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AB0566

NAILFOLD EXTENT OF REDUCED CAPILLARY DENSITY IS ASSOCIATED WITH DIGITAL ULCERS AND WITH AN INCREASED RISK OF DIGITAL ULCERS IN SYSTEMIC SCLEROSIS

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Background: A growing evidence supports the role of microvasculopathy as a primary pathogenic event in systemic sclerosis (SSc). The most commonly used imaging technique to identify microangiopathy in SSc is high magnification videocapillaroscopy (NVC), and reduced capillary density and/or capillary loss, which is a typical feature of "scleroderma microangiopathy", easily identified by NVC, has been associated with digital ulcers (DUs). Different approaches have been proposed to measure capillary density or capillary loss. Some of these were qualitative methods, others semi-quantitative, others only concerned a limited nailfold area, without ever evaluating the overall density, which is more suitable for quantitative estimate.

Objectives: To assess the association between the extent of different values of nailfold capillary density and the presence of DUs and to identify the risk of developing DUs, based on quantitative parameters.

Methods: The study involved 54 SSc selected patients (47 women and 7 men, mean age 59.5 years, 50 with limited and 4 with diffuse). The study population came from an ongoing database, that includes clinical and laboratory data of patients with definite SSc. A videocapillaroscope (VideoCap® 3.0, DS Medica, Milan, Italy) with a 200x optical probe was used. During examination, eight fingers (fingers 2–5 of each hand), 4 fields per finger, according to the standard literature were assessed. For each patient, a total of 32 images were collected, then classified as having either "normal", "non-specific" or the "scleroderma pattern" (SP). Capillary density was defined as the number of capillaries/mm in the distal row, regardless of its shape and morphology. Avascular areas were defined by the absence of loops within a width/area extending over more than 500 microns. For each patient, the SP images were further graded with no/slight reduction of the capillary density (7-9 loops/mm) (NOR), with a well-defined reduction of capillary density (6-4 loops/mm) (RED) and with loss of capillaries (<4) plus avascular areas (AA). Then, the overall percentages were calculated (the number with SP, the number with NOR, with RED and with AA, respect to 32), thus obtaining the quantitative measures. All data were analysed using the MedCalc® version 18.6; 64-bit (MedCalc Software, Mariakerke, Belgium).

Results: A total of 1728 images were analyzed. Patients with DUs were 16/54 (29.6%). All patients had a SP, but only five patients showed a SP along the entire nailfold. A comparison between patients with or without DUs showed a significant difference both for the overall extent of AA ($p=0.032$), and particularly for the overall extent of RED ($p<0.001$). No significant difference was found regarding the overall extent of the SP ($p=0.085$). Factor significantly associated with DUs in multivariate analysis was the overall extent of RED ($p=0.0286$). The ROC curve was very effective at discriminating the capillary feature able to distinguish patients with DUs from patients without DUs. The discriminatory power of the overall extent of RED was very good, with an AUC of 0.948 (95 % CI 0.852 ± 0.990). Then, we calculated the cut-off values of the overall extent of RED for presence/absence of DUs with the highest combination of sensitivity and specificity. The resulting cut-off value (Yourden index of 0.825) was >68.7 (sensitivity 92.31 %; specificity 90.24 %) with a LR+ of 9.46.

Conclusion: Our data strongly support that the capillary density between 4 and 6 loops/mm is the best capillaroscopic quantitative measure associated with DUs and able to discriminate the probability of having DUs. If all SSc-specific antibodies and/or other laboratory/clinical parameters are not yet available, the overall capillary density can allow physicians to assess SSc patients easily, regarding DUs and risk for developing DUs.

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AB0567

CHARACTERIZATION OF PATIENTS WITH IDIOPATHIC INFLAMMATORY MYOPATHY AND MYOCARDIAL INVOLVEMENT: A MONO-CENTRIC EXPERIENCE.

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Background: Idiopathic inflammatory myopathies (IIM) are immune-mediated disorders of the skeletal muscle, with dermatomyositis (DM), polymyositis (PM), inclusion body myositis (IBM) and immune-mediated necrotizing myopathy (IMNM) representing major subtypes. Beyond skeletal muscle, other organs may be affected and myocardial involvement may lead to severe life-threatening complications. The exact prevalence of myocardial involvement among IIM patients and its impact on other disease characteristics remain unclear.

Objectives: To investigate the prevalence of myocarditis in patients affected by IIM in and to determine whether the presence and extent of myocardial involvement identify a distinct disease phenotype.

Methods: 42 longitudinally followed IIM patients were routinely screened for myocardial involvement during a median [IQR] follow-up time of 4.2 [2-8.5] years. Patients with secondary causes of myocardial dysfunction were not included. Patients were considered to have myocarditis in case of: *i*) abnormal elevation of both circulating troponin T and troponin I, *ii*) signs of myocardial inflammation or necrosis/fibrosis at cardiac MRI, or *iii*) positive myocardial tissue histology. Demographic, clinical and serologic features of patients with myocarditis were compared to those with no sign of myocardial involvement. Moreover, we determined whether the extent of myocardial involvement based on troponin levels predicts skeletal muscle disease severity.

Results: 57.1% (24 of 42) of patients had myocarditis. The frequency of myocardial dysfunction was similar among patients with DM, PM, IBM or IMNM and was not related to autoantibody positivity. Myocarditis was not associated with sex or ethnicity. Patients with or without myocarditis were similar in terms of age at disease onset and extra-muscular manifestations including dysphonia, dysphagia, arthralgias or arthritis, Raynaud phenomenon or interstitial lung disease. Independent of the IIM subtype, the presence of perimysial macrophages at skeletal muscle biopsy seems to protect from myocarditis development ($p=0.04$). Patients with myocarditis had higher median [IQR] levels of aldolase (10.9 [7.8-15.8] vs. 5.6 [4.9-8.6], $p=0.014$) and creatine kinase (1785 [966-5852] vs. 685 [168-2255], $p=0.04$) compared to patients with no myocardial dysfunction. Among patients with myocarditis, levels of troponin I negatively correlated with manual muscle testing 8 (MMT8) score ($r=-1$, $p=0.01$), strength in biceps ($r=-0.95$, $p=0.014$) and wrist extensors ($r=-0.95$, $p=0.014$) at last visit. Troponin T and troponin I titers were similar among patients with different IIM subtypes. C-reactive protein ($p<0.04$) but not erythrocyte sedimentation rate was found to predict myocardial involvement.

Conclusion: Our findings suggest that myocarditis is a frequent occurrence among patients with IIM and should be routinely ruled out. A more severe skeletal muscle disease is associated with an increased likelihood of myocarditis development, presumably due to higher systemic disease activity or inefficient disease control. The extent of myocardial damage faithfully reflects the severity of skeletal muscle dysfunction.

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AB0568

BASELINE EUROPEAN PATIENT DEMOGRAPHICS AND DISEASE CHARACTERISTICS IN A PHASE 3 STUDY OF SAFETY AND EFFICACY OF LENABASUM, A CB2 AGONIST, IN DIFFUSE CUTANEOUS SYSTEMIC SCLEROSIS

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Background: We previously presented on the baseline characteristics of a large cohort of diffuse cutaneous systemic sclerosis (dcSSc) patients enrolled in a Phase 3 trial of lenabasum, a selective cannabinoid receptor type 2 (CB2) agonist. Lenabasum, was safe and well-tolerated in a prior Phase 2

study in dcSSc patients and associated with improvements in ACR Combined Response Index Systemic Sclerosis (CRISS) score and multiple secondary efficacy outcomes.

Objectives: We now report on the background standard of care and baseline disease characteristics of European (EU) patients in order to assess variability by geographic regions.

Methods: The RESOLVE-1 Phase 3 study was designed with input from study investigators and regulatory authorities. An important intent of the design was to have eligibility criteria that allow testing of efficacy and safety of lenabasum in an inclusive group of dcSSc subjects to maximize relevance to patients in current practice. The study is ongoing and remains blinded.

Results: Primary efficacy outcome is the ACR CRISS score at 12 months, comparing lenabasum 20 mg BID to placebo. Key inclusion criteria are males and females ≥ 18 years of age with dcSSc and disease duration ≤ 6 years who are on stable standard of care medicines, with background stable immunosuppressive medications allowed. Baseline mRSS needed to be ≥ 15 if disease duration was > 3 to ≤ 6 years at enrollment. The study enrolled 110 EU subjects over 15 months who received ≥ 1 dose of study drug at 20 sites in 7 countries. Baseline characteristics as shown in Table 1. The majority were middle-aged, female, and white, and 80% were on immunosuppressive drugs in EU region; methotrexate (MTX) used in 30% of subjects, mycophenolate/mycophenolic acid (MMF) used in 46% of subjects, and 43% of subjects took ≥ 2 concurrent immunosuppressive drugs. There were regional differences in background immunosuppressive with use of MTX, MMF and corticosteroids highest in EU, NA and Asia, respectively.

Table 1. Patient Baseline Demographics and Disease Characteristics by Regions (Blinded)

Characteristic at First Dose	Mean (SD) or %		
	Region		
	Europe N = 110 (30.1%)	US, CA, AU, IL N = 189 (51.8%)	Asia N = 66 (18.1%)
Years of age	51 $\pm$ 11.7	51 $\pm$ 13.5	49 $\pm$ 13.2
Female	75%	78%	71%
ILD	55%	40%	58%
Caucasian	101 (91.8%)	148 (78.3%)	0 (0.0%)
Asian	2 (1.8%)	10 (5.3%)	66 (100.0%)
Black	2 (1.8%)	16 (8.5%)	0 (0.0%)
Other	5 (4.6%)	15 (7.9%)	0 (0.0%)
Any immunosuppressive drug	80%	89%	79%
≥ 2 immunosuppressive drugs	43%	48%	38%
Mycophenolate	46%	70%	26%
Corticosteroids	31%	31%	53%
Methotrexate	30%	22%	23%
Other	31%	41%	26%
Modified Rodnan Skin Score	21.9 $\pm$ 7.75	23.8 $\pm$ 8.41	20.0 $\pm$ 7.72
Physician Global Assessment	5.9 $\pm$ 1.57	5.3 $\pm$ 1.56	5.0 $\pm$ 1.50
Patient Global Assessment	4.9 $\pm$ 2.02	5.0 $\pm$ 2.25	4.8 $\pm$ 1.89
HAQ-DI with aids/devices	1.0 $\pm$ 0.69	1.3 $\pm$ 0.76	0.7 $\pm$ 0.77
Forced vital capacity % predicted	83.2 $\pm$ 18.92	77.5 $\pm$ 16.41	82.5 $\pm$ 14.73

Conclusion: This is the first Phase 3 study to use ACR CRISS as the primary efficacy outcome, a composite outcome of multiple clinically relevant measures of SSc, and the largest interventional study to date in diffuse cutaneous SSc. While the use of background immunosuppressive therapies is significant irrespective of geographic regions, MTX use is highest in the EU. Benefits of having inclusive eligibility criteria are that they facilitated timely full enrollment and will make the study more relevant to real-world practice. This study provides a model for future Phase 3 trials in dcSSc and will afford valuable information regarding scleroderma care in practice as well as evaluating the efficacy and safety of lenabasum.

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AB0569

SPECIFIC FEATURES OF VASCULAR DISORDERS IN SYSTEMIC SCLEROSIS-OVERLAP SYNDROMES.

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Background: The Systemic Sclerosis-overlap syndromes are a typical representative of the well-known group of overlap syndromes in rheumatology, causing great difficulties in diagnostic and therapeutic aspects.

Objectives: To identify specific features of vascular disorders in patients with Systemic Sclerosis-overlap syndromes.

Methods: 100 patients (pts) were followed, including 68 pts with Systemic Sclerosis-polymyositis/dermatomyositis (SSc-PM/DM) (f:m 52: 16), aged 17 to 74 years (mean 43 $\pm$ 13.9) and mean disease duration 5 [2-7] years, and 32 pts with Systemic sclerosis-Rheumatoid arthritis (SSc-RA) (f:m 31:1), aged 17 to 74 years (mean age 48 $\pm$ 14.8) and average disease duration 11.5 [5-18,5] years. The comparison group consisted of 100 pts with Systemic sclerosis (SSc) (f:m 90:10), aged 51 to 75 years (mean 51 $\pm$ 12.9) and mean disease duration 10.6 [5-13,5] years.

Results: In 1/3 of pts with SSc-PM/DM, the Raynaud's phenomenon (RP) preceded the emergence of skin lesions and was the first symptom of the disease (33%), developing in the first year in the majority (68%) of cases, being a unique sign of the disease in only 6 (9 %) pts, while in all other cases it was associated with articular involvement, skin lesions and muscle disease. In the first year of the disease 7 pts (10%) already had signs of digital ischemia (scars, ulcers), and by the end of 3 years such signs were present in 1/3 of SSc-PM/DM pts (32%). 29 pts (43%) developed recurrent digital trophic disorders, such as digital scars in 12 (18%), digital ulcers in 16 (23.5%) and digital necrosis of the distal phalanx in 1 pts (1.5%).

In 25 (78%) SSc-RA pts there was a gradual, monosymptomatic – with isolated RP - onset of the disease, similar to chronic cutaneous cSSc. In 29 SSc-RA (91%) pts, RP developed in the first year, and in 23 (72%) it was the first sign of the disease, and in 12 (37.5%) it preceded the development of skin and joint symptoms. Vascular disorders progressed with increasing duration and activity of the process. 7 patients (22%) developed recurrent digital trophic disorders - predominantly finger scars, while 3 (9%) pts had digital ulcers, developing in 11.66 $\pm$ 7.62 years on average from the onset of the disease. Correlation analysis revealed a link between patients' age of and presence of telangiectasias ($p<0.02$). Digital trophic disorders were significantly more frequent in patients with longer disease duration ($p<0.05$).

Comparing of SSc-overlap syndromes and SSc pts showed, that although RP was present in all of them, nevertheless digital vascular-trophic disorders such as scars, ulcers ($p<0.02$) and necrosis ($p<0.001$) were less likely to develop in pts with SSc-overlap syndromes, similarly, telangiectasia and osteolysis were also significantly less frequent ($p=0.04$) distinguishing SSc-overlap syndromes from limited SSc (Table). Although, SSc-overlap syndromes pts had more severely affected muscles and joints as compared to SSc.

Table. Comparative characteristics of vascular disorders in SSc and SSc patients

Analyzed features	SSc n=100 (%)	SSc- overlap syndromes n=100 (%)	SSc-PM/DM n= 68 (%)	SSc-RA n=32 (%)
Raynaud phenomenon	100 (100)	100 (100)	68 (100)	32 (100)
Digital trophic disorders:				
scars	19 (19)	19 (19)**	12 (18)	7 (22)
ulcers	34 (34)**	19 (19)**	16 (23,5)	3 (9)**
necrosis	16 (16)***	1 (1)***	1 (1,5)***	0 (0)***
Telangiectasia	60 (60)*	46 (46)*	34 (50)	12 (37,5)*
Osteolysis	37 (37)*	24 (24)*	16 (23,5)	8 (25)

* $p<0,05$, ** $p<0,03$, *** $p<0,001$

Conclusion: Digital trophic disorders (ulcers, necrosis), as well as telangiectasia and osteolysis are significantly less likely to develop in SSc-overlap syndromes than in SSc, which should be taken into account when planning therapeutic strategies in this category of patients.

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