by myoblasts following an interaction between CD40 expressed on myoblasts and CD40L expressed on infiltrating T cells (38).

However, the expression of IL-15 may depend on the grade of differentiation of the muscle fibers (22). IL-15 synthesis has been found to be increased in PM and DM muscle biopsies (20), and circulating IL-15 levels were higher in patients than in controls (11, 39). Recently, IL-15 expression has been demonstrated in macrophages in muscle biopsies from patients with IIM, but not in T cells (22).

Moreover, the IL-15 receptor (IL-15R) has been observed in muscle tissue (20), in particular in mononuclear cell infiltrates and endothelial cells (22).

IL-17, produced by T cells, plays an important role in host defense, inflammation, and autoimmunity (26), and its expression is increased in inflammatory tissues, including IIM (21). Since the identification of Th17 cells in inflamed muscle tissue, IL-17 has been proposed as a co-actor in the immune response that could lead to muscle destruction, and higher serum levels of IL-17 and IL-23, the IL-17 main inducer, have been observed in the sera of PM/DM patients than in HCs (27). Consistently, we found

a strong correlation between IL-17 and IL-15 serum levels in IIM patients and we hypothesize that also in IIM IL-15 acts as a strong inducer/regulator of IL-17 synthesis, even if muscle tissue findings are lacking. In addition, exploring the serum levels of IL-15 and IL-17 in patients with amyopathic DM may help the comprehension of their role in the pathogenesis of IIM.

An inverse correlation between baseline IL-17 serum levels and muscle strength, as measured by the 5-MMT, was observed in our study, suggesting that IL-17 might be a potential biomarker of clinical outcome. However, these findings should be interpreted with caution as MMT score did not substantially vary over time in contrast to IL-17 levels.

In addition, follow-up data are available in a small subpopulation and need to be confirmed in larger studies. We did not find a significant correlation between IL-15 serum levels and the 5-MMT, while a negative correlation between IL-15 muscle expression and the myositis function index has already been reported, although different samples and muscle strength measurements were used in the two studies (22).

The data we have obtained need to be confirmed in larger cohorts of IIM patients. Our future proposal is to investigate IL-15 and IL-17 serum levels at the disease onset before starting any treatment. A better understanding of the IL-15 and IL-17 interplay, especially in the DM subset, may provide further insights into the pathogenesis of muscle damage and identify novel therapeutic targets.

Key messages

- IL-15 and IL-17 serum levels are strongly correlated in patients with IIM, especially in DM.
- Higher IL-15 serum levels have been found in DM than in PM.
- A significant inverse correlation has been found between IL-17 levels and MMT scores.

Conflict of interests: the authors declare no conflict of interests.

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