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: 521% (24 of 42) of patients had myocarditis. The frequency of myocardial dysfunction was similar among patients with DM, PM 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 perimyosial 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 extenders (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.

References:

Disclosure of Interests: None declared

DOI: 10.1136/annrheumdis-2020-eular.6248
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 20mg 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/methylprednisolone (MMF) used in 46% of subjects, and 43% of subjects took ≥ 2 concurrent immunosuppressive drugs. There were regional differences in background immunosuppressive use with MTX, MMF and corticosteroids highest in EU, NA and Asia, respectively.

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

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<th>Characteristic at First Dose</th>
<th>Mean (SD) or %</th>
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<td>Europe</td>
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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.


DOI: 10.1136/annrheumdis-2020-eular.3020