Results: RTX quantifications using ELISA and miRAMM were highly correlated, but miRAMM measured consistently higher serum levels, suggesting its ability to detect total serum RTX (including free and complexed rituximab). RTX PK was highly variable between patients, with W2 levels ranging between 43 and 259 μg/mL and AUC ranging between 2,668 and 17,513 μg/mL by miRAMM. W2 RTX levels and AUC were significantly lower in males and in newly-diagnosed patients, and were negatively correlated with body surface area, baseline B-cell count, and BVAS/WG. In multivariate analyses, the main determinants of RTX PK were sex and new diagnosis. Patients with a new diagnosis had higher baseline B-cell counts and BVAS/WG. Patients reaching complete remission at month 6 had similar mean RTX levels compared to patients who did not reach complete remission (W2 level by miRAMM: 136±44 vs 139±46, p=0.76; AUC: 8420±2875 vs 8558±3452, p=0.85). Patients with higher RTX levels generally experienced longer B-cell depletion durations, but RTX levels at the different time-points and AUC were not associated with time to any relapse or time to severe relapse. Similar results were observed when using rituximab quantification by miRAMM and by ELISA.
Conclusions: Despite a dosing protocol adjusted for body surface area, rituximab PK is highly variable between patients, its main determinants being sex and newly diagnosed disease. We did not observe an association between rituximab PK and clinical outcomes. Serum rituximab level monitoring does not seem clinically useful in this context.
Disclosure of Interest: None declared
DOI: 10.1136/annrheumdis-2017-eular.3527

OP0321 RISK OF CORONARY ARTERY DISEASE AND ISCHEMIC STROKE IN PATIENTS WITH ANCA-ASSOCIATED VASCULITIS. A FRENCH POPULATION-BASED STUDY

M. Mourguet[1], D. Chauveau[2], A. Huart[3], D. Ribes[4], S. Faguer[5], L. Sailler[1], G. Pugnet[1]. *[1]Service de Médecine Interne, CHU Toulouse Purpan; [2]Département de Néphrologie et transplantation d'organes; [3]Departement de Néphrologie et Transplantation d'organes; [4]Département de Néphrologie et transplantation d'organe; [5]Département de Néphrologie et transplantation d'organertement de Néphrologie et transplantation d'organe, CHU Toulouse Rangueil, Toulouse, France*

Background: ANCA-associated vasculitis (AAVs), including granulomatosis with polyangiitis and microscopic polyangiitis, are small vessel vasculitides. Modern treatments have greatly improved survival in AAV patients, but significant long-term morbidity and mortality such as cardiovascular disease (CVD) are still associated with this disease.
Objectives: The aim of our study was to assess the incidence, mortality and predictors of CVD in patients with AAVs
Methods: We conducted a retrospective study of AAV diagnosed in Toulouse France teaching hospital between 1981 and 2015. Patients with granulomatosis with polyangiitis (GPA) and microscopic polyangiitis (MPA) were included and classified, after thorough medical chart review, according to the criteria proposed by the Chapel Hill Consensus Conference. Eosinophilic granulomatosis with polyangiitis were excuded. A survival analysis was performed. Hazard ratios and the comparative morbidity and mortality figure (CMF) was calculated as the ratio of expected number of deaths in the standard population to those observed as well as predictors of CVD in patients with AAV were also assessed.
Results: We identified 361 subjects, only 125 met the inclusion criteria, 99 GPA and 26 MPA, 65 (42%) were men and mean age was 61.3±15.7 years at CVD occurrence with a mean follow-up of 88.4±78.3 months since diagnosis.Coronary artery disease (CAD) developed in 10 patients, and ischemic stroke developed in 9 patients (incidence rates of 8.5 per 1,000 person-years and 10.2 per 1,000 person-years, respectively). CAD incidence for AAV patients is two times more than in the general population, independent of age differences between the two populations using the Midi-Pyrénées county CAD registry as a reference (CMF of 1.96; 95CI 0.88 to 4.36). Ischemic stroke incidence for AAV patients is three times more than in the general population, independent of age differences between the two populations (CMF of 3.36; 95CI 1.75 to 6.46).
Smoking habits and history of CAD at AAV diagnosis was strongly associated with CAD occurrence (adjusted HR 8.8; 95CI 2.12 to 36.56, p=0.003 and adjusted HR 10.3; 95CI 1.02 to 104.5, p=0.003, respectively). An ENT flare (adjusted HR 0.12) was a independent protective factor for CAD occurrence. We did not find any statistically significant associated factor with ischemic stroke occurrence in our cohort.
Using direct standardisation, the age adjusted mortality rate for the AAV cohort was 22.5 per 1,000 person-years and for the general population 10.2 per 1,000 person-years. This indicates that mortality for AAV patients is one and a half times more than in the general population, independent of age differences between the two populations (CMF of 1.56; 95CI 1.02 to 2.39).
Conclusions: Patients with AAV have a significantly increased risk of mortality and ischemic stroke and a non–statistically significant trend toward an increased risk of CAD. Monitoring for this complication and vigilance in modifying risk factors are particularly warranted in this patient population.
Disclosure of Interest: None declared
DOI: 10.1136/annrheumdis-2017-eular.6143

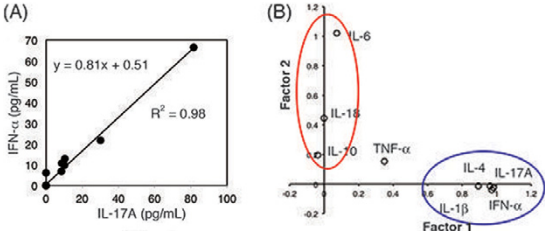
FRIDAY, 16 JUNE 2017

Cytokine taxonomy: reflection in the therapy of arthritides and other IMIDs

OP0322 A NOVEL HIERARCHICAL RELATIONSHIP BETWEEN INTERLEUKIN-17A AND INTERFERON-ALPHA IS INDICATED BY ANALYSIS OF MULTIPLE CYTOKINES IN THE SERUM OF ADULT-ONSET STILL'S DISEASE AND BEHÇET'S DISEASE

K. Sato, Y. Aizaki, Y. Araki, T. Mimura. *Department of Rheumatology and Applied Immunology, Saitama Medical University, Saitama, Japan*

Background: Adult-onset Still's disease (AOSD) and Behçet's disease (BD) are both systemic inflammatory diseases, the causes of which are largely unknown. They have been recently classified as autoinflammatory diseases, a group of diseases in which innate rather than acquired immunity plays important roles in their pathogenesis. As AOSD and BD are clinically distinct diseases, their cytokine networks should also be different.
Objectives: In this study, we attempted to quantify the levels of multiple cytokines in the serum of patients by utilizing a beads-array technique and ELISA, and then compared the serum cytokine profiles of the two diseases by factor analysis. We then sought to clarify the hierarchical relationship between interleukin (IL-) 17A and interferon (IFN-) α using peripheral blood mononuclear cells (PBMCs).
Methods: We quantified the serum levels of 10 cytokines (IFN-α, IFN-γ, IL-1β, IL-2, IL-4, IL-6, IL-10, IL-12p70, IL-17A and tumor necrosis factor α) in 16 AOSD patients and 28 BD patients using multiplex bead array assays and IL-18 along with ELISA. The data were then subjected to factor analysis. We next stimulated PBMCs from three healthy volunteers *in vitro* with class A CpG oligodeoxynucleotides (ODNs) in the presence or absence of IL-17A for 15 hours. We performed flowcytometric analysis to examine the expression of intracellular IFN-α in plasmacytoid dendritic cells (pDCs).
Results: Two factors were extracted from the factor analysis using the data on 8 cytokines that were detectable in the serum of the patients. IL-17A and IFN-α, the levels of which showed a strong positive correlation in the serum of BD patients (Fig. A), were the main components of Factor 1, while Factor 2 consisted of IL-6, IL-10 and IL-18 (Fig. B). Patients were also plotted on a plane determined by Factors 1 and 2 according to each patient's factor scores. Those who were high in Factor 1 but low in Factor 2 were likely to be BD patients and vice versa, many of those who were high in Factor 2 but low in Factor 1 were AOSD patients. In terms of flowcytometric analysis, IL-17A alone did not induce IFN-α expression in pDCs, but it did substantially increase IFN-α-positive pDCs induced by CpG ODNs.



Conclusions: The cytokines examined were clearly separated into distinct groups by the factor analysis. Similarly, the AOSD and BD patients could be separated, although roughly. High levels of serum IL-6, -10 and -18 suggest AOSD while high levels of IFN-α and IL-17A indicate BD. To establish patterns of correlation among cytokines, it is important to focus on the cytokine concentrations in each patient, rather than the average cytokine concentrations in each of the diseases. In terms of the hierarchical relationship between IFN-α and IL-17A, a previous report suggested that IFN-α blocks IL-17A production in PBMCs from BD patients. Thus, we examined the effect of IL-17A on IFN-α production. It should be noted that the real stimulus for IFN-α release in BD is unknown. In addition, cells other than pDCs may be involved in the production of IFN-α. Nevertheless, understanding the hierarchical relationship among cytokines should prove to be helpful in clarifying the pathogenesis of various inflammatory diseases.
Disclosure of Interest: None declared
DOI: 10.1136/annrheumdis-2017-eular.1678

FRIDAY, 16 JUNE 2017

Personalised care for back pain

OP0323 DISCOPATHY ASSOCIATED WITH MODIC CHANGES IS NOT RELATED TO ANY INFECTIOUS PROCESS: A PROSPECTIVE MONOCENTRIC STUDY

S. Ahmed Yahia[1], J.-W. Decousser[2], C.H. Flouzat-Lachaniette[3], F. Robineau[3], E. Audureau[4], A. Hourdille[1], F. Eymard[1], X.-J. Chevalier[1]. *[1]Rheumatology; [2]Microbiology; [3]Orthopaedic; [4]Public health, Henri Mondor hospital, Creteil, France*

Background: Low back pain (LBP) is strongly associated with Modic changes. The

hypothesis of local infectious origin was raised, especially with Proprionibacterium acnes (PA).The possibility of contamination with saprophyte germs coming from the skin during surgery by posterior approach or by epidural infiltration preceding the surgery was also discussed, but not proved.

Objectives: The main objective of this study was to evaluate the prevalence of slow growing bacterias (SGB) in the intervertebral disc (IVD) obtained during a lumbar spine surgery by anterior approach in Modic 1 and 2 changes. A secondary objective was to compare the prevalence of SGB in IVD in lumbar spine surgery obtained by anterior approach to that obtained by posterior approach in herniated disc.

Methods: 45 patients with chronic LBP or sciatica were included in the study, representing 48 IVD. When patients underwent lumbar spine surgery by an anterior approach, 2 samples of the disc were collected for bacteriological analysis: one sample from the anterior part of the disc distant from epidural space and one sample from the posterior part of the disc. 77 discs samples were obtained, 32 discs samples in Modic 1 or 2 changes by anterior approach, 26 discs samples in no Modic IVD by anterior approach, 19 disc samples obtained by posterior approach. The method to collect disc material was strictly aseptic. Samples were analysed by conventional microbial *cultures* with specialised enrichmen, molecular detection by universal rRNA gene PCR *plus* sequencing assay. Additionally, all clinical specimens were specifically tested for PA detection using a highly sensitive specific PCR

Results: Regarding bacterial cultures, 12 out 77 disc samples were positive (16%), including 10 (13%) for PA. The PA specific PCR was positive for one (1%) specimen obtained by posterior approach. The 16s RNA detection was positive for 6 specimen (8%), including one for PA (1%).Modic 1–2: Cultures were positive in 5 cases (16%) with 3 for PA (10%). No specific PA PCR was positive. Only one sample was positive for PA in both culture and 16s PCR. Comparison between anterior and posterior approach: Among the PA positive cultures, 5 were identified from anterior specimens (8.62%) and 5 from posterior specimens (26.32%). Regarding PA cultures,the posterior fragments were more frequently positive than the anterior fragments (p=0.046). The number of epidural infiltrations of the lumbar spine does not seem to influence the bacterial contamination prevalence p=0.746. The time between the epidural infiltration of the lumbar spine and the surgery does not seem to influence the bacterial contamination prevalence (more or less 6 month) p=0.23.

Conclusions: SGB has been identified in culture in 16% of the samples obtained in Modic 1 and 2 changes. The prevalence of PA in culture was significantly higher in samples of IVD collected by a posterior approach compared to anterior approach in spine surgery suggesting a contamination. The results of the specific PCR PAs with a single weakly positive sample reinforce the hypothesis of contamination.

Disclosure of Interest: None declared

DOI: 10.1136/annrheumdis-2017-eular.6873

OP0324 MANAGEMENT OF MUSCULOSKELETAL PAIN USING AN ALGORITHM FOR SELECTION OF ANALGESICS

A. Karateev, A. Tsurgan, N. Gontarenko. *V. A. Nasonova Research Institute of Rheumatology, Moscow, Russian Federation*

Background: Musculoskeletal pain is the most common manifestation of osteoarthritis (OA) and non-specific back pain (BP). Treatment of pain includes medications with a different mechanism of action such as paracetamol, non-steroidal anti-inflammatory drugs (NSAIDs), opioid analgesics, muscle relaxants, antidepressants or local glucocorticoid (GC) injections. However, a uniform approach to sequential and complex therapy with these medications is not so far available.

Objectives: The study aims at evaluating the efficacy of combined therapy of musculoskeletal pain in real clinical practice.

Methods: In the open-label study were included 3304 patients (54.3% women and 45.7% men with average age of 48.9±14.6 years) with acute/subacute pain due to OA or BP. The exclusion criteria were the presence of severe co-morbidities and BP in association with neurological disorders. Treatment was carried out in accordance with the following algorithm: for a moderate/severe pain (>4 scores according to an 11-point numeric rating scale, NRS) use of NSAID (aceclofenac), when NSAIDs are contraindicated – tramadol with/without paracetamol, in case of mild pain – topical NSAID with/without paracetamol, and muscle relaxants as indicated. Control of treatment efficacy was carried out on day 7 (a total of 4 visits). Change of therapy could be done at each visit and include switching to the other NSAID if the prescribed drug proved to be ineffective or intolerant, local glucocorticoid (GC) injection, addition of tramadol with/without paracetamol or administration of antidepressants or anticonvulsants. The results of treatment were assessed based on the dynamics of pain using NRS, a number of patients in whom pain was relieved completely and treatment satisfaction (a 0 to 5 rating scale where 0 is the absence of the effect or pain aggravation and 5 is an excellent effect).

Results: The first prescribed medication in 97.5% of patients was oral NSAID (aceclofenac 200 mg per day) and in 67.6% of patients it was aceclofenac in combination with muscle relaxant. By visit 4, pain decreased from 6.9±1.5 to 2.2±1.3 points. Pain was completely relieved in 77.0% of patients. 227 patients (6.9%) dropped out of observation, and 16.1% of patients continued the use of analgesics after four weeks of treatment. The vast majority of patients (88.4%) evaluated treatment results as “good” or “excellent”. Switching to the other NSAID was required in 8.1% of patients, local injection of GC in 1.9%, administration of antidepressant or anticonvulsant in 1.5%, and hospitalization in 0.25% of patients. Adverse reactions (mostly dyspepsia) were noted in 2.2% of patients.

Conclusions: The use of treatment algorithm based on a complex pathogenetic approach ensures that patients receive an effective and relatively safe pain relief. Oral NSAIDs are the most expedient as first-line treatment in patients with moderate and severe musculoskeletal pain.

Disclosure of Interest: None declared

DOI: 10.1136/annrheumdis-2017-eular.4447

FRIDAY, 16 JUNE 2017

Regulatory molecules in connective tissue

OP0325 TGF-BETA-INDUCED ED-A FIBRONECTIN PRODUCTION BY FIBROBLAST-LIKE SYNOVIAL CELLS CONTRIBUTES TO INFLAMMATION IN OSTEOARTHRITIS

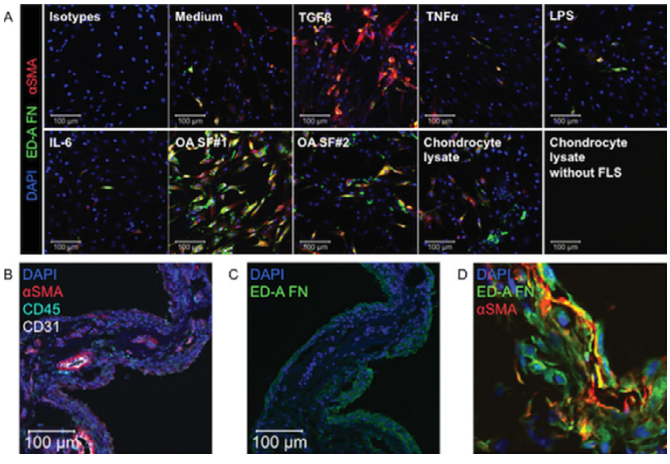
T.W. Kragstrup[1,2,3], D.H. Sohn[1,4], C.M. Lepus[1], K. Onuma[1], Q. Wang[1], W.H. Robinson[1], J. Sokolove[1]. *[1]Department of Immunology and Rheumatology, Stanford University, Stanford, United States; [2]Department of Rheumatology, Aarhus University Hospital; [3]Department of Biomedicine, Aarhus University, Aarhus C, Denmark; [4]Department of Microbiology and Immunology, Pusan National University, Pusan, Korea, Republic Of*

Background: The pathophysiology of osteoarthritis (OA) involves wear and tear, and a state of low-grade inflammation. Wear and tear leads to tissue degradation followed by tissue repair responses including TGFβ-induced myofibroblast production of extracellular matrix (ECM). Fibronectins are an essential part of the ECM, and injection of fibronectin fragments into rabbit joints is an established animal model of OA. Recently, alternatively spliced fibronectin containing the ED-A domain (ED-A FN) has been shown to activate Toll-like receptor 4.

Objectives: In this study, we hypothesize that FN fragments containing the ED-A domain could be one mechanism transducing mechanical events into inflammatory signals in OA.

Methods: Samples of synovial membrane and cartilage were obtained from patients with knee OA undergoing joint replacement surgery. Immunostaining was performed on synovial membranes. Fibroblast-like synovial cells (FLS) isolated by enzymatic digestion of remnant synovial membrane were stimulated with TGFβ, TNFα, lipopolysaccharide, IL-6, OA synovial fluid from two different donors, or chondrocyte lysate, and culture supernatants were analyzed for ED-A FN by immunofluorescence staining. ED-A FN fragments were obtained by plasmin digestion of cellular FN. Synovial cells isolated by enzymatic digestion and human monocyte-derived macrophages (MDM) were incubated with recombinant ED-A FN, plasmin, cellular FN, or cellular FN digested with plasmin; and culture supernatants were analyzed for MCP-1 and TNFα.

Results: We hypothesized that ED-A FN is produced by OA FLS in response to products reflecting tear and wear in OA. Indeed, the production of ED-A FN by OA FLS was increased by TGFβ, OA synovial fluid, and lysed chondrocytes in all experiments (n=3, see figure). ED-A FN co-localized with the myofibroblast marker αSMA in both the OA FLS (n=3) and in the OA synovial membranes (n=8). We further hypothesized that ED-A FN expression is associated with inflammation in OA. ED-A FN staining was associated with both number of lining layer cells (rho=0.85 and p=0.011) and infiltrating sublining cells (rho=0.88 and p=0.007) in the OA synovium (n=8), and co-localized with both MCP-1 and TNFα (n=5). Recombinant ED-A FN increased the production of both MCP-1 and TNFα by MDM (n=3) and OA FLS (n=3). Finally, we demonstrated that the FN fragments containing the ED-A domain generated the same production of both MCP-1 and TNFα as recombinant ED-A FN.



Conclusions: The disease process in OA shares features with the chronic