S.2.4

JOINT AND TENDON INVOLVEMENT PREDICT SEVERE DISEASE PROGRESSION IN SYSTEMIC SCLEROSIS: A EUSTAR PROSPECTIVE STUDY

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Objective. To determine whether inflammatory joint involvement (synovitis and tendon friction rubs) may predict the progression and severity of systemic sclerosis (SSc) in a large cohort with longitudinal follow-up.
Methods. We included patients from the EUSTAR database (MEDS online) with disease duration less than 3 years and with a follow-up of at least two years. We extracted data regarding the presence or not of synovitis (tender and swelling joints) and tendon friction rubs (rubbing sensation detected as the tendon was moved) and data related to disease progression. Skin progression was defined by a >10% worsening of the modified Rodnan skin score (mRSS). Lung progression was defined by the new onset of pulmonary fibrosis on high resolution CT scan, or the deterioration of lung volume (>10% of forced vital capacity, FVC). Cardiovascular worsening was defined for skin by new ischemic digital ulcers (DU), for lung by pre-capillary pulmonary arterial hypertension (PAH) on right heart catheterization, and for heart by the reduction of the left ventricular ejection fraction below 50% on echocardiography. Renal progression was defined by the occurrence of scleroderma renal crisis.
Results. From the 9165 patients included in the database, 1301 patients (1079 females) met our inclusion criteria (mean ± SD age of 55±15 years, mean ± SD follow-up: 4.5±2.2 years).
In univariate analysis, synovitis and tendon friction rubs were identified as predictors of skin progression (Log-rank test, p=0.0008 and p=0.0002 respectively). In multivariate analysis, after stratification for disease subset and autoantibody status, synovitis and tendon friction rubs remained predictive of skin progression (Hazard Ratio, HR: 1.69, 95% confidence interval, CI: 1.09-2.63 and 1.68, 95%CI: 1.04-2.72 respectively). No impact on lung outcomes was identified. In multivariate analysis, synovitis independently predicted cardiovascular progression both for the occurrence of new ischemic DU (HR: 1.36, 95%CI: 1.01-1.83) and left ventricular dysfunction (HR: 2.20, 95%CI: 1.06-4.57). Tendon friction rubs independently predicted in multivariate analysis scleroderma renal crisis (HR: 3.78, 95%CI: 1.01-6.19).
Conclusion. This first report of the prospective follow-up of EUSTAR patients identified for the first time the merit of inflammatory joint involvement in early SSc patients. These results obtained through the largest worldwide database support the use of these easily detected clinical findings for the risk stratification of SSc patients. These parameters might be used in the future to select high-risk patients, guide therapies and might be regarded as potential surrogate markers for severity.

Session 3: *The Great Debate*

S.3.1

THE GREAT DEBATE - "THE PLACE OF CORTICOSTEROIDS IN SSc"

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The potent anti-inflammatory effects of corticosteroid (CS) therapy find clinical application in (1) early inflammatory diffuse cutaneous SSc; (2) arthritis/tenosynovitis; (3) myositis; (4) pleuritis/pericarditis; (5) rare presentations of myocarditis; and (6) management of inflammatory manifestations of various overlap syndromes. CS therapy remains widely used although there is little hard evidence of clinical efficacy. A recent survey of > 1700 SSc patients in Germany revealed that 41.3% were receiving CS therapy with 16.1% receiving daily doses of 15 mg prednisone equivalents or more.
Adverse effects of CS are numerous and well known to rheumatologists and include fluid retention, weight gain, hypertension, diabetes mellitus, cataracts, increased risk of infection, osteopenia, avascular necrosis of bone and others. A disease-specific complication of CS is thought to be an increased risk of scleroderma renal crisis (SRC). A widely accepted case control study demonstrated an odds ratio of 4.37 for development of SRC associated with CS doses at or above the 15 mg threshold. Similar data suggested that >30 mg per day increased risk of normotensive SRC. Prednisone exposure and dose were subsequently associated with SRC in large French and Italian series.
This clinical scenario is biologically plausible. Glucocorticoids suppress endothelial production of both prostacyclin and nitric oxide and enhance arterial contractile sensitivity to catecholamine. Bradykinin-influenced prostacyclin release is sensitive to CS while influence on arachidonic acid and COX-2 mediated effects are absent. However, CS do exert a protective effect on renal ischemia-reperfusion injury through stimulation of ERK 1/2 phosphorylation and inhibition of caspase release.
Risk factors for SRC independent of CS include a rapid rate of skin thickness progression, palpable tendon friction rubs and the presence of anti-RNA polymerase III antibody. A key question remains unanswered. Is SRC a drug-related toxicity or is the clinical setting in which the CS is employed the dominant risk factor? In a retrospective analysis of early diffuse SSc in the US study of D-penicillamine, measures of disease activity/severity were strongly associated with SRC (skin scores >20; large joint contractures). If these features were lacking, there was no association of prednisone therapy with SRC. The highest risk of SRC was in patients with high disease activity AND corticosteroid.
Question 1: Would you use CS, and, if so, at what dose, in a 38-year-old woman with severe skin thickening (MRSS 25 after only 6 months of disease) who also has definite synovitis and inflammatory myopathy (proximal weakness, CPK 4X normal)?
Question 2: Would you use CS, and, if so, in what dose, in the following clinical scenarios? (a) a patient with progressive interstitial lung disease (FVC declined from 78% to 53% predicted with worsened extent of disease on HRCT). This patient has anti-topoisomerase 1 antibody and mild skin involvement (MRSS 12). (b) A antiU1RNP positive patient with limited cutaneous disease who presents with acute pericarditis with increased effusion unresponsive to NSAID (c) a 67 year old patient is anticentromere positive with limited cutaneous SSc. She is postmenopausal, osteoporotic and receiving PPI for reflux esophagitis. She presents with Sjogren syndrome and a rheumatoid-like arthritis.
In the absence of more robust data, we conclude that early active diffuse scleroderma has a high risk of SRC and these high risk patients are more likely to receive CS. In turn, CS appears to further increase risk of SRC in this clinical setting. Alternate strategies for control of inflammatory features should be considered. If CS remains clinically indicated, efforts should be made to limit dose and exposure