Dear Reader,

We are happy to present the seventh issue of the ‘Press Review and Journal Club’ newsletter that is part of a 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 during the last 4 months (May-August 2019). The article selection includes translational and clinical research papers and reflects personal views of the contributors and thus is inevitably incomplete. Nevertheless, it provides an overview of interesting studies published during the last months. In case you want to read an 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 October 9th at 8:30PM GMT (9:30PM CET). ‘Save the date’ reminders will be sent in advance. Where possible, key authors involved in selected articles will be invited to participate. Details on the article selected and 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!

Paul Studenic, Richard Conway, Alessia Alunno, Elena Nikiphorou, Casper Webers, George Fragoulis, Achilles Floudas, Mariana Luis and Mikhail Protopopov, on behalf of the EULAR-EMEUNET Journal Club team

**Differential synovial tissue biomarkers among psoriatic arthritis and rheumatoid factor/anti-citrulline antibody-negative rheumatoid arthritis**

*Arthritis Research & Therapy* 2019 May 9;21(1):116. ([full text here](#))

Differential diagnosis among psoriatic arthritis (PsA) and seronegative rheumatoid arthritis (Ab-neg RA) might be challenging, as both diseases may have a similar peripheral phenotype and are rheumatoid factor and anti-CCP negative. The authors aimed on identifying synovial tissue biomarkers for PsA and Ab-neg RA, and testing their predictive value for therapeutic response. Performing ultrasound-guided synovial tissue biopsy and immunohistochemistry for CD68+, CD3+, CD20+, CD21+, CD117+, and CD138+ cells in 34 PsA and 55 Ab-neg RA patients, they revealed that certain cell populations are unequally distributed among PsA and Ab-neg RA. PsA patients showed higher levels of CD117+ cells, while Ab-neg RA patients had higher levels of CD138+ cells. A lower score of CD3+ cells in treatment-naïve PsA as well as a lower score of sublining CD68+ cells in treatment-naïve Ab-neg RA were associated with a higher chance of reaching minimal disease activity/remission. Overall, this study proves that synovial tissue histology may help to differentiate between the two diseases and predict therapy success.

The online Journal Club will take place on:

**Wednesday 9th October 2019 at 8:30PM GMT (9:30PM CET)**

- duration 1 hour -

Follow the accounts [@EULAR_JC](#), [@eular_org](#) and [@EMEUNET](#)

Use the hashtag #EULARJC to follow and join the discussion

**Gradual tapering TNF inhibitors versus conventional synthetic DMARDs after achieving controlled disease in patients with rheumatoid arthritis: first-year results of the randomised controlled TARA study**

*Annals of the Rheumatic Diseases 2019 Jun;78(6):746-753.* ([full text here](#))

Tapering medication in patients with rheumatoid arthritis (RA) who are in remission is common nowadays. However, the optimal tapering approach has yet to be determined. In a Dutch multicentre, single-blinded, superiority trial of RA patients with controlled disease under a combination of conventional synthetic DMARDs (csDMARDs) and a TNF inhibitor (TNFi), van the authors assessed the effectiveness of two tapering strategies: gradually tapering csDMARDs (n=94) or gradually tapering TNFi (n=95). After up to 9 months, the cumulative rate of flares (the primary outcome, defined as DAS44 >2.4 and/or SJC >1) was comparable in both groups. After 1 year, a non-significant 10% difference in favour of csDMARD was observed (csDMARDs 33%, 95% CI 24-43%; TNFi 43%, 95% CI 33-53%). Other outcomes, such as quality of life (QoL) and adverse events, were comparable in both groups. As TNFi tapering was not superior to csDMARD tapering, the results support tapering TNFi before csDMARDs in RA as a possible means of cost reduction. Nonetheless, flares might negatively affect QoL and increase costs for society, and the cost-effectiveness of these strategies will be addressed in a follow-up analysis.

*Explore this paper in greater detail through an exclusive interview with co-author*

Interview available [here](#)

The EMEUNET Paper of the Month is selected by an online vote of selected articles from each of the rheumatology journal contributions.

*Watch out for our next poll!*
In *systemic lupus erythematosus* (SLE), a 2019 update of the EULAR management recommendations was published (pp 736-745). Treatment aims at remission/low disease activity and preventing flares. Hydroxychloroquine (≤5 mg/kg real body weight) is recommended in all patients with SLE. Glucocorticoids (GC) should be minimised to <7.5 mg/day or withdrawn during maintenance treatment. Appropriate initiation of DMARDs can expedite the tapering of GC. In persistently active or flaring extrarenal disease, add-on belimumab, and in organ-threatening, refractory disease, add-on rituximab may be considered. Updated specific recommendations are provided for cutaneous, neuropsychiatric, renal and hematological disease. Tedeschi et al. (pp 634-640) presented the analysis process used to develop new EULAR/ACR SLE classification criteria. Tselios et al. (pp 802-806) showed all-cause and cause-specific standardised mortality ratios (SMRs) in SLE significantly decreased over time (1970s - 13.5, 95% CI 8.6-18.5; recent years - 2.2, 95% CI 1.4-3.1), both being particularly high for patients <40 years old. Rahman et al. (pp 957-966) highlighted a pro-inflammatory role of low-density granulocytes (LDG) in SLE. LDG frequency is elevated in SLE, and LDG-to-lymphocyte ratio is associated with disease activity. Supernatants from SLE patient-derived LDG, following in vitro culture, induced CD4 T cell pro-inflammatory cytokine responses. The authors hypothesize that LDG represent a novel pro-inflammatory cell subset in SLE. Azzouz et al., (pp 947-956) demonstrated microbiome diversity to be decreased in SLE patients compared to healthy controls. Importantly, a marked expansion of Ruminococcus gnavus (RG) was seen, while potentially protective bacterial species were reduced. RG specific antibodies were detected in patients with active nephritis. RG could represent a gut commensal with a potential to contribute to pathogenesis of lupus nephritis. Mortality in patients with *rheumatoid arthritis* (RA) is thought to be higher than in the general population. Poppelaars et al. (pp 586-589) show similar mortality after 23 years of follow-up in patients with early RA compared with the general population in the COBRA early RA cohort (standardised mortality ratio 0.80; 95%CI 0.59-1.06). In a randomized controlled trial, Van Mulligen et al. (pp 746-753) evaluate the effectiveness of two tapering strategies (csDMARD and anti-TNF tapering) after achieving controlled disease in RA patients, during 1 year of follow-up. The cumulative flare rates were, respectively, 33% (95% CI 24-43%) and 43% (95% CI 33-53%, p=0.17), meaning tapering anti-NF was not superior to tapering csDMARDs. Takeuchi et al. (pp 899-907) showed denosumab inhibits progression of joint destruction in RA patients taking csDMARDs. The mean changes in the mTSS at 12 months were 1.49 (95% CI 0.99-1.99) in the placebo group and 0.99 (95% CI 0.49-1.49) in the denosumab group (60 mg/6 months (p=0.0235).
Alpizar-Rodríguez et al. (pp. 590-593) demonstrated intestinal dysbiosis with a significant enrichment of Prevotella spp. in individuals at risk for rheumatoid arthritis (RA) prior to the development of the disease, compared with first-degree relatives of RA patients with no risk factors. Glatt et al. (pp. 1033-1040) showed a beneficial effect of bimekizumab add-on therapy in patients with RA and inadequate response to certolizumab pegol (CPZ-IR). At week 20, there was a greater reduction in DAS28-CRP in the CZP-IR plus bimekizumab group compared with CZP-IR plus placebo (change in DAS28-CRP [SD] -1.40 [1.32] vs. -1.04 [0.90]). Humby et al. (pp. 761-772) identified specific cellular/molecular synovial signatures associated with disease severity/progression and treatment response in RA at disease onset prior to DMARD initiation. Xie et al. (pp. 1048-1054) displayed in a meta-analysis of RCTs no significant change in cardiovascular risk for JAK-inhibitor-treated RA patients in a short-term perspective (OR 1.04; 95% CI 0.61-1.76); however, post-marketing data are necessary before any firm conclusions can be drawn. Mankia et al. (pp. 781-786) showed MRI inflammation of the hand interosseous tendons to be common in at-risk individuals before RA onset: 19% of CCP positive, 49% of early and 57% of late RA had ≥1 interosseous tendon inflamed, versus none in healthy controls. Liu et al. (pp. 1070-1078) identified disease-associated T cell clones that can potentially serve as diagnostic markers for RA and SLE. A high degree of heterogeneity of SLE specific T cell clones and high homogeneity of RA specific T cell clones was noted. Fedrowski et al. (pp. 807-816) validated the Scleroderma Clinical Trials Consortium Damage Index (SCTC-DI): the first tool to quantify organ damage in systemic sclerosis (SSc). Damoiseaux et al. (pp. 879-889) presented The International Consensus on antinuclear antibodies (ANA) Patterns (ICAP) on the clinical relevance of 29 distinct HEp-2 IIFA patterns, widely used for detection of ANA. Elhai et al. (pp. 979-987) showed, in an cohort of SSc patients, that rituximab use, compared with propensity-score matched untreated patients, is associated with improvement of skin fibrosis (OR 2.79, 95% CI 1.47–5.32), but not with interstitial lung disease (ILD) improvement. Zulian et al. (pp. 1019-1024) presented recommendations for the management of juvenile localised scleroderma. Van Meens et al. (pp. 610-616) showed the combination of golimumab plus methotrexate (GLM+MTX) as a first-line treatment to be superior to MTX alone in inducing remission in early psoriatic arthritis. DAS remission at week 22 was almost doubled with GLM+MTX versus MTX alone (81 vs 42%, p=0.004). Sabbagh et al. (pp. 988-995) demonstrated anti-Ro52 autoantibodies to be present in 14% of patients with juvenile myositis. These were associated with ILD, more severe disease and worse prognosis. Finally,Gattorno et al. (pp. 1025-1032) proposed classification criteria for autoinflammatory recurrent fever.
Recently, new ACR-EULAR classification criteria for systemic lupus erythematosus (SLE) were proposed. Gegenava et al. (e000895) evaluated the performance of these in a cohort of 360 suspected SLE patients with neuropsychiatric (NP) symptoms. Although sensitivity of the criteria was high (87%), specificity was suboptimal (74%), possibly due to referral bias. The authors suggest removing ANA positivity as entry criterion and specifying the NP domain, as this increased sensitivity without reducing specificity. Tani et al. (e000916) investigated glucocorticoid discontinuation (GCD) in a SLE cohort. Over 6 years, GCD was attempted in 91 patients (61.5%) and successful in 77 (84.6% of those attempting). Compared to those who failed GCD, patients with successful GCD had lower disease activity and more often were in full remission (54% vs. 21%), highlighting, in a real-world setting, that GC tapering/discontinuation could be attempted in those in low disease activity or remission. Ilar et al (e000978) investigated the association between occupational exposure to asbestos and silica and the risk of developing rheumatoid arthritis (RA) in a large case-control study. The adjusted risk of developing (seropositive or seronegative) RA was increased in asbestos- or silica-exposed males. When stratified by smoking status, the risk was highest in exposed male smokers (asbestos: OR 3.0, 95% CI 2.0-4.4 and silica: OR 2.9, 95% CI 2.0-4.3, compared to non-exposed male non-smokers). Animal models can help to study the synovial microenvironment during preclinical phases of RA. Yahagi et al. (e000853) studied knock-in gp130F759 mice, which develop RA-like arthritis. Histological changes in the synovia and serological changes preceded clinical arthritis, and IL-6 dependent PAD4 production was observed. The authors propose a model for the molecular events during the preclinical phase of RA, involving the IL-6-PAD4 axis. The generalisability of RCT results is often debated, due to strict inclusion criteria. In a retrospective cohort of psoriatic arthritis (PsA) patients initiating a biologic, Palsson et al. (e000984) compared those who would (INC) and would not (EXC) have been eligible for a biologics RCT. Disease activity and treatment response over time were similar in both groups, as was drug survival, suggesting biologic RCT results in PsA are generalisable. Treatment options for eosinophilic granulomatosis with polyangiitis (EGPA) are limited, and treatment often includes high GC exposure. Teixeira et al. (e000905) retrospectively investigated efficacy and safety of rituximab in 69 EGPA patients. Response to treatment was observed in 41%/77% at 6/24 months, and the median daily GC dose decreased from 12.5mg to 5mg over 24 months. Relapse occurred frequently (54%), however, possibly limiting the usefulness of rituximab for EGPA.
Recently, awareness has been raised on the issue of cardiovascular safety of baricitinib. Taylor et al. (pp 1042–1055) pooled data from nine rheumatoid arthritis (RA) studies (7,860 patient-years of exposure) and found no association between baricitinib and cardiovascular events, including arterial thrombotic events (IR 0.5 per 100 patient-years for both baricitinib and placebo). Incidence of venous thrombotic events (TE), however, was higher in the baricitinib group (IR 0.5–0.6 per 100 patient-years for 2 and 4 mg per day dosages) compared to placebo (IR 0). It should be noted that warnings have been issued on the potential association between (high-dose) JAK-inhibitor use and venous TE. Patients with RA in clinical remission may have subclinical synovial inflammation. Orange et al. (pp 1034–1041) reviewed the histological results from 135 RA patients submitted to arthroplasty and found histological presence of synovitis in 27% and 31% of those in remission or low disease activity, respectively. Biological therapy is thought to inhibit spinal progression in spondyloarthritis (SpA), but whether this effect also applies to the sacroiliac joints (SIJ) is debatable. In patients treated with etanercept for up to 6 years, Rodriguez et al. (pp 722–728) proved that long-term (2-4 year) therapy decelerated progression of structural damage in the SIJ of 42 patients. Increased CRP levels and osteitis on MRI were independent predictors of radiographic sacroiliitis progression. Results from past studies have put IFNα dysregulation in the center of immunological abnormalities observed in systemic lupus erythematosus (SLE). However, there is no validated or standardized technique to quantify IFNα in clinical practice. In a study performed by Mathian et al. (pp 756–765), digital ELISA-assessed IFNα was both sensitive and specific to distinguish healthy blood donors from inactive SLE and from active SLE patients. The first ACR recommendations for the treatment of juvenile idiopathic arthritis (JIA) date from 2011, with an update in 2013 focused on the treatment of systemic arthritis. In 2019, two new updates were made: the first focusing on arthritis, sacroiliitis and enthesitis by Ringold et al. (pp 846–863) and the second approaching JIA-associated uveitis by Angeles-Han et al. (pp 864–877). In both of them, quality of available evidence was globally low. Main differences from the 2011 recommendations include different definitions of risk factors and assessment of disease activity and added recommendations for escalating care in the setting of low disease activity. Another important difference is the preference given to DMARDs over NSAIDs in the event of new onset polyarthritis. Regarding JIA-associated uveitis, regular ophthalmic screening is recommended for all children and the frequency of screening must be based on individual risk factors.
Appani et al. (pp 869–873) showed that methotrexate (MTX) ≥15 mg/week with targeted escalation resulted in significant improvement in psoriatic arthritis: Minimal Disease Activity was achieved in 63%, PASI75 response in 67.9% and major cDAPSA response in 58.9% of patients. Khan et al. (pp 776–785) looked at the reported financial conflicts of interest (FCOIs) among authors of drug therapy RCTs for rheumatoid arthritis (RA) and their association with study outcomes. Not FCOIs themselves but receipt of honoraria/consulting fees was independently associated with a positive study outcome (adjusted OR 3.24 (95% CI 1.06–9.88). Mori et al. (pp 1274–1284) revealed no difference in tocilizumab (TZC) retention regarding MTX use in RA. Kaplan-Meier estimates for TZC retention were 48.3 months (95% CI 42.0-54.5) for monotherapy and 50.0 (95% CI 45.9-54.0) for combination therapy. Sepriano et al. (pp 798–802) highlight an association of sacroiliac joint inflammation on MRI with future radiographic progression in axial spondyloarthritis (axSpA) in two multicentric cohorts - ASAS (OR 3.2, 95% CI 1.3-7.9) and DESIR (OR 7.6, 95% CI 4.3-13.2). Zhao et al. (pp 811–819) observed in a large cross-sectional study that current or past smoking is independently associated with an adverse disease profile in axSpA, including worse fatigue, sleep, anxiety and depression, and higher odds of psoriasis, as well as with higher BASDAI and BASFI (current smoking - β=0.9, 95% CI 0.6–1.2 and β=1.3, 95% CI 1.0–1.6 respectively). Olofsson et al. (pp 1176–1187) showed that faecal calprotectin levels are significantly higher in both radiographic (geometric mean (GM) 41; 95% CI 32 to 54 mg/kg) and non-radiographic axSpA (GM 24; 95% CI 16 to 38 mg/kg) compared to controls (GM 12; 95% CI 9.2 to 16 mg/kg), both univariably and in adjusted analyses. Zobbe et al. (pp 836–839) showed the increase of annual incidence rate of gout by almost 80% in Denmark between 1995 and 2015 using the data of the nationwide Danish National Patient Registry. Likewise, an increase in the gout prevalence from 0.29% (95% CI 0.29-0.30) in 2000 to 0.68% (95% CI 0.68-0.69) in 2015 was observed. Janssen et al. (pp 1344–1352) showed anakinra to be non-inferior to standard treatment in acute gout flares (difference in changed pain score in ITT population: −0.18, 95% CI −0.44–0.08). Wang L et al. (pp 820–830) observed that male sex was independently associated with worse prognosis in response to glucocorticoid-based therapy in IgG4-related disease – HR for relapse 3.14 (p=0.003). Wang LH et al. (pp 1245-1249) report a bidirectional relationship between systemic lupus erythematosus (SLE) and non-Hodgkin’s lymphoma (NHL): in patients with one condition, the risk for another one was higher compared to the general population. The standardized incidence ratio (SIR) for NHL in the patients with SLE was 4.2 (95% CI 2.9-5.9), while the SIR for SLE in the patients with NHL was 2.0 (95% CI 1.1-3.4).
Casper is a rheumatologist in training and PhD candidate at the Maastricht University Medical Center, the Netherlands. His major research focus is spondyloarthritis (SpA). His past work involved gender-attributable differences and comorbidity in radiographic axial SpA, as well as socioeconomic outcomes, such as employment and sick leave. Currently, he is working on an economic evaluation of axial SpA. He is also involved in a Dutch registry for SpA. Casper is the leader of the Newsletter Subgroup.

Mariana is a rheumatology fellow at the Centro Hospitalar e Universitário de Coimbra, Coimbra, Portugal. Her main research interests include epidemiology, systemic lupus erythematosus and overdiagnosis and overtreatment in rheumatology. She has been working on glucocorticoids side effects and the (over)use of antinuclear antibodies to screen for connective tissue diseases. She is a member of the Social Media Subgroup.

In rheumatoid arthritis (RA), Boeters et al. (21:121) investigated whether serological biomarkers at disease onset were associated with sustained DMARD-free remission. In ACPA-negative patients, moderate and high multi-biomarker scores were independently associated with DMARD-free remission (HR high vs. low multi-biomarker score: 8.2, 95% CI 1.1-61.8); individual biomarkers associated with the outcome were CRP, SAA and MMP-3. Of note, in ACPA-positive patients, no such associations were observed. These results show that ACPA-negative RA can be divided in clinically relevant subtypes using biomarker profiles. Most current biological treatments in RA target cytokines produced by activated macrophages. As an alternative, folate receptor-beta-specific antibodies (anti-FR-β) directly target activated macrophages. Hu et al. (21:143) examined the potential therapeutic effects of anti-FR-β in RA. FR-β+ macrophage infiltration was shown to be present in human tissue samples of several autoimmune diseases, making it a potential treatment target. In a murine model of RA, anti-FR-β reduced arthritis, indicating that selective elimination of activated macrophages could be a potential new treatment mechanism in autoimmune disease. Alivernini et al. (21:116) investigated synovial tissue (ST) biomarkers in psoriatic arthritis (PsA) and seronegative RA patients. PsA patients had high CD117+ (mast cell) and low CD138+ (plasma cell) cell scores, while the opposite was observed for RA patients. CD3+ and CD68+ cell scores were predictive of treatment response for methotrexate in PsA and RA patients, respectively. Histological analysis of ST could help in differentiating PsA and seronegative RA. In axial spondyloarthritis, Zhao et al. (21:177) investigated the effect of smoking on TNF-inhibitor (TNFi) discontinuation in 758 patients from a British biologics registry who initiated their first TNFi. Despite worse disease activity in current smokers at time of TNFi initiation, the risk of (all-cause or cause-specific) TNFi discontinuation was not increased in current (all-cause discontinuation - HR 0.79, 95% CI 0.53-1.20) or ex-smokers (all-cause discontinuation - HR 0.68, 95% CI 0.45-1.04) compared to never smokers. Of note, information on smoking history was limited, possibly affecting the results. In systemic lupus erythematosus (SLE), Qin et al. (21:176) evaluated the utility of four urinary thrombogenic and thrombolytic biomarkers for lupus nephritis (LN) using urine samples from 113 biopsy-proven LN patients, 45 patients with CKD (disease controls) and 41 healthy controls (HC). Urine plasmin was the strongest predictor of renal function and renal disease status, and in combination with urine tissue factor pathway inhibitor was able to sufficiently discriminate active LN from HC (AUC 0.97) and inactive LN (AUC 0.86), outperforming conventional markers (anti-dsDNA and complement C3).
Rheumatoid arthritis (RA) is closely linked to other health conditions. McGuire et al. (pp 602-610) demonstrated higher incidence of chronic obstructive pulmonary disease in patients with RA (47% greater risk of COPD hospitalization than controls after adjusting for potential confounders). Linauskas et al. (pp 777-786) showed, in a population-based prospective cohort study including 55,037 subjects, higher body fat percentage, higher waist circumference, and presence of obesity (HR 1.46; 95% CI 1.12–1.90) to be associated with a higher risk of developing RA, but only in females. Liu et al. (pp. 914-924) confirmed the association of current smoking and increased risk of seropositive – but not seronegative – RA (multivariable HR 1.67, 95% CI 1.38–2.01). While a decreased trend for the risk of seropositive RA was observed with increasing duration of smoking cessation, 30 years after smoking cessation the risk for seropositive RA was still slightly increased compared to never smokers. A study by Smith et al. (pp. 1019-1027) revealed that women with RA have an increased risk of preterm delivery versus women without autoimmune disease (RR 2.09; 95% CI 1.50–2.91); active RA at any time during pregnancy (ARR 1.52 [95% CI 1.06–2.18]) and corticosteroid use in every trimester (2- to 5-fold increased risk) were independently associated with preterm delivery. Wearable activity trackers (WATs) could be a promising strategy to detect and also improve physical activity in patients with rheumatic and musculoskeletal diseases (RMDs). Davergne et al. (pp 758-767) demonstrated in a systematic review of 17 studies (most compared WAT to usual care/education) that the use of WATs in patients with RMDs was effective in promoting physical activity, significantly increasing the number of steps (mean difference 1,520 steps [95% CI 580 to 2,460]) and time spent in moderate-to-vigorous physical activity. In systemic lupus erythematosus (SLE), low disease activity (LDA) is a potential treatment target along with remission. In a study by Tselios et al. (pp. 822-828), 18% of 267 included patients attained prolonged LDA, and SLE was in complete remission for 76% of the follow-up time in these patients. Choi et al. (pp. 893-902) confirmed that the frequency of true ANA-negative SLE is very low. In their study, 92.3% of the 1,137 patients had positive nuclear staining, and additionally 1.5% of patients had isolated cytoplasmic staining. Losina et al. (pp. 855-864) explored the cost-effectiveness of adding an intensive diet and exercise program to usual care for overweight and obese patients with knee osteoarthritis (OA) and found that intervention to be cost-effective, resulting in the incremental cost-effectiveness ratio of $30,000/QALY from the societal perspective. The 2019 American College of Rheumatology/Arthritis Foundation Guidelines for the Screening, Monitoring, and Treatment of Juvenile Idiopathic Arthritis—Associated Uveitis (Angeles-Han et al, pp. 703-716) were published in June issue.
Methotrexate (MTX) is the cornerstone therapy for patients with rheumatoid arthritis (RA) with well-established efficacy. However, safety can be a concern, especially with regard to the elderly. Widdifield et al. (pp 467-474) conducted an inception cohort study of 23,994 patients with RA diagnosed after age 65, and evaluated the cardiovascular risk in these patients. Both early and continuous use of MTX were associated with a decreased cardiovascular risk (HR 0.84, 95% CI 0.72-0.96 and HR 0.79, 95% CI 0.70-0.88, respectively). On a similar topic, Lee et al. (pp 527-531) compared hepatic safety of allopurinol versus febuxostat in patients with gout and fatty liver. While febuxostat was less hepatotoxic than allopurinol (incidence of hepatotoxicity 9.4% vs. 35.3%), this toxicity increased in the presence of diabetes and colchicine use. Outcome measures in systemic vasculitis are mostly physician-based and don’t capture the patient’s perspective. Tomasson et al. (pp 928-934) tested the feasibility of the Patient Reported Outcomes Measurement Information System (PROMIS) in systemic vasculitis. PROMIS showed a good correlation with SF-36 but not with physician global assessment. Bruni et al. (pp 603-608) proposed a clinical assessment score for digital ulcers in systemic sclerosis (SSc) (DUCAS). Its preliminary validation included the use of several well-established patient reported outcomes (PROs). Overall, DUCAS showed significant positive correlations with all tested PROs, coming up as a promising tool for digital ulcer evaluation in SSc. Enthesitis is the hallmark of the spondyloarthritis (SpA). As its clinical assessment is difficult, previous studies tried to use ultrasound (US) with low concordance rate reached when compared to clinical examination. Macchioni et al. (pp 904-911) evaluated the prevalence of enthesitis in PsA, psoriasis and fibromyalgia (FM) patients in the ULISSE study. The authors found clinical enthesitis to be more frequent in FM (92%, versus 66% in PsA and 59% in psoriasis) while US enthesitis prevailed in both PsA and psoriasis equally (90%, versus 75% in FM). Apparently, clinical enthesitis is common in all 3 disease entities, and cannot distinguish between them. Immunosuppressed patients are more susceptible to infections, some of them preventable through proper vaccination. However, the use of immunosuppressants may result in attenuation of the immune response to vaccines. Also, not all vaccines can be administered in immunosuppressed patients due to the risk of reversion to virulence of live attenuated vaccines. According to the most recent guidelines by Papp et al. (pp 751-754), the risks and benefits of immunization should be weighed to determine patient eligibility and appropriate timing of vaccine administration relative to immunosuppressive therapy.
Achilleas Floudas and Mikhail Protopopov

Tertiary lymphoid organ (TLS) formation remains a staple of pathology in rheumatoid arthritis (RA). In an intriguing study, Nayar et al. (Proc Natl Acad Sci USA, 116:13490-13497) explored the potential contribution of fibroblasts in the formation of TLS. The authors identified TLS associated fibroblasts as prodoplanin (pdpn) and FAP positive. TLS fibroblasts precede lymphocyte accumulation and their proliferation is dependent on the IL-22/IL-22R axis. Interestingly, in lymphocyte deficient RAG2 mice, while TLS fibroblast expansion was inhibited, TLS fibroblast initial activation was intact, highlighting that lymphocytes are potentially dispensable for the initial activation of these cells. In order to assess the dependency of TLS formation of pdpn+ fibroblasts, the authors utilised DM2 mice in order to specifically deplete pdpn+ fibroblasts; following depletion, TLS formation was severely compromised. This study highlights a novel role for a population of fibroblasts in the formation of TLS that opens up the possibility of therapeutically targeting specific fibroblast sub-populations. Smolen et al. (Lancet, 393:2303-2311) reported that monotherapy with upadacitinib, an oral Janus kinase (JAK)1-selective inhibitor, showed statistically significant improvements in clinical and functional outcomes versus continuing methotrexate in methotrexate inadequate-responders with RA. At week 14, an ACR20 response was achieved by 41% in the continued methotrexate group, 68% receiving upadacitinib 15 mg, and 71% receiving upadacitinib 30 mg (p=0.0001 for both doses vs continued methotrexate). DAS28-CRP 3.2 or lower was met by 19%, 45% and 53% respectively (p=0.0001 for both doses vs continued methotrexate). Distler et al. (NEJM 380:2518-2528) investigated the efficacy of nintedanib, a tyrosine kinase inhibitor, in interstitial lung disease associated with systemic sclerosis (SSc), which is a common manifestation and a leading cause of SSc–related death. The adjusted annual rate of change in forced vital capacity (FVC) was −52.4 ml per year in the nintedanib group and −93.3 ml per year in the placebo group (difference, 41.0 ml per year; 95% CI 2.9-79.0; p=0.04), while no clinical benefit of nintedanib was observed for other manifestations of SSc. Hong et al. (J Exp Med 216:1154-1169) performed a detailed characterisation of the immune system of healthy pregnant women and pregnant women with systemic lupus erythematosus (SLE). A pregnancy in healthy women was associated with increased neutrophil cell signature but decreased IFN and plasma cell signatures and a marked increase in transitional B cells post-partum, an uncomplicated SLE pregnancy shared similar characteristics with a healthy pregnancy but with an increase IFN response. Adverse SLE pregnancy outcomes were associated with early neutrophilia, high plasma cell and IFN signatures.
Intermediate Ultrasound Course & Paediatric Musculoskeletal Ultrasound Course
- When and Where: 3 – 5 Oct 2019, Antalya, Turkey
- Website: http://www.antalyaultrasound.com/int2019/index.html

5th International Symposium Intra Articular Treatment
- When and Where: 3 – 5 Oct 2019, Lisbon, Portugal
- Website: https://www.isiat2019.com/

9th Advanced Academic Rheumatology Review Course
- When and Where: 11 – 14 Oct 2019, Abu Dhabi, United Arab Emirates
- Website: https://course.adarrc.org/

3rd EULAR Registers and Observational Drug Studies (RODS) Meeting
- When and Where: 18 – 19 Oct 2019, Amsterdam, the Netherlands
- Website: https://esor.eular.org/theme/lc_eular/layout/enrol.php?id=12

European Large Vessel Vasculitis Imaging Course (EULVIC)
- When and Where: 18 – 19 Oct 2019, Innsbruck, Austria
- Website: https://www.eulvic.eu/

2nd Global Update in Joint Imaging Pathology & Orthopaedic Surgery Congress
- When and Where: 19 – 20 Oct 2019, Kuala Lumpur, Malaysia
- Website: http://penangmskrad.com/

7th Annual Meeting of the International Cytokine & Interferon Society
- When and Where: 20 – 23 Oct 2019, Vienna, Austria
- Website: https://vienna.cytokinesociety.org/
THE EULAR ONLINE COURSES

All EULAR courses, as electronic ways of continuous medical education in rheumatology, are managed by a scientific course committee responsible for the structure and content of the courses and for ensuring regular quality control and advancement. Teams of expert authors are regularly reviewing and updating the courses to keep up with the newest developments in the field.

REGISTRATION OPEN SINCE END OF JUNE 2019 – CLOSING ON 30 NOVEMBER 2019

<table>
<thead>
<tr>
<th>Course</th>
<th>Duration</th>
</tr>
</thead>
<tbody>
<tr>
<td>14th EULAR Online Course on Rheumatic Diseases</td>
<td>2 years</td>
</tr>
<tr>
<td>11th EULAR Online Course on Connective Tissue Diseases (CTD)</td>
<td>1 year</td>
</tr>
<tr>
<td>1st EULAR Online Course for Systemic Lupus Erythematosus</td>
<td>1 year</td>
</tr>
<tr>
<td>2nd EULAR Online Course on Imaging in RMDs</td>
<td>1 year</td>
</tr>
<tr>
<td>9th EULAR Online Course on Systemic Sclerosis (SSc)</td>
<td>9 months</td>
</tr>
<tr>
<td>8th EULAR Online Introductory Ultrasound Course</td>
<td>7 months</td>
</tr>
<tr>
<td>6th EULAR / PReS Online Course in Paediatric Rheumatology</td>
<td>1 year</td>
</tr>
<tr>
<td>5th EULAR Online Course for Health Professionals</td>
<td>9 months</td>
</tr>
</tbody>
</table>

Visit the EULAR School of Rheumatology for more information and registration

THE OPINION OF TWO PARTICIPANTS:

“Ultrasonography is essential for the training of Rheumatologists and represents a key aspect of patient’s evaluation. The EULAR Online Introductory Ultrasound Course offers theoretical basic skills on musculoskeletal ultrasound in rheumatic diseases as well as in healthy subjects. The high quality of contents as well as the experience of the Faculty are the two main reasons to join this course. Moreover, the website is straightforward and very easy to use. Upon passing the final examination, EULAR releases a certificate. This course is very useful for Rheumatologists who would like to acquire a basic theoretical knowledge on musculoskeletal ultrasound.”

“I attended the EULAR Online Introductory Ultrasound Course. It is a well structured basic course on ultrasonography that is divided in different modules according to the different anatomical sites. Each module includes specific exercises and the final test. I found this course very interesting and it provided me with a complete overview of ultrasonography in rheumatology. I would recommend this course as to me it was overall more useful and formative compared to some different on-site courses I previously attended.”
EMEUNET ON COURSE

EMEUNET is testing a new initiative for rheumatologists taking the EULAR online courses called #EMEUNETonCourse. The purpose of the initiative is to create a platform for interaction while taking one of the EULAR online courses. The idea is that this will make learning more effective for the course attendants and at the same time get more rheumatology related content on #MedicalTwitter.

The initiative is grounded on Twitter. Anyone can Tweet anything with relevance to one of the EULAR online courses they are taking. E.g. a summary to help others, special clinical pearls, controversies for debate etc. The hashtags used are the same as the name of the course, e.g. hashtag for the EULAR online course on rheumatic diseases (the 2-year course based on the EULAR Textbook on Rheumatic Diseases) is #EULAROnlineCourseOnRheumaticDiseases. Further, the hashtag #EMEUNETonCourse is used in all Tweets. Other hashtags can be used to specify the chapter or topic of the Tweet.

See https://emeunet.eular.org/eular_online_courses.cfm for more information!

Because courses contain copyright content, it is stressed that all posts should comply with normal copyright regulations, e.g. do not post anything without proper citations and do not copy paste content from the courses.
EULAR OUTCOME MEASURES LIBRARY (OML)

The EULAR Outcome Measures Library (OML) aims to be a comprehensive database of validated instruments (indices, questionnaires, scales, or others), with an emphasis on patient-reported outcomes (PRO) used in rheumatology. The EULAR OML was created by rheumatologists, health professionals, students and patients, all of whom are engaged in the field of rheumatology.

The OML includes detailed descriptions of each instrument, such as the settings in which it has been validated, recommendations for use and different language versions of each instrument. Also, guidelines for interpretation of results in both practice and research settings are provided. Instruments are categorized by disease or by topic. The OML is an ongoing project, and is frequently updated with the most recent information on PROs in rheumatology.

For more information visit:
http://oml.eular.org/
JOIN EULAR TASK FORCES AND COMMITTEES

Young investigators of EMEUNET are an integral part of all task forces and committees working on new EULAR recommendations. This is a wonderful chance for EMEUNET to increase its visibility and for you to accelerate your academic career.

EMEUNET members with interest in methodology and previous experience in EULAR Task Forces can also have the opportunity to become junior methodologists. For further information, please contact emeunet.education@gmail.com

Take a look at emails from EMEUNET and find the opportunity most suitable for you!

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!

Complete this quick and easy survey to help us improve and grow: https://www.surveymonkey.com/r/LWPM2H2. 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!

More information about EMEUNET can be found at http://emeunet.eular.org

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EMEUNET Tube