FRI0352

DIFFERENCES IN ANTISYNTHEASE SYNDROME DEFINITION AND RELATED DIAGNOSTIC PERFORMANCE. A SYSTEMATIC LITERATURE REVIEW INFORMING THE NEW ACR/EULAR CLASSIFICATION CRITERIA

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Background: Antisynthetase syndrome (ASSD) lacks of established clinico-serological classification criteria. A taskforce by EULAR and ACR is working on to develop and validate classification criteria for ASSD.

Objectives: To systematically upraise literature to retrieve the available definitions of ASSD and to evaluate their diagnostic performance.

Methods: This systematic review followed a pre-specified protocol. Two research questions (Q1: how is ASSD defined; Q2: what is the diagnostic performance of the definitions) were rephrased into PICO terms to create search strategies. Studies on patients with suspect or confirmed ASSD, including a definition of the disease with any study design, excluding case-reports and narrative reviews, were eligible for inclusion. The diagnostic performance had to be tested against the reference standard of expert opinion. PubMed and Embase were searched from 01/01/1984 to 06/11/2018. Moreover, the ACR and EULAR congress abstracts (2017-2018) were hand searched. The titles and abstracts of the retrieved studies were screened by pairs of reviewers, the full-text of studies fulfilling the inclusion criteria was assessed to confirm eligibility. The references of the included studies were also evaluated in search of additional studies. Data from primary studies were extracted into a pre-specified extraction form and, if possible, 2x2 tables to assess diagnostic performance were completed. Sensitivities, specificities, positive and negative likelihood ratios (LR) were calculated for each study. If the diagnostic performance of a definition or variable was assessed in at least 4 studies, a meta-analysis of diagnostic performance was undertaken. The risk of bias (RoB) was assessed using the most appropriate tool depending on study design.

Results: After the exclusion of duplicates, the searches retrieved 4358 studies, of which 375 suitable for full-text review. Finally, 77 studies were included, along with 1 additional study from hand search and 3 congress abstracts. 72 studies were included in Q1 and 9 in both Q1 and 2. The presence of antisynthetase antibodies (70 studies), mainly anti-Jo1 (57 studies); myositis (51 studies), mainly defined clinically (32 studies); and interstitial lung disease (38 studies) were the variables most frequently used to define ASSD. Other variables, such as arthritis (19 studies), Raynaud's phenomenon and skin manifestations (10 studies each) were included less frequently. Most commonly, ASSD was defined by a combination of clinical and serological variables. However, no study evaluated the diagnostic performance of such combined definitions. Most of the studies included in Q2 (6) evaluated specific variables of muscle biopsy, one evaluated MRI and 2 clinical variables, with a wide variability in the performance of each item. It was possible to meta-analyze data only to assess the performance of perifascicular necrosis/atrophy: pooled sensitivity (95%CI) was 0.53 (0.33,0.72) and specificity 0.63 (0.47,0.76), pooled LR+ 1.45 (0.72,2.89) and LR- 0.73 (0.40,1.34).

Conclusion: ASSD is defined according to a variety of combinations of serological, clinical and histological variables. The performance of these combined definitions however has not been tested, and from the limited evidence available single muscle biopsy variable (perifascicular necrosis/atrophy) seem to perform poorly. The systematic review confirms the need of data and consensus driven classification criteria for ASSD.

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FRI0352B

COMPARISON OF TWO ILOPROST REGIMENS IN TERMS OF ECONOMIC IMPACT AND EFFECTIVENESS

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Background: Systemic sclerosis (SSc) is an autoimmune chronic disease characterized by prominent vascular involvement. Intravenous iloprost (IV ILO), according to the recently updated EULAR recommendations, is indicated for SSc Raynaud's phenomenon (RP) after failure of oral therapy. Moreover, IV ILO could be useful in DU healing and may represent a potential disease modifying medication. However, there are no uniform data regarding type of regimen (dosage, duration and frequency) and infusion modality.

Objectives: The purpose of this study was to compare effectiveness (in terms of DUs) and direct costs, of two regimens of IV ILO infusion in the same cohort of consecutive SSc subjects.

Methods: Protocol A (A): the patient was admitted and 100 mcg of ILO was diluted in 500 ml of normal saline or 5% dextrose solution and infused continually at the maximum tolerated dose until exhaustion.

Protocol B (B): the patient was followed as outpatient at infusion clinic and 50 mcg of ILO was diluted in 250 of normal saline or 5% dextrose and infused at a dose range from 0.5 to 1.5 ng/Kg/min. The dose was escalated at 30 minutes intervals and maintained at the maximum tolerated dose for 5 consecutive hours for two consecutive days. The intervals between the infusions were between 6-8 weeks in both protocols depending on clinical response and availability of places at the Unit.

44 patients who received long term IV ILO as inpatients (Cohort A), after a wash out of 3 months, were switched to ambulatory administration (Cohort B). Thereafter, after one year of follow-up 24 patients of the protocol B were lost to follow-up and 20 patients were maintained on this regimen. Comparison was made between Cohort A (44 patients=A44) in the period between march 2015 and October 2016 (period A), Cohort B (44 patients=B44) between October 2016 and March 2017 (period B44), Cohort B (20 patients=B20), between October 2017 and March 2018 (period B20). Comparison between groups was made by non parametric tests and contingency table analysis when appropriate. Costs were estimated multiplying data related to resource use (drug consumption, hospital stay, outpatient visits, management of complications, etc) by unit cost obtained from the accounting office of the Hospital. All costs were expressed in Euro

Results: Mean number of DUs at the end of period A was 0,37±0,98 in A44 as compared to 0,90±1,39 of period B44 cohort B44 (p=0,045) and 0,55±0,95 of period B20 Cohort B20 (p=n.s.). Cumulative number of DUs was 9/44 in Cohort A (20.5%) as compared to 20/44 in Cohort B44 (45% p=0.002) and 7/20 in cohort B20 (35% p=0.05). High number of drop outs (24/44) in protocol B was due mainly to statistical significant difference in tolerability (adverse events 11% protocol A vs 42% protocol B p < 0,01). Direct costs were higher in protocol A (3132±883 Euros vs 2687±556 Euros) as compared to protocol B, despite the differences were not statistically significant between the two modalities

Conclusion: Protocol A seems to represent a regimen better tolerated and more effective than protocol B. Moreover, protocol B is affected by high rate of drops out due mainly to worse tolerability. Admitting SSc-patients for continuous IV ILO infusion seems to represent a better tolerated and more effective choice than following them as outpatients at infusion clinic, with substantially comparable direct costs in the same SSc cohort.

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Spondyloarthritis – etiology, pathogenesis and animal models

FRI0353

MISREGULATION OF BMP/TGFB SHEDS LIGHT ON THE PATHOGENICITY OF HLA-B27 IN SPONDYLOARTHRITIS

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Background: The class I MHC allele, HLA-B27 is the main genetic factor predisposing to ankylosing spondylitis (AS) and related spondyloarthritis (SpA), a group of osteo-articular disorders combining inflammation with ossification. Until now, hypotheses to explain such striking association discovered 45 years have speculated either on the presentation of particular peptides to CD8⁺ T cells or on aberrant behaviors of the HLA-B27 molecule independent of its antigen presenting function, including slow folding and homodimers formation

Objectives: To unravel aberrant function(s) of HLA-B27 independent of antigen presentation that may explain its pathogenicity.

Methods: *Drosophila* transgenic for SpA-associated HLA-B*27:04 or HLA-B*27:05 or non-SpA -associated HLA-B*07:02, alone or in combination with human β 2-microglobulin (h β 2m) were produced. Genetic interaction tests were used to identify altered pathway(s). Protein-protein interactions were evidenced by proximity ligation assay. Phosphorylation of Smad2/3 was tested on CD4⁺ T cells from HLA-B27+ SpA patients and HLA-B27-neg healthy controls (6-10/group) by PhosFlow.

Results: *Drosophila* transgenic for HLA-B*27:04 or HLA-B*27:05 but not for control HLA-B*07:02 allele, in the presence of h β 2m that allows expression of well-folded HLA-B molecules at the cell surface, developed crossveinless phenotype. This was due to a disturbance of BMP signaling by HLA-B27/h β 2m which repressed Saxophone (Sax) BMP type I receptor (BMPRI) function, resulting in widening of phosphorylated Mad, the *Drosophila* receptor-mediated Smad, gradient, and increased expression of its target genes *dpp* and *omb*. Consistently, HLA-B27/h β 2m well-folded conformers co-localized with Sax at the surface of *Drosophila* cells and also with Sax mammal ortholog ALK2, on immune cells from SpA patients. As predicted, given that Sax orthologs ALK1 and ALK2 are known to exert antagonistic function on TGF β /BMP signaling, we found heightened p-Smad in response to TGF β or Activin A in CD4⁺ T cells from HLA-B27+ SpA patients (p<0.05).

Conclusion: The pathogenic role of HLA-B27 in SpA may result from a TGF β /BMP signaling misregulation due to specific antagonistic interaction with ALK1/ALK2 BMPRI1, at the crosstalk between inflammation and ossification. Interestingly, ALK2 mutations are responsible for the rare mendelian disorder, Fibrodysplasia Ossificans Progressiva that mimicks AS (Ref).

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FRI0354

ASSESSING THE ROLE OF TENDON-T CELL INTERACTIONS IN THE DEVELOPMENT OF CHRONICITY IN SPONDYLOARTHRITIS

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Background: Enthesitis is a hallmark of spondyloarthropathies[1], with mechanical stress or damage in the tendon being proposed as a trigger for the development of inflammation at the enthesis that propagates to the synovial compartment through what has been termed "synovio-entheseal complex"[2]. Increasing evidence supports the role that stromal cells play in the shift of the inflammatory process towards chronicity promoting T cell migration, retention and survival[3]. Therefore, we hypothesize that after tendon damage the crosstalk between stromal and immune compartments contributes to the development of chronic inflammation.

Objectives: We aimed to assess the effect of tendon stromal cells (tenocytes) on T cell migration and activation and the impact of these activated T cells on the stroma.

Methods: Tenocytes were explanted from tissue obtained from anterior cruciate ligament (ACL) reconstructions. The effect of damage on tenocytes after stimulation with conditioned media from tendon explants or IL-1 β was evaluated by qPCR. A transwell membrane system was used to test the impact of conditioned media from tenocytes on T cell migration. T cells and tenocytes were co-cultured with or without the presence of a transwell membrane to quantify T cell activation (CD69 by FACS and IFN- γ by ELISA). Changes in gene expression on tenocytes after co-culture with activated T cells were analysed by qPCR.

Results: In the presence of damage, tenocytes upregulated inflammatory mediators (IL-6, COX2), chemokines (CCL2, CCL5, CXCL10, CXCL12) and adhesion molecules (ICAM-1). Conditioned media, particularly after stimulation with IL-1 β , from tenocytes induced T cell migration. Co-cultures of tenocytes and T cells resulted in activation of T cells that was contact dependant. In turn, these activated T cells upregulated the production of inflammatory mediators in tenocytes and increased the COL3/COL1 ratio.

Conclusion: Our results support a communication between the stromal and immune compartment within the tendon that could be involved in the progression towards chronicity in the context of spondyloarthritis. Following damage, tendon stromal cells are able to induce the recruitment of T cells, that once enter the tissue interact with the stroma. Stromal cells are then further activated to produce inflammatory cytokines and chemokines that amplify and maintain this inflammatory response.

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