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POS0888

EPIDEMIOLOGICAL AND CLINICAL DIFFERENCES BETWEEN ANTI-MDA5 PHENOTYPES: DATA FROM A LARGE COHORT (MEDRA5) STUDY

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Background: Idiopathic inflammatory myopathies are a heterogeneous group of systemic autoimmune diseases. Several phenotypes have been linked to specific autoantibodies. Clinically amyopathic dermatomyositis with rapidly progressive interstitial lung disease, the most severe form of ILD, is associated with the anti-MDA5 antibodies. However not all the patients with dermatomyositis and anti-MDA5 positive antibodies develop this severe condition.

Objectives: We aim to define different phenotypes from a large cohort of patients diagnosed with dermatomyositis who were positive to anti-MDA5 antibodies.

Methods: We retrospectively analyzed the clinical and immunological data of 90 anti-MDA5 patients [50 female, 55.6%, mean (SD) age at diagnosis 47 (15.4) yrs.] with dermatomyositis recruited from a multicenter register in Spain (MEDRA5) including 30 hospitals. All the patients fulfill de International Myositis Classification Criteria (EULAR/ACR) for dermatomyositis (score >90%). Anti-MDA5 were detected by means of commercial immunoblot (EUROIMMUN®). The chi-square test was used to assess the relationships between qualitative variables. The Kruskal-Wallis test was used to compare medians between groups.

Results: Sixty-six patients (73.3%) were diagnosed with clinically amyopathic dermatomyositis. Three different phenotypes linked with the anti-MDA5 antibody were identified. Group 1: patients with rapidly-ILD phenotype (28 patients, 31.1%), group 2: antisynthetase-like phenotype (23 patients, 25.5%), and group 3: non-ILD phenotype (39 patients, 43.3%). Clinical and immunological comparison between the groups disclosed that age at disease onset was higher (median, IQR) in patients from group 1 [53 (43-60)] vs. group 2 [46 (40-56)] or group 3 [42(41-51)] ($p=0.01$); disease onset was more frequent in spring in patients from group 1 (46.5%) than in the rest of the groups (21.7% and 28.9%) ($p<0.01$). Cancer was detected in 7 patients, only associated with myositis in 3 cases (3 years interval between cancer and dermatomyositis) without significant differences between phenotypes. Vasculitis (one case ANCA positive) was detected in 9 cases (6 limited to skin, 1 renal and 1 intestinal), 6 of them in the group 3 (statistical significance, in comparison with group 1 and 2, $p<0.01$). Mortality rate was higher in group 1 (51.9%, 16 out of 17 due to refractory respiratory failure) vs group 2 (12.5%) or 3 (0%) ($p<0.001$). Anti Ro52 positivity was more frequent in group 1 (65.4%) vs. group 2 (25%) or 3 (35.5%) ($p<0.017$), although it did not reach statistical significance in terms of mortality ($p=0.173$) or patients admitted in the intensive care unit ($p=0.173$). Mechanic hands were more frequent in group 2 (40.6%) than in groups 1 (25%) and 3 (34.4%) ($p=0.05$). Fever was significantly most frequent in group 1 (52.6%) than in group 2 (21.1%) and 3 (26.3%) ($p=0.001$). Other clinical or immunological features such as arthritis, myositis, or the number of characteristic skin lesions among others were not more frequent in one group or another.

Conclusion: Three different phenotypes of patients positive to anti-MDA5 were identified. The presence or not of ILD, or the different type (rapidly progressive or not) of ILD were the main feature that allow to differentiate these phenotypes, which are relevant in clinical practice.

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POS0889

CO PRESCRIPTION OF ANTI-ACID THERAPY REDUCES THE BIO AVAILABILITY OF MYCOPHENOLATE MOFETIL IN SYSTEMIC SCLEROSIS PATIENTS

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Background: Mycophenolate mofetil (MMF) is an effective treatment option for systemic sclerosis (SSC). However, many patients require co administration of proton pump inhibitors (PPI) or H2 receptor blockers (HRB) because of significant gastrointestinal manifestations in SSC. Co-treatment with PPI or HRB have shown to be associated with reduced drug exposure in post-transplant patients.^{1, 2} There is scarcity of data among patients with SSC. We evaluated the drug concentration of MMF over 12 hours of exposure and assessed the impact of ranitidine and PPI in twenty patients with SSC.

Objectives: To assess the effect of esomeprazole or ranitidine on the bioavailability of MMF in SSC patients who are on a stable dose of MMF.

Methods: Twenty SSC patients, who were on a stable dose of MMF (1.5-3 g) for the past 3 months were selected for the study after obtaining informed written consent. All patients were given either MMF (without PPI or HRB), MMF + esomeprazole, MMF + ranitidine for one month each. At the end of each month, EDTA plasma samples were collected at various time points including 0, 1/2, 1, 1½, 2, 2½, 3, 4, 5, 6, 8 and 12 hours following drug administration to determine the 12-hour area under curve (AUC) of mycophenolic acid (MPA) levels. Estimation of MPA levels was carried out using reverse phase high performance liquid chromatography (HPLC). Total gastrointestinal score was calculated at the end of each month using UCLA Scleroderma Clinical Trial Consortium GIT 2.0 scoring. To compare the mean AUC, linear mixed effect model was fit by considering treatment as the fixed effect and subject as the random effect. MMF was set as the reference treatment for the other three treatments and these were analysed together using Linear mixed effect model.

Results: All patients were females with mean age of 45 years. Addition of either ranitidine or esomeprazole significantly reduced the mean AUC and C max of the MMF over 12-hour time period. On the other hand, PPI or HRB helped in reduction of the total GI score at the end of 1 month. Details of pharmacokinetics are depicted in the table 1.

Table 1. Pharmacokinetics and GI score with MMF in combination with PPI / HRB

	MMF	MMF+ R	MMF + E	p
AUC	67.97 (62.73, 73.20)	53.04 (44.80, 61.27)	45.69 (41.10, 50.28)	<0.001*
mean (95% CI)				
T- MAX	42.00 (33.60, 50.40)	46.50 (32.48, 60.52)	79.50 (58.99, 100.01)	<0.001*
mean (95% CI)				
C-MAX	29.61(26.74, 32.48)	15.14 (11.32, 18.97)	12.62 (10.58, 14.66)	<0.001*
mean (95% CI)				
Mean GI score	0.28 (0.15,0.40)	0.19 (0.09, 0.30)	0.14 (0.06,0.23)	0.009
mean (95% CI)				

AUC, area under curve Mycophenolic acid; C-MAX, maximum concentration of MPA in 12 hours following MMF; CI confidence interval; Mean GI score, UCLA Scleroderma Clinical Trial Consortium GIT 2.0 scoring; MMF, mycophenolate mofetil; MMF+E, mycophenolate mofetil + esomeprazole; MMF+R, mycophenolate mofetil+ ranitidine; *p value < 0.05 considered as significant

Conclusion: As co administration of PPI or HRB can significantly reduce the bio-availability of MMF in patients with systemic sclerosis. To avoid therapeutic failure of MMF drug level monitoring is essential when these agents re prescribed with MMF.

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POS0890

MACROVASCULAR DYSFUNCTION AND ITS CLINICAL IMPLICATION IN SYSTEMIC SCLEROSIS

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Background: Even though microvascular dysfunction has been implicated in pathogenesis of scleroderma (SSc), there is minimal evidence to suggest presence of macrovascular dysfunction. The clinical implication of macrovascular dysfunction in SSc is unknown. Moreover, data on the correlation between dysfunction in small and large blood vessel is inconclusive. [1-2]

Objectives: To study the correlation between macrovascular dysfunction as assessed by percent change in flow mediated vasodilation (FMD) of brachial artery and microvascular dysfunction as assessed by nail fold capillaroscopy (NFC) findings in SSc. To assess the clinical impact of macrovascular dysfunction.

Methods: This cross-sectional comparative study enrolled patients with SSc and age and gender matched healthy controls. FMD change was calculated using standard USG probe of 5 to 6 MHz in right brachial diameter from the average of 3 consecutive end diastolic frames. NFC was performed using portable nail fold capillary microscope at 800X magnification. Clinical features of SSc were compared between SSc patients with and without macrovascular dysfunction.

Results: This study enrolled 59 SSc patients including 29 (49.2%) diffuse, 20 (20.4%) limited, 08 (10.2%) sine SSc and 2 patients (3.4%) with myositis overlap. SSc patients had significantly (p<0.0001) lower % FMD change compared to healthy controls. NFC showed significantly higher architecture distortion (p<0.0001), loss of capillaries (p<0.0001) and abnormal capillaries (p<0.0001). There was no correlation between FMD change and capillary density (p=0.381), avascular area (p=0.266) and abnormal capillaries (p=0.899). None of the clinical features like pulmonary hypertension, digital ulcer burden, acro-osteolysis and auto amputation were different between SSc with and without macrovascular dysfunction.

Conclusion: Macrovascular dysfunction in SSc is substantial and it seems to be independent of the microvascular dysfunction. The clinical implications of macrovascular dysfunction are yet to be identified.

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Table 1. Comparison of various parameters between the SSc patients with healthy controls.

Parameter	Frequency (percentage)/median (interquartile range)	
	SSc patients (n=59)	Healthy controls (n=64)
Demographic details		
Age in years	38 (27-46)	36.5 (28.25-42)
Gender		
Male	03 (5.1%)	03 (4.7%)
Female	56 (95.1%)	61 (95.3%)
FMD findings		
FMD % change*	4.54 (3.13-8.82)	10.30 (8.33-13.16)
NFC findings		
Number of capillaries*	51 (38-63)	121 (113-128)
Average capillary density*	3.19 (2.38-3.94)	7.56 (7.06-8)
Disorganized architecture (%)*	37.5 (12.5-37.5)	0
U shape (%)*	50 (36.59-68.09)	85.51 (82.97 – 88.53)
Abnormal (%)*	36.11 (14.03-55.26)	0
Enlarged (%)*	10.63 (2.94-23.68)	0
Giant (%)*	21.05 (0-45.45)	0
Microhemorrhages (%)*	6.25 (0-12.5)	0
Neoangiogenesis (%)*	3.85 (0-20)	0
Avascular area (%)*	50 (31.25- 75)	0

*parameters with statistically significant (p value< 0.0001) difference among two groups. SSc: Systemic Sclerosis, FMD; flow mediated vasodilatation, NFC; nail fold capillaroscopy

Figure 1. Scatter plot showing correlation between FMD percentage change and average capillary density. (r= 0.116) (P-value - 0.381)

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POS0891

IMPROVED SURVIVAL IN SYSTEMIC SCLEROSIS PATIENTS DURING LAST DECADE: CURRENT FINDINGS AND COMPARISON WITH DIFFERENT PREVIOUS ITALIAN COHORTS

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Background: Systemic Sclerosis (SSc) is a chronic rheumatic disease characterized by an autoimmune disorder with vasculopathy that leads to an excess in collagen and other extracellular matrix proteins deposition. This process results in progressive fibrotic and vascular damage of skin and visceral organs.