Dear Reader,

We are happy to present the ninth issue of the ‘Press Review and Journal Club’ newsletter that is part of EULAR School of Rheumatology (ESOR) educational initiative, the EULAR–EMEUNET Journal Club. This newsletter includes an overview of relevant articles published both in top rheumatology journals and in major internal medicine journals. In comparison to the previous issues, where we only reviewed articles in print, in this issue we included articles published electronically from August 2020 to November 2020, to bring you the latest updates in the field. The article selection includes translational and clinical research papers; in case you want to read the article in more detail, a hyperlink will redirect you to the respective journal. Among the selected articles, one has been chosen by the ESOR faculty to be discussed in a few weeks in an online Twitter Journal Club. Another article, the ‘EMEUNET Paper of the Month’ has been selected by popular vote through a survey circulated among the rheumatology community. For the latter, a video interview with the first author explaining the main findings of the paper is available on our YouTube channel.

The Journal Club aims to bring together rheumatologists, clinical researchers, basic scientists, and anyone else who might be interested in the topic, to participate in an online, lively discussion. These ‘meetings’ take place on Twitter at pre–specified times and dates; the next is planned on February 24th at 8:00 PM GMT (9:00 PM CET). ‘Save the date’ reminders will be sent in advance. Where possible, key authors involved in selected articles will be invited to participate. Details of the article selected and of the Journal Club are included on page 3 of this issue.

We hope that you will enjoy reading this newsletter and look forward to ‘seeing’ you soon at our Twitter JC meeting!

Javier Rodriguez Carrio, Aurélie Najm, Polona Zigon, Elena Nikiphorou, Richard Conway, Paul Studenic, Alessia Alunno, Mikhail Protopopov, Maria Sokolova, Tadeja Kuret, George Fragoulis, Stephanie Shoop-Worrall and Renaud Felten on behalf of the EULAR EMEUNET Journal Club team
FACULTY CHOICE FOR THE JOURNAL CLUB

The online Journal Club will take place on:

**February 24th, 2020 at 8:00PM GMT (9:00PM CET)**

- duration 1 hour -

Follow the accounts @EULAR_JC, @eular_org and @EMEUNET
Use the hashtag #EULARJC to follow and join the discussion

**Community poll winner:**

Fabian Proft, Laura Spiller, Imke Redeker, Mikhail Protopopov, Valeria Rios Rodriguez, Burkhard Muche, Judith Rademacher, Anne-Katrin Weber, Susanne Lüders, Murat Torgutalp, Joachim Sieper & Denis Poddubnyy

**Comparison of an online self-referral tool with a physician-based referral strategy for early recognition of patients with a high probability of axial SpA?**


The diagnostic delay in axial spondyloarthritis (axial SpA) remains unacceptably high, with one of the reasons being a late referral. The authors evaluated the performance of an online self-referral (OSR) tool for patients with back pain and compared it to an established physician-based referral strategy. The proportion of patients diagnosed with axial SpA among self-referred patients (19.4%) was clearly higher than the assumed 5% prevalence of axial SpA in patients with chronic back pain, although lower compared to the physician-referral group (39.2%). Axial SpA patients from the OSR group were more often HLA-B27 negative, females, and were more frequently at a non-radiographic stage as compared to axial SpA patients who came via the physician-based tool; both groups had similar disease burden.

**Runners-up:**


*RMD Open. 2020 Sep;6(3):e001392.*


*Rheumatology, 2020; keaa497*
The impact of seropositivity on the effectiveness of biologic anti-rheumatic agents: results from a collaboration of 16 registries.


The authors conducted a pooled analysis of 16 observational RA registries (27583 patients) to compare the impact of seropositivity (defined by the presence of RF and/or ACPA) on drug discontinuation and effectiveness of bDMARDs in patients with RA, using head-to-head comparisons in a real-world setting. Drug retention rates were analysed using Cox proportional hazards models adjusted for gender, age, smoking status, BMI, concomitant therapy with csDMARDs and GCs, number of prior bDMARDs and baseline values of disease activity and disease duration. The association of seropositivity with discontinuation differed significantly across bDMARDs. The adjusted hazard ratios (HRs) of discontinuing the bDMARD for seropositive patients compared with seronegative patients were 0.70 (0.59, 0.84) for rituximab, 0.80 (95% CI 0.72, 0.88) for abatacept, 0.89 (95% CI 0.78, 1.02) for tocilizumab and 1.01 (95% CI 0.95, 1.07) for TNFi. Adjusted differences in remission and low disease activity rates between seropositive and seronegative patients followed the same pattern, with no difference in TNFIs, a small difference in tocilizumab, a larger difference in abatacept and rituximab. Results of the study help moving towards a personalized choice of bDMARDs in RA.
The interleukin (IL)-23/IL-17 axis is believed to be key in psoriasis and psoriatic arthritis (PsA) pathogenesis. Nerviani et al. (10.1136/annrheumdis-2020-218186) determined the relationship between synovial versus skin transcriptional/histological profiles in patients with active PsA in 27 patients who underwent biopsies of synovium and paired lesional/non-lesional skin before starting anti-tumour necrosis factor or ustekinumab. Molecular analysis of 80-inflammation-related genes and protein levels for interleukin (IL)-23p40/IL-23p19/IL-23R axis revealed distinct clustering of synovial vs skin tissue gene expression. While IL12B, IL23A and IL23R were homogeneously expressed in skin lesions, their expression was extremely heterogeneous in paired synovial tissues. The study provided a plausible mechanistic explanation for the divergent skin and joint clinical response to IL-23 inhibitors. Resolution of inflammation has been recognized as an important process in treating chronic rheumatic diseases, which was the main objective of a study, performed by Andreev et al. (10.1136/annrheumdis-2020-218902). They combined mice models with eosinophilic asthma and K/BxN serum-induced arthritis, single cell RNA sequencing analysis of mice lungs and synovium, as well as synovial tissue of rheumatoid arthritis (RA) patients. The induction of eosinophilic asthma caused resolution of murine arthritis. A specific subset of regulatory eosinophils (rEos) was found in the joints, distinct from eosinophils in the lungs. Synovial rEos expanded on systemic upregulation of IL-5 released by lung innate lymphoid cells type 2. rEos were consistently present in the synovium of patients with RA in remission, but not in active stage. Furthermore, in patients with RA with concomitant asthma, mepolizumab (anti-IL-5 antibody) treatment induced relapse of arthritis. In another study by Tsuchiya et al. (10.1136/annrheumdis-2020-218189) the inflamed synovium in RA was studied in terms of genetic contribution to molecular regulatory networks. Synovial fibroblasts (SFs) from RA and osteoarthritis (OA) patients (n=30 each) were stimulated with eight different cytokines (IFN-α, IFN-γ, TNF-α, IL-1β, IL-6/sIL-6R, IL-17, TGF-β1, IL-18), followed by an integrative analysis approach. Activated SFs expressed CD40 which was significantly affected by an RA risk SNP (rs6074022). An RA risk SNP (rs28411362) formed 3D contact with the promoter of metal-regulatory transcription factor-1 (MTF1) gene, whose binding motif showed significant enrichment in stimulation specific-SFs. Consistently, inhibition of MTF1 suppressed cytokine and chemokine production from SFs and ameliorated mice model of arthritis. Lopez-Iscar et al. (10.1136/annrheumdis-2020-218481) performed a genome-wide association study (GWAS) in 3305 patients with juvenile idiopathic arthritis (JIA) and 9196 healthy controls, and used a Bayesian model selection approach to investigate the associated loci across JIA clinical subtypes. Their analysis identified five novel significant loci. Fine-mapping nominated causal SNPs with posterior inclusion probabilities ≥50% in five JIA loci. They identified RELA and EBF1 as key transcription factors contributing to disease risk, highlighted mechanistic insights for the disease biology and IL6ST as a potential drug target.
Venous thromboembolism (VTE) is common in patients with rheumatic diseases. Molander et al. (doi: 10.1136/annrheumdis-2020-218419) examined data from 46,316 rheumatoid arthritis (RA) patients from the nationwide Swedish registry having 322,601 visits from 2006-2018 and recorder the VTE episodes occurred the year following the visit. Compared to age/sex/area of residence-matched healthy population, the risk ratio for VTE was 1.88 (95% CI 1.65 to 2.15) for RA. Risk ratio for VTE was found to be associated with disease activity. Absolute risk was 0.52% following visits in remission and 1.08% following visits with high disease activity. Cohen et al. (doi: 10.1136/annrheumdis-2020-218510) presented safety data from 5 phase 3 RCTs for upadacitinib in RA. Examining 3834 patients with 4020.1 years of follow-up, it was found that rates of serious infection were comparable between upadacitinib 15 mg and adalimumab as were the rates of deaths, malignancies, major adverse cardiovascular events and VTEs. Herpes zoster and CPK elevations were higher in patients treated with upadacitinib vs those received methotrexate and adalimumab. Effect of tocilizumab in Sjögren’s syndrome (SS) has been studied by Felten et al. (doi: 10.1136/annrheumdis-2020-218467). In a double-blind RCT, 110 patients with SS activity index (ESSDAI) ≥5 from 17 centers were recruited and randomized to receive 6 monthly tocilizumab infusions or placebo. Primary endpoint was defined as combination of a decrease ≤3 points in the ESSDAI, no occurrence of moderate/severe activity in any new ESSDAI domain and no worsening in physician’s global assessment on (VAS) at week 24. The percentage of patients achieving primary endpoint was not statistically different between the tocilizumab group (52.7%) and the placebo group (63.6%), difference of −11.4% (95%CI −30.6 to 9.0) (Pr[Toc >Pla]=0.14]).

Tocilizumab has been also tested for its efficacy in osteoarthritis (OA) by Richette et al. (doi: 10.1136/annrheumdis-2020-218547). In a multicentre, 12-week RCT, 91 patients with pain VAS≥40, at least 3 tender joints and Kellgren-Lawrence grade ≥2) were randomized to receive two tocilizumab doses (8 mg/kg i.v. at week 0 and 4, 45 patients) or placebo (46 patients). Primary endpoint was change in pain at week 6. Active drug was not more efficient compared to placebo, with a mean change −7.9 (SD 19.4) for tocilizumab and −9.9 (SD 20.1) for placebo (p=0.7). Baraliakos et al. (doi: 10.1136/annrheumdis-2020-218669) aimed to identify factors predicting presence of MRI lesions in suggesting spondyloarthritis (SpA) in individuals aged<45 years included in a population-based cohort. MRIs from 793 patients were evaluated by two trained blinded readers for presence and extension of bone marrow oedema (BME). Presence of BME in sacroiliac joints was associated with delivery during the last year (OR 4.47, 95%CI 1.49–13.41). Extension of BME on SJ-MRIs or on spine was associated with: delivery in the last year (IRR 4.52, 95% CI 1.48 to 13.84), HLA-B27-positivity (IRR 2.32, 95% CI 1.30 to 4.14), BMI 25–30 Vs <25 kg/m²: (IRR 1.86, 95% CI 1.19 to 2.89). Associations were found for age per decade (IRR 1.46, 95%CI 1.13–1.90) and physically demanding work (IRR 1.46, 95%CI 1.06–2.00).
Tadeja is a postdoctoral research associate at Institute of Cell Biology, Faculty of Medicine, University of Ljubljana in Slovenia. Her major research interests include primary systemic vasculitis (giant cell arteritis and IgA vasculitis), chronic inflammation, biomarker discovery, single cell RNA sequencing and systems biology. Tadeja is a member of the Newsletter Subgroup.

George is a rheumatologist at “Laiko” hospital, Athens, Greece. His main research interests include rheumatoid and psoriatic arthritis, Sjögren’s syndrome and IgG4-related disease. He holds an honorary research fellow position at the University of Glasgow, UK, carrying out research focused on inflammatory arthritis. George is a member of the Newsletter Subgroup.

Galloway et al. (doi: 10.1136/rmdopen-2020-001392) aimed to investigate the risk of venous thromboembolism (VTE) in patients with immune-mediated diseases (IMID), including ulcerative colitis, Crohn’s disease, rheumatoid arthritis (RA) and psoriatic arthritis (PsA), compared with healthy population. 53,378 people with IMID, identified between 1999-2019, were compared with 231,512 people without. The former exhibited increased risk for VTE (1.46, 95% CI 1.36 to 1.56). Risk was increased for RA (aHR 1.54, 95% CI 1.40 to 1.70) but not for PsA (aHR 1.21, 95% CI 0.96 to 1.52). In IMID patients, male gender, obesity, current smoking, fracture history and abnormal platelet count were identified as risk factors. Infections are a common side effect in patients with rheumatic diseases. Kremer et al. (doi: 10.1136/rmdopen-2020-001389) aimed to investigate whether there is any effect of hydroxychloroquine in respiratory infections in RA. Data from Corrona RA registry (2008-2020) were reviewed. Adjusted comparisons for respiratory infections (or only for upper respiratory infections (URI) or bronchitis or serious respiratory infections) were made between biologic/targeted synthetic-DMARDs naïve patients, starting HCQ or other conventional DMARD. No differences were found in the incidence of any respiratory infection (URI, bronchitis, pneumonia) between the two groups (for HCQ; HR=0.87 (0.70 to1.07) in adjusted analyses and HR=0.90 (0.70 to 1.17) in adjusted matched analysis). JAK inhibitors seem to be efficacious beyond the field of inflammatory arthritis. Baker et al. (doi: 10.1136/rmdopen-2020-001490) ran a phase 2 RCT assessing the efficiency of filgotinib (JAK1-inhibitor) and lanraplenib (tyrosine kinase inhibitor) for Systemic Lupus Erythematosus (SLE) membranous nephropathy. 5 and 4 patients received filgotinib and lanraplenib, respectively. 4/5 and 1/4 completed week 16. For the former, a median reduction of 50.7% in 24-hour urine protein was recorded and SLE activity scores remained stable. Another study performed by Strasser et al. (10.1136/rmdopen-2020-001261) provided an in-depth preclinical and clinical characterisation of the treatment effect of cenerimod, a sphingosine-1-phosphate receptor type 1 (S1P1) modulator in the MRL/lpr lupus mouse model, as well as patients with SLE. In MRL/lpr mice treated with cenerimod, peripheral CD19+ B lymphocytes (~78.9%), CD4+ (~98.9%) and CD8+ (~90.4%) T lymphocytes were reduced, leading to reduced T cell infiltrates in the kidneys, and reduced severity of histological damage (median severity score of 1.0; IQR: 1.0–2.0), decreased proteinuria, and increased survival. Cenerimod was potent and efficacious in inducing S1P1 receptor internalisation in lymphocytes of patients with SLE. 12-week cenerimod treatment (n=44 patients) resulted in reduction of blood CD4+ T (~94%), CD8+ T lymphocytes (~63%) and B lymphocytes (~90%), antibody-secreting cells, and plasma IFN-α in SLE patients compared with placebo group (n=16). Mofors et al. (doi: 10.1136/rmdopen-2020-001402) investigated the association between cigarette smoking and subsequent development of primary Sjögren’s syndrome, showing that the fraction of patients with pSS having ever smoked prior to diagnosis was lower than in controls (OR 0.67, 95% CI 0.55 to 0.81).
Deodhar et al. (doi: 10.1002/art.41477) investigated the efficacy of secukinumab (SCK) (anti-IL17A) in patients with active nonradiographic axial spondyloarthritis in tumor necrosis factor inhibitor (TNFi)–naive patients. In this phase III study, 555 patients were randomized (1:1:1) to receive subcutaneous SCK 150 mg with a loading dose ([LD] group), SCK 150 mg without a loading dose ([NL] group), or placebo. The primary end point was 40% improvement in disease activity according to the Assessment of SpondyloArthritis international Society (ASAS40) criteria. The proportion of patients who met ASAS40 was significantly higher for LD at week 16 (41.5%) and NL at week 52 (39.8%) versus placebo (29.2% at week 16 and 19.9% at week 52; both P < 0.05). No new safety findings were reported. Salivary gland epithelial cells (SGECs) play an active role in primary Sjögren’s syndrome (pSS) pathophysiology. Rivière et al. (doi: 10.1002/art.41558) studied the interactions between salivary gland epithelial cells (SGECs) and T cells in pSS and the role of the IL-7/IFN axis. IL-7 serum level was increased in pSS patients versus controls and was associated with B-cell biomarkers. IL7R expression was decreased in T cells from pSS patients versus controls. Interestingly, explants cultured with anti-IL-7R antibody showed decreased IFN-stimulated gene expression. Their results suggest an IL-7-IFNγ amplification loop involving SGECs and T cells in pSS. An anti-IL-7R antibody decreased the IFN signature in T cells during pSS and could be of therapeutic interest in this difficult-to-treat disease. The use of JAK inhibitors (JAKi) has been limited by venous thromboembolism (VTE) risk warnings. Yates et al. (doi: 10.1002/art.41580) evaluate the VTE risk of JAK inhibitors (JAKi) in patients with immune mediated inflammatory diseases (IMIDs) by a meta-analysis of phase II and III double blinded randomized controlled trials (RCTs) of JAKi at licensed doses. A total of 42 studies were included, from an initial search of 619. There were 6,542 JAKi patient exposure years (PEY), compared to 1,578 placebo PEY. Only 15 VTE events in the JAKi group and 4 in the placebo group were registered. The pooled Incidence rate ratio (IRR) of VTE in patients receiving JAKi were 0.68 (95% CI 0.36 to 1.29) and do not support current warnings around VTE risk for JAKi. Tu et al. (doi: 10.1002/art.41584) investigated the efficacy of intensive acupuncture versus sham acupuncture for knee osteoarthritis (OA) in 442 patients. The primary outcome was response rate defined as the proportion of participants who simultaneously achieved minimal clinically important improvement (MCII) on the NRS and the WOMAC function subscale at week 8. The response rates were 60.3% (91 of 151), 58.6% (85 of 145), and 47.3% (69 of 146) in the electro-acupuncture (EA), manual acupuncture (MA), and sham acupuncture (SA) groups, respectively. Intensive EA resulted in less pain and better function at week 8 (p = 0.0234), compared with SA, and these effects persisted through week 26.
In a multicentre randomised controlled trial, Adams et al. (doi: 10.1093/rheumatology/keaa726) explored the clinical and cost effectiveness of thumb splints in 349 patients with thumb osteoarthritis randomized to receive a therapist supported self-management programme (SSM), a SSS plus a verum thumb splint (SSM+S), or a placebo thumb splint (SSM+PS). Australian/Canadian (AUSCAN) hand pain at 8 weeks was the primary outcome. All groups improved, with no mean treatment difference between groups: SSM+S vs SSM −0.5 (95% CI: −1.4, 0.4); SSM+PS vs SSM −0.1 (95% CI: −1.0, 0.8); and SSM+S vs SSM+PS −0.4 (95% CI: −1.4, 0.5). Courvoisier et al. (doi: 10.1093/rheumatology/keaa393, EMEUNET paper of the Month) explored seropositivity and response to biological DMARDs in 27,583 people with rheumatoid arthritis (RA) from 16 observational registries. Using multivariable Cox regressions, they reported lower drug discontinuation in seropositive patients prescribed abatacept (HR: 0.80, 95% CI 0.72, 0.88) and rituximab (HR: 0.70, 95% CI 0.59, 0.84), but not TNF-inhibitors. López-Medina et al. (doi: 10.1093/rheumatology/keaa398) assessed the influence of psoriasis on disease burden in 2296 people with spondyloarthritis from the Spanish REGISPONSER registry. Psoriasis was independently associated with HLA-B27 (OR 0.27), uveitis (OR 0.46), synovitis (OR 2.59), dactylitis (OR 2.78) and the use of conventional synthetic DMARDs (OR 1.47). In 519 children and young people with juvenile dermatomyositis, Deakin et al. (doi: 10.1093/rheumatology/keaa497) identified two different patterns of physician global scores in the 10 years following diagnosis: Improvers (89%) and Persistent Disease (11%), associated with disease activity, respiration, disease duration and lipodystrophy. Three illness perception patterns in RA were identified by Gwinnutt et al. (doi: 10.1093/rheumatology/keaa615) in 1087 people starting methotrexate (MTX) using latent class growth models: Negative Illness Perception (n=49%), Positive Illness Perception (n=30%) and Improvers (21%). The Negative group had worse disability, pain and fatigue over follow-up compared with the other groups, controlling for inflammation. In 502 people with systemic lupus erythematosus, Arnaud et al. (doi: 10.1093/rheumatology/keaa671) used latent class analysis to analyse patterns of fatigue. The analysis revealed three patterns of fatigue, distinguishing between distinguish patients with active disease (in whom remission will be achieved) from those with no or mild activity but high levels of fatigue, depression and anxiety, for whom psychological counselling should be prioritized. Ahn et al. (doi: 10.1093/rheumatology/keaa682) quantified familial incidence and risk of Behçet's disease in a cohort of 12 million families. In 53,687 people with first-degree relatives affected, the incidence was 3.57 per 10^4 person-years. Familial risks were higher within-generation than between-generation, and showed age dependence, being higher in younger age groups.
Mekinian et al. (doi: 10.1186/s13075-020-02311-y) examined the efficacy of tocilizumab in treatment-naïve patients with Takayasu arteritis in an open-label trial. 13 patients received steroids (0.7 mg/kg/day) and 7 infusions of tocilizumab (8 mg/kg/month). 54% achieved the primary endpoint (discontinue steroids after 7 infusions of tocilizumab). Disease activity has significantly decreased after 6 months of treatment. During the 12-month follow-up after tocilizumab discontinuation, relapse occurred in 5/11 who had achieved remission after 6 months of tocilizumab. Rodrigues Manica et al. (doi: 10.1186/s13075-020-02288-8) examined whether the reason for discontinuing the first TNF inhibitor (TNFi) affected the efficacy of the next one in patients with axial spondyloarthritis (axSpA). 193 axSpA patients switching TNFi between 2008 and 2018 were included. Reasons for discontinuation included: primary failure (no response ≤ 6 months), secondary failure (response ≤ 6 months but lost thereafter), adverse events, and others. As assessed by ASDAS clinically important improvement, reason for discontinuation of the first TNFi did not influence the response to the second TNFi. However, ASDAS-inactive disease (a more stringent outcome) was most likely to be achieved with the second TNFi in patients who discontinued their first TNFi due to secondary failure (OR 7.3, 95%CI 1.9 to 27.7), adverse events (OR 9.1, 95%CI 2.5 to 33.3), or other reasons (OR 7.7, 95%CI 1.6 to 37.0) as compared to primary failure. The pathogenicity of autoantibodies specific for systemic sclerosis (SSc), embedded in immune complexes (IC) was investigated by Raschi et al. (doi: 10.1186/s13075-020-02360-3). ICs were purified from the sera of SSc patients bearing antibodies against DNA topoisomerase I (ATA), centromeric proteins (ACA), RNA polymerase (ARA), and Th/To. Human umbilical vein endothelial cells (HUVECs) were incubated with ICs, followed by measurement of gene and protein expression. All SSc-IC stimulated IL-6 secretion; ACA-ICs and anti-Th/To-ICs increased ICAM-1 expression; all SSc-ICs but anti-Th/To-ICs augmented IL-8 levels; all SSc-ICs but ACA-ICs and ARA-ICs upregulated et-1, and all SSc-ICs but ARA-ICs affected TGF-β1 secretion. When healthy skin fibroblasts were stimulated with supernatants from HUVECs incubated with SSc-ICs, TGF-β1 secretion, collagen 1, c-SMA, and IL-6 expression levels were significantly modulated, showing a pro-fibrotic phenotype. Intra-articular glucocorticoid (GC) injections are widely used as a symptomatic treatment for osteoarthritis (OA). Pemmari et al. (doi:10.1186/s13075-020-02289-7) studied the effect of GC on gene expression in OA chondrocytes using RNA sequencing. Chondrocytes were isolated from the cartilage from OA patients and cultured with or without GC for 24 h. GC increased the expression of 480 and reduced that of 755 genes with a fold change (FC) 2.0 or greater. Several genes were associated with inflammation and cartilage anabolism/catabolism as well as lipid and carbohydrate metabolism. NGF, PI3KR1, and VCAM1 were identified as central genes among those most strongly affected by GC.
Yen et al. (doi: 10.1002/acr.24411) explored trends in systemic sclerosis (SSc) mortality in the US over 48 years from 1968 to 2015. In total, 46,798 deaths were recorded due to SSc, increasing to 2000 and decreasing from 2001 to 2015. Age-standardized mortality rate was higher in women (3.5, 95%CI 3.1 to 3.9) and Black ethnicities (4.9, 95%CI 3.8 to 6.1) than in men (1.8, 95%CI 1.5 to 2.1) and White (2.4, 95%CI 2.2 to 2.6) ethnicities. In 97 people with systemic lupus erythematosus and a history of venous thromboembolic events, Gkrouzman et al. (doi: 10.1002/acr.24508) reported that African Americans were 66% less likely (95% CI 0.12 to 0.96) to have clinically significant antiphospholipid antibody profile than Causcasians. Therefore, antiphospholipid profile are less predictive of of venous thromboembolic events in African Americans. Espinosa-Ortega et al. (doi: 10.1002/acr.24498) investigated the association between autoantibody positivity and ACR/EULAR 2016 response to immunosuppressive therapies in 156 people with idiopathic inflammatory myopathies using multivariable logistic regression analysis. Dermatomyositis-specific autoantibodies were associated with moderate response (OR: 4.2, 95% CI 1.2 to 16.5) as compared to seronegativity. Sepriano et al. (doi: 10.1002/acr.24449) tested predictive associations of structural changes on MRI of the sacroiliac joints (MRI-SIJ) and spine in 202 people with axial spondyloarthritis. Both the presence of bone marrow oedema on MRI-SIJ (OR 4.2, 95%CI 2.4 to 7.3) and on MRI-spine (OR=10.7, 95%CI 2.4 to 49.0) at baseline were predictive of 5-year damage (≥3 fatty lesions) on MRI-SIJ and MRI-spine, respectively, when adjusted for CRP. Liebling et al. (doi: 10.1002/acr.24483) explored the temporal relationship between juvenile idiopathic arthritis disease activity and uveitis activity in 98 children and young people using multivariable repeated-measures logistic regressions. Arthritis activity was associated with uveitis activity over time (OR 2.5, 95%CI 1.7 to 3.5), suggesting that arthritis flares should prompt swift referral to ophthalmology. In 2794 people with knee osteoarthritis, Carlesso et al. (doi: 10.1002/acr.24437) reported constant +/- intermittent pain associated with lower pressure pain thresholds (OR 0.8, 95%CI 0.7 to 0.9) and adequate conditioned pain modulation (OR 1.5, 95%CI 1.1 to 1.9) compared with intermittent pain only. Pain sensitisation was also associated with higher likelihood of unpredictable pain. In 31,381 people with rheumatoid arthritis, Baker et al. (doi: 10.1002/acr.24469) used multivariable Cox regression models to assess time-varying weight fluctuation and risk of cardiovascular events. Greater risk was observed in those that experienced 10% weight loss (HR 1.18, 95%CI 1.0 to 1.4) or weight gain of 10% (HR: 1.2, 95% CI 1.04, 1.38) per year. The association between weight change and CV events was stronger among participants with BMI <25.
Scott et al. (doi: 10.1016/j.semarthrit.2020.07.014) investigated the effectiveness of intensive management in people with moderately active rheumatoid arthritis (RA) already taking conventional synthetic disease modifying anti-rheumatic drugs (csDMARDs) in the TITRATE trial, a 12-month multicentre individually randomised trial comparing standard care with monthly intensive management appointments delivered by specially trained healthcare professionals and incorporated monthly clinical assessments, medication titration and psychosocial support. The primary outcome was 12-month remission assessed using the DAS28-ESR. 335 patients were randomised (168 intensive management; 167 standard care); Intensive management increased DAS28-ESR 12-month remissions as compared to standard care (32% vs 18%, p=0.004) and remissions using a range of alternative remission criteria. There was no evidence for adverse events differences between managements. Proft et al. (doi: 10.1016/j.semarthrit.2020.07.018, EULAR-EMEUNET Twitter JC Article) evaluated an online self-referral (OSR) tool for patients with back pain and compared it to an established physician-based referral tool. 361 consecutive patients (180 referred via the OSR and 181 via the physician-based referral tool) were included in the study. A total of 35 patients (19.4%) in the self-referral group and 71 patients (39.2%) in the physician-referral group were finally diagnosed with axial spondyloarthritis `(axSpA). Despite the better performance of the physician-based referral strategy, the proportion of axSpA among self-referred patients (19.4%) was clearly higher than the assumed 5% prevalence of axSpA in patients with chronic back pain. AxSpA patients from the OSR group were more often HLA-B27 negative, females, and were more frequently at a non-radiographic stage as compared to the physician-based tool. Yuan et al. (doi: 10.1016/j.semarthrit.2020.06.004) conducted a systematic review and meta-analysis to investigate the clinical characteristics and risk factors of infection in systemic lupus erythematosus (SLE). 39 studies (3709 infection SLE patients and 10526 non-infection SLE patients) were included. This study confirms many factors including thrombocytopenia (OR 1.61, 95%CI 1.4 to 1.85), anemia (OR 2.294, 95%CI 1.402 to 3.755), hypoproteinemia (OR 2.336, 95%CI 1.408 to 3.876), hypocomplementemia (OR 1.890, 95%CI 1.190 to 3.002), renal involvement (OR 2.692, 95%CI 2.000 to 3.623), and diabetes mellitus (OR 3.890, 95%CI 2.450 to 6.160) to be associated with infection in SLE patients. In addition, glucocorticoids (OR 3.116, 95%CI 1.959 to 4.957) and immunosuppressants (e.g. cyclophosphamide) rendered SLE patients more susceptible to infection, while antimalarial drug administration (hydroxychloroquine) was a protective factor against infection in SLE patients (OR 0.634, 95%CI 0.451 to 0.892).
Stephanie is a postdoctoral researcher at the University of Manchester, UK. Her focus is on improving stratified treatment of juvenile idiopathic arthritis using novel machine learning approaches. Stephanie is a member of the Social Media Subgroup.

Renaud is an Assistant Professor in the Department of Rheumatology - National Reference Centre for Rare Systemic Autoimmune Diseases at University Hospital of Strasbourg, France. His major research interests include DMARDs, immunosuppressive drugs in the fields of auto-immune diseases and inflammatory rheumatism and spondyloarthritis. Currently, he is a PhD student looking for new therapeutic targets in Sjögren’s syndrome. Renaud is a member of the Social Media Subgroup.

Black et al. (NEJM, doi: 10.1056/NEJMoa1916525) evaluated the risk–benefit profile of bisphosphonate (BP) use to compare associated atypical fractures with osteoporotic fractures. Among 196,129 women 50 years of age or older, 277 atypical femur fractures (1.74 fractures per 10,000 patient-years) and 9102 hip fractures (58.90 per 10,000 person-years) occurred. After multivariable adjustment, the risk of atypical fracture increased with longer duration of BP use: the HR as compared with less than 3 months of BP use increased from 8.86 (95%CI 2.79 to 28.20) for 3 to 5 years to 43.51 (95%CI 13.70 to 138.15) for 8 years or more. The number of fractures prevented for each fracture type far outweighed bisphosphonate-associated atypical fractures at all time points. For example, in White patients after 3 years, there were 2 BP-associated atypical fractures as compared with 149 hip fractures and 541 clinical fractures prevented. Furie et al. (NEJM, doi: 10.1056/NEJMoa2001180) evaluated the efficacy and safety of intravenous belimumab when added to standard therapy (mycophenolate mofetil or cyclophosphamide–azathioprine) in adults with active lupus nephritis. The BLISS-LN trial, a phase 3 multicenter randomized placebo-controlled study, assigned 448 adults with biopsy-proven, active lupus nephritis in a 1:1 ratio to receive intravenous belimumab (10 mg per kilogram of body weight) or matching placebo (+ standard therapy). The primary end point at week 104 was a primary efficacy renal response (composite criteria). At week 104, significantly more patients in the belimumab group than in the placebo group had a primary efficacy renal response (43% vs. 32%; OR 1.6; 95%CI 1.0 to 2.3; p=0.03) and a complete renal response (30% vs. 20%; OR 1.7; 95%CI 1.1 to 2.7; p=0.02). The safety profile of belimumab was consistent with that in previous trials. Hamilton et al. (BMJ, doi: 10.1136/bmj/m3576) explored whether targeted rehabilitation could improve outcomes in people with osteoarthritis undergoing total knee arthroplasty and at risk of poor outcomes. In a parallel randomised controlled trial, 334 people at risk of poor outcome based on the Oxford knee score were randomised to a) therapist led outpatient rehabilitation (n=163) or b) single physiotherapy review and home exercise (n=171) over 6 weeks postoperatively. Adherence to interventions exceeded 85% and no differences were reported between arms for Oxford knee score (the between group difference was a non-clinically meaningful 2.25 points (0.61 to 3.90, p=0.01), average or worse pain, post-intervention function or satisfaction with outcome. In a randomised trial in 80 people with chronic Achilles tendinopathy, van der Vlist et al. (BMJ, doi: 10.1136/bmj.m3027) receiving either high volume injection of saline and lidocaine or placebo, with both groups performing a 24 week exercise programme, pain and function were not significantly different at 24 weeks (adjusted between group difference in VISA-A score 0.5 points, 95%CI −17.8 to 18.8) and no secondary outcomes differed between the groups.
Tadeja is a postdoctoral research associate at Institute of Cell Biology, Faculty of Medicine, University of Ljubljana in Slovenia. Her major research interests include primary systemic vasculitis (giant cell arteritis and IgA vasculitis), chronic inflammation, biomarker discovery, single cell RNA sequencing and systems biology. Tadeja is a member of the Newsletter Subgroup.

George is a rheumatologist at “Laiko” hospital, Athens, Greece. His main research interests include rheumatoid and psoriatic arthritis, Sjögren’s syndrome and IgG4-related disease. He holds an honorary research fellow position at the University of Glasgow, UK, carrying out research focused on inflammatory arthritis. George is a member of the Newsletter Subgroup.

Data regarding the real-life predictors of low disease activity (LDA) in rheumatoid arthritis (RA) patients are limited. Thomas et al. (Ther Adv Musculoskelet Dis. doi: 10.1177/1759720X20937132), assessed the rates and the predictors of low disease activity (LDA) in a large real-life prospective cohort of rheumatoid arthritis (RA) patients. They found that after 12 months, LDA was achieved in 57% of patients. In regression analysis, male sex was positively associated with LDA (OR 2.29, 95%CI 1.62 to 3.23), whereas advanced age (OR 0.98, 95%CI 0.97 to 0.99), high Health Assessment Questionnaire (HAQ) score (OR 0.57, 95%CI 0.45 to 0.72), use of glucocorticoids (OR 0.75, 95%CI 0.57 to 0.98), ≥2 bDMARDs (OR 0.61, 95%CI 0.44 to 0.84), high co-morbidity index (OR 0.86, 95%CI 0.76 to 0.96) and obesity (OR 0.62, 95%CI 0.46 to 0.84) were negative predictors of LDA. Frequency of cardiovascular manifestations in Sjögren’s syndrome (SS) remains unclear. Nishiwaki et al. (J Rheum. doi: 10.3899/jrheum.200352) studied cardiac fibrosis in the context of SS. From the 52 female patients included in the study, myocardial fibrosis, as assessed by late gadolinium enhancement (LGE) was detected in 19%. Myocardial edema (high intensity on T2-weighted images) was seen in 5.8% of the patients. Interestingly, in multivariable analysis, focus score ≥ 3 in salivary gland biopsies, was independently associated with positivity for LGE (OR 11.21, 95%CI 1.18 to 106.80). Gkrouzman et al. (J Rheum. doi: 10.3899/jrheum.200513) determined in persistently antiphospholipid antibody (aPL)-positive patients whether clinically meaningful aPL profiles at baseline (defined as positive lupus anticoagulant (LA) test and/or anticardiolipin (aCL)/anti-β2 glycoprotein-I (β2GPI) IgG/M ≥40 U) remain stable over time. Of 472 patients with clinically meaningful aPL profile at baseline (median follow up: 5.1 years), 366/472 (78%) patients had stable aPL profiles over time, 54 (11%) unstable; and 52 (11%) inconclusive. Baseline triple aPL positivity decreased (OR 0.25, 95% CI 0.10 to 0.64) and isolated LA test positivity increased (OR 3.3, 95%CI 1.53 to 7.13) the odds of an unstable aPL profile over time. Bruce et al. (Lancet Rheumatol. doi: 10.1016/S2665-9913(20)30342-8) performed a multicentre, randomised, double-blind, placebo-controlled, phase 2 study exploring the effects of subcutaneous anifrolumab in patients with systemic lupus erythematosus (SLE), active skin disease, and high type I interferon (IFN) gene signature. 36 patients were randomly assigned to receive 150 mg (n=14), 300 mg of anifrolumab (n=13), or placebo (n=9). At week 12, the median percentage neutralisation of the type I IFN gene signature was higher with 150 mg (88.0%) and 300 mg (90.7%) of anifrolumab than with placebo (18.5%), and more patients in the anifrolumab than in the placebo group had neutralisation of 75% or more (67% vs. 77% vs. 11%). The safety profile was consistent with previous studies of intravenous anifrolumab. The results support the continued development of anifrolumab as a subcutaneously administered therapy for patients with SLE.
COVID-19 AND RHEUMATOLOGY

Mikhail Protopopov

Mikhail is a rheumatologist and a junior researcher at the Department of Gastroenterology, Infectiology and Rheumatology, Charité University, Berlin, Germany. His major research interests include spondyloarthritis and psoriatic arthritis (clinical aspects, imaging, epidemiology and outcomes). Mikhail is the Leader of the Newsletter Subgroup.

The body of literature regarding COVID–19 and its impact on patients with rheumatic and musculoskeletal diseases (RMD) continues to expand rapidly. Akiyama et al. (Ann Rheum Dis 2020. doi: 10.1136/annrheumdis-2020-218946) performed a metaanalysis of 2 observational studies including a total of 319 025 patients to assess the prevalence and clinical outcomes of COVID–19 in autoimmune diseases. The prevalence of COVID–19 was 0.011 (95%CI 0.005 to 0.025). Meta-analysis of seven case–controlled studies demonstrated that the risk of COVID–19 in autoimmune diseases was significantly higher than in control patients (OR 2.19, 95%CI 1.05 to 4.58). The rates of hospitalisation and mortality were 0.35 (95%CI 0.23 to 0.50) and 0.066 (95%CI 0.036 to 0.12), respectively. Older age (β-coefficient 0.068, 95%CI 0.048 to 0.089), a higher proportion of hypertension (β 0.034, 95%CI 0.022 to 0.045) and diabetes (β 0.038, 95%CI 0.012 to 0.064) were associated with a higher mortality rate due to COVID–19 in patients with autoimmune diseases. Glucocorticoids, as well as csDMARDs and b/tsDMARDs–csDMARDs combination therapy increased the risk of unfavourable outcomes, whereas b/tsDMARDs monotherapy, particularly anti-TNF agents, were associated with a lower risk of hospitalisation and death. Dejaco et al. (Ann Rheum Dis 2020. doi: 10.1136/annrheumdis-2020-218697) explored how the first wave of COVID–19 pandemic influenced decisions of rheumatologists regarding the management of patients with RMDs by an online survey tool, analysing 286 responses from 35/45 EULAR countries. 82% of respondents indicated cancellation/postponement of face-to-face visits of new patients and 91% of follow-up visits. Treatment decisions were frequently postponed (34%), and the majority (74%) of respondents stated that it was less likely to start a bDMARD/tsDMARD treatment. Shortage of hydroxychloroquine and tocilizumab was reported by a significant share of responders. The results highlight the negative impact of COVID–19 pandemic on implementing early treatment and treat-to-target strategies. Gianfrancesco et al (Arthritis Rheumatol 2020. doi: 10.1002/art.41567) examine the association between race/ethnicity and COVID–19 outcomes in patients with RMDs, showing that African American (OR 2.74, 95%CI 1.90 to 3.95), Latinx (OR 1.71, 95%CI 1.18 to 2.49), and Asian patients (OR 2.69, 95%CI 1.16 to 6.24) had higher odds of hospitalization compared to White patients, with no differences in mortality. Chandan et al. (Arthritis Rheumatol 2020. doi: 10.1002/art.41593) explored whether use of non-steroidal anti-inflammatory drugs (NSAIDs) increases susceptibility to developing COVID–19 compared to the use of other common analgesics and did not observe any increased risk associated with NSAIDs (adjusted HR for subsequent mortality 0.85, 95%CI 0.61 to 1.20). Ciaffi et al. (BMC Rheumatol 2020. doi: 10.1186/s41927-020-00165-0) performed a systematic review and meta-analysis to assess the prevalence of rheumatic manifestations in patients with COVID–19, discovering pooled estimates of 19% for muscle pain and 32% for fatigue as initial symptom of COVID–19 presentation and, respectively, of 16 and 36% during the disease course. Vasculitis, chilblains, presence of autoantibodies have also been reported.
EULAR continues to provide valuable content and guidance for clinicians and patients with Rheumatic Musculoskeletal Diseases (RMDs) around the world during the COVID-19 pandemic.

Access the EULAR COVID-19 Repository for clinicians - a dedicated space for clinicians and patients where all COVID-related resources and guidelines are concentrated.

- EULAR guidelines:
  - COVID-19 Clinic visit guidelines
  - EULAR provisional recommendations for the management of rheumatic and musculoskeletal diseases in the context of SARS-CoV-2

- Factors associated with COVID-19-related death in people with rheumatic diseases

- Plain Language Summaries of the COVID-19 Global Rheumatology Alliance

- EULAR - COVID-19 Reporting database for rheumatologists and other clinicians.
  - The EULAR - COVID-19 Database is a European pediatric and adult database to report on outcomes of COVID-19 in patients with RMDs. It has been updated with Module 2 – reports on cases of vaccination against SARS-CoV-2 of patients with RMDs are now being collected. The page also contains national registries.

- Information on vaccination against SARS-CoV-2 in patients with RMDs:
  - EULAR December 2020 View points on SARS-CoV-2 vaccination in patients with RMDs by Prof. Johannes Bijlsma.
  - EULAR PARE Webinar on COVID-19 and vaccination in RMD patients: What we know so far

Recently the EULAR points to consider on pathophysiology and use of immunomodulatory therapies in COVID-19 have been published in Annals of Rheumatic Diseases. They summarize information that has been gathered so far on available treatment options and pathogenic mechanisms in COVID-19, based on published studies. These are the points to consider for finding optimal management options in patients with SARS-CoV-2 infection.
All over Europe, COVID-19 cases have been rapidly increasing again. This has mainly been driven by the younger population. @EMEUNET is starting a call to action to join the social media campaign: #wearamask. The aim of this is to raise awareness for the need to wear a mask and follow social distancing to slow the infection rate of COVID-19 and “flatten the curve”. Through our social media channels, we want to spread the message, especially to the younger population, to slow down the infection rates and therefore protecting vulnerable groups like elderly people and people with RMD’s and to reduce the amount of hospitalized COVID-19 patients. Therefore, EMEUNET will be sharing pictures and videos of its members wearing a mask and sharing important messages of who they are wanting to protect. We encourage all of you to join in! Share your photos and messages marking them with the #wearamask hashtag, and do not forget to endorse the @EMEUNET Twitter or @EMEUNET Facebook account!.

Check out a message from our Chair Felice Rivellese on our Youtube channel!
EULAR | EMEUNET's “Improve your poster presentations!” webinar

Following the success of the Eular | EMEUNET webinar on oral presentations, Sebastián Rodriguez-García and Manouk De Hooge developed a new event on poster presentations that will be held next March 16th at 8 pm (CET). It aims to provide tools for creating posters from scratch and present them at scientific congresses. It is designed as an interactive exercise where attendants could share their views and doubts with the faculty. This year, we have again the support of Loreto Carmona and Catherine Haines who will share with us their experience on this topic.
EMEUNET PODCASTS!

Are you too busy to read the whole Newsletter? 
Do you want to keep updated about the main EMEUNET activities and save time?

With our Podcasts, you can get updated while on the go, with extracts of the recent newsletters, highlights of the most recent publications in the field of Rheumatology, selected for you by EMEUNET members (What Is New), interviews and review of other EMEUNET activities.

Where to listen:

SHARE YOUR IDEAS!

Over the years EMEUNET has developed several projects covering different topics and areas of interest. However, we always appreciate any suggestions and welcome new ideas to expand on what we currently offer to EMEUNET members. Make your voice heard and share your ideas with us!

For additional suggestions and ideas, just write down some lines to summarize your proposal and send it either via email at emeunet@eular.ch or through our website (http://emeunet.eular.org/contact_us.cfm). Don’t forget to provide your contacts so we can come back to you for additional details!

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