Dear Reader,

We are happy to present the 14th issue of the EMEUNET-EULAR ‘Press Review and Journal Club’ newsletter that is a part of the EULAR School of Rheumatology (ESOR) educational initiative, the EULAR–EMEUNET Journal Club. In this issue you will find an overview of relevant articles published in top rheumatology journals and in major internal medicine journals. In this newsletter we once again included articles published electronically in the period between April 2021 and July 2021 to bring you the latest updates in the field. The article selection includes translational and clinical research papers, sorted by the journals they were published in. In case you want to read the article in more detail, you can access it directly through a hyperlink.

Among the selected articles, one has been chosen by our Twitter account (@EMEUNET) subscribers to be discussed in a few weeks in an online Twitter Journal Club (@EULAR JC). Additionally, the ‘EMEUNE’s Choice’ scientific paper in the field of rheumatology has been selected by a popular vote through an online 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 have interest in rheumatology to participate in an online, lively discussion. These ‘meetings’ take place on Twitter at pre-specified times and dates; the next is planned on November, the 3rd, 2021 at 8:00 PM GMT (9:00 PM CET). Key authors of the selected paper will be participating in the discussion and answer questions. Details on the selected article and the Journal Club you can find on the page 3 of this issue and in our Twitter JC account (@EULAR JC).

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

Javier Rodriguez Carrio, Aurélie Najm, Polona Zigon, Mikhail Protopopov, Maria Sokolova, Diego Benavent, Lianne Kearsley-Fleet, Mrinalini Dey and Pierre-Antoine Juge on behalf of the EULAR EMEUNET Journal Club team
The online Journal Club will take place on:
**November 3rd, 2021 at 7:00PM GMT (8:00PM CET, 3:00PM EDT)**
- duration 1 hour -

Follow the accounts @EULAR_JC, @eular_org and @EMEUNET

Use the hashtag #EULARJC to follow and join the discussion

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**EMEUNET COMMUNITY CHOICE FOR THE JOURNAL CLUB**

Tadej Avčin  
Ljubljana University  
Slovenia

Xenofon Baraliakos  
Ruhr-University Bochum  
Germany

Christopher Edwards  
University Hospital Southampton  
United Kingdom

Annamaria Iagnocco  
University of Turin  
Italy

The ongoing COVID-19 pandemic has had a significant impact on people with rheumatoid arthritis (RA), many of whom are treated with biologic or targeted synthetic disease-modifying antirheumatic drugs (b/tsDMARDs). The authors aimed at investigating the use of b/tsDMARDs and COVID-19 outcomes in patients with RA, analyzing the data of the COVID-19 Global Rheumatology Alliance physician registry (from 24 March 2020 to 12 April 2021), including 2869 patients with RA (mean age 56.7 years, 80.8% female) on b/tsDMARD at the onset of COVID-19. It was revealed that patients with RA treated with rituximab (OR 4.15, 95%CI 3.16 to 5.44) or JAK inhibitors (OR 2.06, 95%CI 1.60 to 2.65) had worse COVID-19 severity than those on TNF inhibitors. There were no associations between abatacept or IL-6 inhibitors and COVID-19 severity. The strong association of rituximab and JAK inhibitors use with poor COVID-19 outcomes highlights prioritization of risk mitigation strategies for these people.

**Associations of baseline use of biologic or targeted synthetic DMARDs with COVID-19 severity in rheumatoid arthritis: Results from the COVID-19 Global Rheumatology Alliance physician registry.**

*Ann Rheum Dis 2021;80:1137–1146; doi:10.1136/annrheumdis-2021-220418*
John A. Reynolds, Jennifer Prattley, Nophar Geifman, Mark Lunt, Caroline Gordon & Ian N. Bruce on behalf of the MASTERPLANS Consortium

Distinct patterns of disease activity over time in patients with active SLE revealed using latent class trajectory models


The authors attempted to distinct the trajectories of disease activity occurring over time in patients with active Systemic lupus erythematosus (SLE) and to identify factors associated with these trajectories. Latent class trajectory models were fitted to a clinical trial dataset of a monoclonal antibody targeting CD22 (Epratuzumab) in patients with active SLE using the numerical BILAG-2004 score (nBILAG). Overall, five trajectories of disease activity were identified, with 3 principal classes: non-responders (NR), slow responders (SR) and rapid-responders (RR). In both the SR and RR groups, significant changes in disease activity were evident within the first 90 days of the trial. The SR and RR patients had significantly higher baseline disease activity, exposure to epratuzumab and activity in specific BILAG domains, whilst NR had lower steroid use at baseline and less change in steroid dose early in the trial, and were less likely to have activity in the constitutional, musculoskeletal or cardiorespiratory systems compared to RR and SR. Changes in disease activity and steroid dose early in the trial were associated with the overall disease activity trajectory, supporting the feasibility of performing adaptive trial designs in SLE.

Explore this paper in greater detail through an exclusive interview with the first author

Interview available on the EMEUNET Tube soon!

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!
Redeker et al (doi: 10.1136/annrheumdis-2021-220651) used data from the German RABBIT register to compare event and incidence rates of herpes zoster (HZ) infection in patients with rheumatoid arthritis (RA) being treated with conventional synthetic (cs), targeted synthetic (ts) or biologic (b) disease-modifying antirheumatic drugs (DMARDs). 13991 patients were included between 2007 and 2020, with 559 HZ events in 533 patients. HZ exposure-adjusted event rate (EAER) was highest for tsDMARDs (21.5, 95% CI 16.4 to 27.9). After adjustment for age, sex and glucocorticoid use, and inverse probability weighting, tsDMARDs (HR 3.66, 95% CI 2.38 to 5.63), anti-TNF drugs (HR 1.63, 95% CI 1.17 to 2.28) and B cell targeted therapy (HR 1.57, 95% CI 1.03 to 2.40) had significantly higher risk of HZ infection compared to csDMARDs. In a meta-analysis, Wouters et al (doi: 10.1136/annrheumdis-2021-220546) investigated human leukocyte antigen-shared epitope (HLA-SE) and smoking, two of the most prominent genetic and environmental risk factors for RA. The authors found that HLA-SE and smoking were both associated with ACPA positivity; OR 2.08 (95% CI 1.24 to 3.49) and OR 2.41 (95% CI 1.31 to 4.43) respectively. However, only HLA-SE was associated with inflammatory arthritis development in individuals with clinically suspect arthralgia; OR 1.52 (95% CI 1.08 to 2.15). This information increases our understanding of how the timing of key genetic and environment risk factors influence the development of RA. Ballal et al (doi: 10.1136/annrheumdis-2020-219646) investigated the association between anticoagulation use and the risk of knee and hip replacements (as indicators for end-stage osteoarthritis). A nested case-control study was performed using UK general practice records in patients with hip or knee replacements and atrial fibrillation, newly prescribed warfarin or direct oral anticoagulants (DOACs). The association between anticoagulation and risk of joint replacement was assessed using conditional logistic regression, comparing warfarin to DOAC use. Duration of warfarin use was also accounted for. 857 patients with joint replacement were included, 64.6% of whom were warfarin users, with 3428 matched controls, 56.1% warfarin users. Warfarin users in both groups were found to have a 1.59 times higher risk of joint replacement than DOAC users (adjusted OR 1.59, 95% CI 1.31 to 1.92). Duration of warfarin <1 year use was associated with a higher risk of joint replacement. Johnson et al (doi: 10.1136/annrheumdis-2021-220125) investigated the association of methotrexate (MTX) use with cardiovascular disease (CVD) in RA using marginal structural models. 2044 patients with RA were included, with 378 CVD events identified. MTX use was associated with 24% risk reduction of CVD events (HR 0.76, 95% CI 0.58 to 0.99) including 57% reduction in heart failure admissions. The associations were not found to be mediated through reduced RA activity. This suggests an alternative mechanism in CVD risk mediation in the RA patient population.
Unizony et al (doi: 10.1136/annrheumdis-2021-220347) aimed to identify predictors of treatment failure in patients with giant cell arteritis (GCA) receiving tocilizumab with glucocorticoids, and in patients receiving only glucocorticoids, conducting a post-hoc analysis of the GCA Actemra trial with 250 patients receiving tocilizumab and prednisone in various combinations and dosing frequencies. Responders for the analysis were patients maintaining remission through week 52. Treatment failure was the inability to achieve remission by week 12 or relapse between weeks 12 and 52. 149 patients were included who received tocilizumab plus prednisone, and 101 who received placebo plus prednisone. Treatment failure was significantly less likely in the group receiving tocilizumab with prednisone, compared to those receiving placebo (OR, 0.2; 95% CI 0.1 to 0.3). Risk of treatment failure was significantly higher in women in the placebo but not in the tocilizumab group. Predictors of treatment failure in the tocilizumab group included lower baseline prednisolone doses and worse baseline patient reported outcome. Both RA and glucocorticoid use increase the risk for cardiovascular events. Ocon et al (doi: 10.1136/annrheumdis-2021-220577) investigated 19902 steroid-naive RA patients from the CorEvitas (formerly Corrona) RA registry to estimate the adjusted hazard ratio for incidence of cardiovascular events in patients who initiated glucocorticoid treatment. Glucocorticoid doses of ≥5–9 mg and ≥10 mg showed increased risk; aHR 1.56 (95% CI 1.18 to 2.06) and 1.91 (95% CI 1.31 to 2.79) respectively. Cumulative dose over the preceding 6 months also showed an increased risk: 751–1100 mg aHR 1.43 (95% CI 1.04 to 1.98) and >1100 mg aHR 2.05 (95% CI 1.42 to 2.94), with similar one-year analyses. No association with risk for CVE was found with daily prednisone of ≤4 mg or shorter cumulative doses and durations. Acosta Felguer et al (doi: 10.1136/annrheumdis-2021-220865) investigated 1719 patients with psoriasis, followed for a median of 7.3 years, and hypothesised that biologics prescribed for treatment of the skin will be able to prevent the development of psoriatic arthritis (PsA). During follow-up, 239 patients (14%) developed PsA, with onset associated with being male (HR 1.7; 95% CI 1.1 to 2.6), higher BMI (HR 1.05; 95% CI 1 to 1.1), and nail involvement (HR 2.7; 95% CI 1.6 to 4.5). Conventional-synthetic or biologic DMARDs were not associated with development of PsA. In contrast, Gisondi et al (doi: 10.1136/annrheumdis-2021-219961) investigated 464 patients with psoriasis with moderate-to-severe plaque psoriasis, and compared those who were prescribed at least 5 years of biologic DMARDs with those treated with narrow-band ultraviolet light B (nb-UVB) UVB phototherapy. Nail psoriasis was associated with PsA development (aHR 3.15; 95% CI 1.63 to 6.06), as well as psoriasis duration of over 10 years (aHR 2.02; 95% CI 1.09 to 3.76). In addition, biologic DMARD use was inversely associated with development of PsA; aHR 0.27 (95% CI 0.11 to 0.66).
Marques et al (doi: 10.1136/rmdopen-2021-001647) conducted a systematic literature review (SLR) to inform the EULAR recommendations for self-management interventions in patients with inflammatory arthritis. Thirty-two studies were included. The most studied self-management components were interactive disease education, problem-solving, cognitive-behavioural therapy, goal setting, patient education and response training. The most studied interventions were multicomponent or single exercise/physical activity, psychosocial intervention and education. Overall, all have beneficial effects on outcomes in patients with inflammatory arthritis. The authors concluded that future research should focus on understanding the complexities of self-management, including the isolated effectiveness of the different components.

Nikiphorou et al (doi: 10.1136/rmdopen-2021-001685) investigated the occurrence of sick leave and impact of clinical and socioeconomic factors on sick leave in patients with early axial spondyloarthritis (axSpA). Patients diagnosed with axSpA from the DEverien des Spondyloarthrites Indifférenciées Récentes (DESIR) cohort with work-related data were studied. 704 axSpA patients were included. 80% of patients were employed at baseline, with 5.7% of these reporting being on sick leave. Incidence of sick leave among those at risk during the study period was 0.05. Male gender and higher education were associated with lower hazard ratio of sick leave (HR 0.41, 95% CI 0.20 to 0.86 and HR 0.48, 95% CI 0.24 to 0.95, respectively). Higher disease activity (HR 1.49, 95% CI 1.04 to 2.13), older age, smoking and anti-TNF use were also associated with higher risk. The authors concluded that the findings suggest a role for socioeconomic factors along with active disease in adverse work outcomes in young working-age individuals with axSpA.

Stouten et al (doi: 10.1136/rmdopen-2021-001671) investigated the comorbidity burden in the first three years after diagnosis of rheumatoid arthritis (RA), psoriatic arthritis (PsA) or spondyloarthritis (SpA), as well as pain medication prescriptions, as compared to controls (matched on age, gender, physician practice and diagnosis date). General practice data from a Belgian registry 1999-2012 were analysed. In total, 738, 229 and 167 patients were included with a diagnosis of RA, SpA or PsA, respectively. Patients with RA or PsA had comparable baseline Rheumatic Diseases Comorbidity Index (RCDI), but higher at year three compared to controls (RA: p=0.010; PsA: p=0.008). Depression was more prevalent in patients with PsA compared to controls, at baseline (20% vs. 11%, p<0.003) and RA patients had a greater three-year incidence of CVD (including myocardial infarction) compared to controls (24.3% vs 16.5%, p<0.035). Patients with RA, PsA and SpA were prescribed more pain medication of any type compared to controls. Thus, patients with chronic inflammatory rheumatic diseases have an increased comorbidity burden, as well as high pain medication (including opioid) use.
Mc Ardle et al (doi:10.1002/art.41899) aimed to identify serum protein biomarkers which might distinguish early inflammatory arthritis (EIA) and psoriatic arthritis (PsA) patients from those with rheumatoid arthritis (RA). The authors used data from three proteomic platforms and machine learning analysis. Models were able to discriminate PsA from RA patients with an area under the curve (AUC) of 0.94 for nano-flow liquid chromatography mass spectrometry, 0.69 for bead-based immunoassay measurements and 0.73 for aptamer-based analysis. A validation analysis in an independent cohort showed that a subset of proteins measured by multiple reaction monitoring assays could differentiate PsA and RA patients with AUCs of 0.79 and 0.85, respectively. Lin et al (doi:10.1002/art.41907) analyzed patients with incident polymyositis (PM) / dermatomyositis (DM) from a nationwide insurance database in Taiwan to determine the risk and time trends of hospitalized heart failure in these patients. A multivariable Cox regression model using data from 2025 PM/DM patients and 196109 controls revealed a greater risk of hospitalized HF in the PM/DM than in the control groups (adjusted HR: 3.29, 95%CI 2.60 to 4.18). After propensity score matching, PM/DM patients were found to have a higher risk of heart failure (HR: 2.06, 95% CI 1.36 to 3.12) compared to healthy individuals. This risk persisted for up to 10 years after the PM/DM diagnosis in stratified analysis. Deodhar et al (doi:10.1002/art.41911) presented the results of the open-label extension of the SELECT-AXIS 1 - a randomized, double-blind, placebo-controlled study evaluating the efficacy and safety of upadacitinib through 1 year in patients with ankylosing spondylitis (AS). Patients were assigned to upadacitinib 15 mg once daily or placebo. After week 14 patients continued in the open-label extension and received upadacitinib up to week 104. Similar proportions of patients in the upadacitinib groups (continuous or placebo-to-upadacitinib) achieved ASAS40 or ASDAS low-disease activity at week 64. >34% of patients achieved ASDAS inactive disease or ASAS partial remission at week 64 (non-responder imputation). No safety concerns were reported. Hanly et al (doi:10.1002/art.41876) aimed at determining predictors for change in neuropsychiatric (NP) event status in patients with systemic lupus erythematosus (SLE). There was association of SLE NP events with male sex (OR 1.35, 95% CI 1.03 to 1.78), concurrent non-SLE NP events (OR 1.83, 95 % CI 1.31 to 2.55), active SLE (OR 1.19, 95% CI 1.04 to 1.36) and corticosteroid use (OR 1.59, 95% CI 1.12 to 2.34). Multivariate analysis revealed resolution of SLE NP events was more common among individuals of Asian ethnicity (OR= 1.77, 95% CI 1.19 to 2.63) and for central/focal NP events (OR 1.66, 95% CI 1.29 to 2.15).
Moghaddam et al (doi: 10.1093/rheumatology/keab362) investigated all-cause and cause-specific mortality in 6092 systemic lupus erythematosus (SLE) patients compared to 60,920 matched non-SLE individuals. All-cause mortality HR was 1.85 (95% CI 1.66 to 2.06) with no statistically significant improvement between early (1997-2005) and late (2006-2014) cohorts. Excess mortality was identified for renal disease (HR = 3.04, 95% CI 2.29 to 4.05), infections (HR = 2.74, 95% CI 2.19 to 3.43) and cardiovascular disease (HR = 2.05, 95% CI 1.77 to 2.38) but not for cancer. No statistically significant improvement in cause-specific mortality was observed between the 2 cohorts. Ahn et al (doi: 10.1093/rheumatology/keab303) compared the prophylactic effect of regular dose (1.2 mg/day) and low-dose (0.6 mg/day) colchicine on gout flare rate when initiating urate-lowering therapy in a retrospective cohort study (n = 419). Patients receiving low-dose colchicine had a lower BMI, estimated glomerular filtration rate and higher incidence of cardio-vascular disease. At 3 months follow-up, no significant difference was observed between the two groups (OR = 1.309, 95% CI 0.668 to 2.566), though low-dose colchicine was associated with lower rate of adverse event (OR = 0.410, 95% CI 0.217 to 0.777). Garrido-Cumberera et al (doi: 10.1093/rheumatology/keab369) investigated data from 2652 patients from 13 European countries using multivariable linear regression analysis in order to identify factors associated with diagnosis delay in axial spondyloarthritis. Mean diagnosis delay was 7.4 (SD 8.4) years. Younger age at symptom onset (b = -0.26, 95% CI -0.28 to -0.023), female gender (b = 1.34, 95% CI 0.73 to 1.96) and higher number of healthcare professionals seen before diagnosis (b = 1.19, 95% CI: 0.95 to 1.43) were associated with a longer diagnosis delay. Mease et al (doi: 10.1093/rheumatology/keab119) compared in a systematic literature review the efficacy of guselkumab to other targeted therapies in psoriatic arthritis (PsA). 26 randomized controlled trials were included. While ACR 20/50/70 response was comparable between guselkumab and IL-17A or TNF inhibitors, PASI response was better than most other agents. For van der Heijde-Sharp score, guselkumab was comparable to other agents except intravenous TNF inhibitors. Regarding adverse events, guselkumab ranked higher in the analysis, though the rarity of events does not allow to make assertive conclusions. Huss et al (doi: 10.1093/rheumatology/keab570) performed an observational register study to estimate the relative risk of incident non-cutaneous cancer in patients with rheumatoid arthritis (RA) treated with biologic (b) and targeted synthetic(ts) DMARDs. Data from 16 Swedish centers were prospectively collected. No statistically significant differences were found for b or tsDMARDs and TNF inhibitors, rituximab or tocilizumab. Mildly increased incidence was observed only for abatacept (HR = 1.2, 95% CI 1.0 to 1.3).
In the BARFOT early rheumatoid arthritis (RA) cohort of 653 patients, Ajeganova et al (doi: 10.1186/s13075-021-02581-0) identified 141 incident cardiovascular events over 11.7 years follow-up. Protective effects of higher levels of IgM anti-phosphorylcholine antibodies (anti-PC) on cardiovascular events were identified in younger patients with RA (HR 0.4 in <55 year olds; 95% CI 0.1 to 0.9) and in those at high risk for an event: in males (HR 0.6; 95% CI 0.3 to 0.96), in obese patients (HR 0.2; 95% CI 0.1 to 0.8), and in patients without remission after 1 year (HR 0.6; 95% CI 0.4–0.9). Iwamoto et al (doi: 10.1186/s13075-021-02582-z) compared the efficacy and safety of the JAK inhibitors in patients with RA in routine clinical practice. After 24-weeks, disease activity was similar (DAS28-esr, SDAI, CDAI) between the 161 patients starting tofacitinib and 81 baricitinib, even without the concomitant use of methotrexate, although fewer previous biologic or targeted-synthetic DMARDs contributed to the clinical response to baricitinib but not to tofacitinib. Maarseveen et al (doi: 10.1186/s13075-021-02553-4) investigated whether machine learning could identify RA patients from electronic health record (EHR) free-text versus manual chart-review. Machine learning performed very well in the independent test (sensitivity=0.85, specificity=0.99, positive predictive value=0.86, negative predictive value=0.99), which enabled fast patient information extraction from a large EHR resource, completing 3326 medical records per second. Using an inception cohort of 232 patients with early RA, recruited in 1995–2005, Eberhard et al (doi: 10.1186/s13075-021-02550-7) identified that over one-third of patients (34%) had unacceptable pain levels after 5 years. Lower baseline swollen joint counts (OR 0.71, 95% CI 0.51 to 0.99) and higher VAS for pain and global assessment of disease activity were predictors of unacceptable pain after 5 years. Unacceptable pain with low inflammation after 5 years was negatively associated with anti-CCP antibodies (OR 0.50, 95% CI 0.22 to 0.98). Using 2 multicentre double-blind randomised placebo-controlled trials of pratuzumab in 1202 patients with active systemic lupus erythematosus (SLE), Reynolds et al (doi: 10.1186/s13075-021-02584-x) identified 5 distinct trajectories of SLE disease activity over time: non-responders (34%), slow-responders (21%), rapid responders (37%), with high disease activity (4%) and with flare (5%). Patients in both of the responder groups were more likely to show improvement in disease activity within the first 90 days of the trial. Coras et al (https://doi.org/10.1186/s13075-021-02575-y) compared 20 psoriasis and 19 psoriatic arthritis patients and found that those with higher PASI score (>2.5) had significantly lower serum concentrations of pro-inflammatory ocylipins, most of them arachidonic acid derived. Joint disease activity was not associated with the concentration of ocylipins. In a systematic review, Roche et al (doi: 10.1186/s13075-021-02549-0) the incidence of uveitis was lower with anti-TNF agents compared to placebo (OR 0.5; 95% CI 0.2 to 0.9) and anti-IL17 (OR 0.3; 95% CI 0.1 to 0.9) in axial spondyloarthritis.
de Jong et al (doi: 10.1002/acr.24743) investigated in a 5-year prospective cohort of seemingly healthy first-degree relatives (FDRs) of HLA-B27-positive axial spondyloarthritis (axSpA) the presence of specific imaging figures and the progression to clinical axSpA. At baseline, 19% reported inflammatory back pain, 32% arthralgia, 3% arthritis, 5% enthesitis and 1% dactylitis. On magnetic resonance imaging (MRI), 10% had a Spondyloarthritis Research Consortium of Canada (SPARCC) score ≥ 2 and 1% fulfilled the modified New-York criteria for radiographic sacroiliitis. After 1 year of follow-up, 6% of the FDRs were clinically diagnosed with axSpA, of whom 86% were HLA-B27 positive. Correll et al (doi: 10.1002/acr.24727) described high-dose biologic use in a registry study including 5352 patients with juvenile idiopathic arthritis (JIA). 1080 patients have ever received a high-dose biologic. After regression, no significant differences in outcomes were observed between patients increasing the biologic dose compared to patients switching biologics at 6 months. Serious adverse events were numerically higher in the high-dose biologic and the biologic switch group compared to the no change group, but without statistical significance (Incidence rate ratio = 2.5, 95% CI: 0.7 to 8.5 and 1.8, 95% CI: 0.7 to 4.6, respectively). Case et al (doi: 10.1002/acr.24758) investigated the post-traumatic stress disorder (PTSD) and systemic lupus erythematosus (SLE) risk in a retrospective study with 10,942 incident SLE cases matched by age, sex and race to 109,420 controls enrolled in the Medicaid healthcare database from 2007 to 2010. Prevalence of PTSD was higher in SLE cases (10.74 per 1000, 95% CI 9.37 to 12.31) than in controls (7.83 (95% CI 7.42 to 8.27)). The multivariate adjusted OR for SLE among those with PTSD was 2.00 (95% CI 1.64 to 2.46). Jin et al (doi: 10.1002/acr.24630) compared in a database cohort study the risk of serious infections in patients with psoriasis or psoriatic arthritis (PsA) initiating ustekinumab or other biologics/apremilast. 123,383 patients were included, and 1514 serious infections occurred. After propensity score stratification, the incidence rates of serious infections among patients on ustekinumab ranged from 0.59 to 0.95 per 100-person-years. Compared to ustekinumab, other biologics and apremilast were associated with 1.4 to 3-times higher risk of serious infections. Kouki et al (doi: 10.1002/acr.24642) investigated the characteristics of metacarpophalangeal (MCP) osteoarthritis (OA) in a cohort of 425 patients with hand OA. MCP OA was present in 138 patients (32.5%) and was more frequent on the dominant hand and in the 1st and 2nd MCP joints. After multivariate analysis, MCP OA was associated with older age (OR = 1.05, 95% CI 1.01 to 1.10 for each year), manual occupation (OR = 3.74, 95% CI 1.21 to 11.54) and scaphotrapezial OA (OR = 2.18, 95% CI 1.27 to 3.72)). MCP OA was not associated with metabolic syndrome or hand OA symptoms.
Damian et al (doi: 10.1016/j.semarthrit.2021.04.008) investigated the incidence and risk factors for venous thromboembolic events in patients with psoriasis and psoriatic arthritis. 2,433 patients with psoriatic disease were included in this multicentre cohort study, with 26 incident venous thromboembolic events (VTE), yielding an incidence rate for VTE of 12 per 10,000 patient-years in patients with psoriatic disease. Older age (HR: 1.05, 95 % CI: 1.02 to 1.08), diabetes (HR: 5.06, 95 % CI: 2.16 to 11.82) and corticosteroid use (HR:11.55, 95% CI: 4.76 to 28.06) were independent risk factors for VTE. Leclair et al (doi: 10.1016/j.semarthrit.2021.07.016) analyzed a cohort of adult patients with idiopathic inflammatory myopathies (IIM) (n = 673) and matched it with general population comparators (n = 3343) to estimate the annual direct and indirect costs associated to IIM. The mean annual costs in IIM were 3 to 5 times higher than in the general population in the 5-year period following diagnosis. These costs started to increase long before diagnosis and were at their peak in the year post-diagnosis. An annual IIM cost of a mean (SD) €21,639 (22,733) in IIM compared to €4,816 (10,701) in the general population was reported. Over the 10-year follow-up period of the study, the indirect costs represented 40 to 60% of the disease-related costs. Wu et al (doi: 10.1016/j.semarthrit.2021.03.015) conducted a meta-analysis and a Mendelian randomization study to investigate the association and causality between rheumatoid arthritis and lung cancer risk. 11 cohort studies involving a total of 183888 patients were included, showing an increased risk of lung cancer among RA patients (RR = 1.44, 95%CI 1.31 to 1.57). Male patients presented a higher lung cancer risk compared to female patients (pooled RR: 1.98 vs 1.33, respectively). Mendelian randomization analysis demonstrated that genetically predisposed RA was not causally associated with the risk of lung cancer. Juge et al (doi: 10.1016/j.semarthrit.2021.07.002) explored the influence of the major risk factor for idiopathic pulmonary fibrosis (IPF) MUC5B rs35705950 on survival and progression in RA-associated interstitial lung disease (RA-ILD), including 10-year follow-up data of 261 patients with RA-ILD. The MUC5B rs35705950 variant did not impact transplant-free survival (HR for the T risk allele carriers=1.26; 95%CI 0.61 to 2.62), neither did it influence the decline in pulmonary function at 2 years in patients with RA-ILD (OR=0.95; 95%CI 0.44 to 2.05), irrespective of the high-resolution computed tomography pattern. Cho et al (doi: 10.1016/j.semarthrit.2021.07.013) analyzed the predictive value of disease characteristics of granulomatosis with polyangiitis (GPA) for subsequent relapses, including ANCA status and type, presence of microscopic hematuria, or serum creatinine level. In multivariate analysis, MPO-ANCA positivity at month 12 of follow-up (± 3) (HR 3.54, p=0.01) and the presence of microhematuria (HR 1.91, p=0.04) were predictors of relapses.
Watterdal-Syversen et al (doi: 10.1001/jama.2021.4172) analyzed whether therapeutic drug monitoring (TDM) during the initiation of infliximab therapy improves treatment efficacy compared with standard infliximab therapy without TDM in patients with chronic immune-mediated inflammatory diseases (IMIDs). 411 adults with different IMIDs were randomized to receive TDM with dose and interval adjustments based on scheduled monitoring of serum drug levels and antidrug antibodies or to a standard infliximab therapy without drug and antibody level monitoring. The proportion of patients who experienced disease remission after 30 weeks was 50.5% in the TDM group and 53.0% in the standard therapy group (adjusted difference 1.5%; 95% CI –2.2% to 11.1%). In a randomized single-center trial, Nguyen et al (doi: 10.1001/jama.2021.4172) included 400 patients with nonspecific subacute or chronic low back pain and compared osteopathic manipulative treatment (OMT) with sham OMT for reducing activity limitations at 3 months. Six sessions (1 every 2 weeks) of OMT were performed. At 3 months and 12 months the mean difference in Quebec Back Pain Disability Index (score range, 0 – 100) was -3.4, 95% CI: -6.0 to 0.7 and -4.3, 95% CI -7.6 to -1.0, respectively. Clinical relevance of this effect was questionable. No statistically significant differences were observed for other secondary outcomes (pain reduction, HAQ, number and duration of sick leaves, analgesics and NSAIDs consumption). McInnes et al (doi:10.1056/NEJMoa2202516) presented the results of the randomized, controlled trial assessing efficacy and safety of upadacitinib in psoriatic arthritis as compared with adalimumab. Patients were randomly assigned in a 1:1:1:1 ratio to receive oral upadacitinib at a dose of 15 mg or 30 mg once daily, placebo, or adalimumab. The primary endpoint, an ACR20 response at week 12, was achieved by 70.6% of patients with 15 mg upadacitinib, 78.5% with 30 mg upadacitinib, 36.2% with placebo (P<0.001 for both upadacitinib doses vs. placebo), and 65.0% with adalimumab. Both upadacitinib doses were noninferior to adalimumab for the ACR20 response at week 12, whereas the 30 mg dose was superior to adalimumab. van der Kooij et al (doi: 10.7326/M20-3419) evaluated safety and efficacy of immune checkpoint inhibitors (ICI) in patients with advanced melanoma with preexisting autoimmune disease (AID) (n = 415, 227 rheumatologic AIDs) as well as without (n = 4367). Response to ICI and overall incidence of any immune-related adverse events of grade 3 or higher were similar in patients with and without preexisting AID. However, patients with inflammatory bowel disease were more prone to colitis (19%, 95% CI 12% to 23% versus 2%, 95% CI 2% to 3%). There was no difference in survival between the groups.
In an observation study of 65 patients with systemic juvenile idiopathic arthritis (JIA) treated with tocilizumab, Nada et al (doi: 10.3389/fmed.2021.665028) identified 25% of the patients achieved minimal disease activity after 1 year, and 35% achieved clinically inactive disease. Patients of younger age (≤5 years; OR 2.1; 95% CI 1.5 to 27), with shorter disease duration (≤3 years; OR 6.5; 95% CI 1.3 to 34), lower disease activity (JADAS10 ≤10; OR 8.1; 95% CI 1.3 to 47), higher serum ferritin (>400; OR 4.4; 95% CI 1.2 to 20) and systemic manifestations (score >3; OR 5.4; 95% CI 1.4 to 25) showed more favourable disease outcomes. To identify whether it is feasible to develop a mapping algorithm using multiattribute measures of health status to predict presenteeism, Jones et al (doi: 10.1007/s11136-021-02936-9) surveyed 472 working individuals with a self-reported rheumatoid arthritis (RA). A strong negative correlation was found between presenteeism (measured using the Work productivity activity impairment [WPAI]) and two existing measures of health status: EQ5D-5 level (r = -0.64) and SF6D (r = -0.60). Using the Spanish biologics register BIOBADASER, Sánchez-Piedra et al (doi: 10.1038/s41598-021-94504-x) analysed 4543 patients with rheumatologic diseases (2193 RA, 1206 psoriatic arthritis (PsA), and 1144 ankylosing spondylitis (AS)) starting on biologic DMARDs between 2007 and 2020. Over time, median time from the diagnosis to the start of a first biologic declined from 5.5 (2007-2009) to 3.4 years (2018-2020; p<0.001). Disease activity (DAS28) at the initiation of biologic therapy also declined from 5.3 to 4.7 in RA patients (p<0.001), and from 4.9 to 4.2 in PsA patients (p<0.001). In the study by Kim et al (doi: 10.1177%2F1759720X211024830) on the healthcare utilization and medical costs invested in patients with seronegative and seropositive RA, the authors found that seropositive patients use significantly more methotrexate (73% versus 30%) and biologic agents (8% versus 3%) than seronegative patients. The number of RA-related outpatient visits (6 versus 4.4 times/year) and annual medical costs per patient ($1027 versus $450/year) were higher among seropositive patients. Using the BARFOT cohort, Nilsson et al (doi: 10.2147/OARRR.S306378) followed 2837 patients with early RA for eight years to assess contributions of age and sex to disease outcomes. For both sexes, disease activity, function and pain improved over time, significantly more in men than in women in all age groups. In men, those <40 years displayed significantly lower DAS28 compared to all other groups. Women ≥70 years showed less improvement in disability. Patients <40 years were more likely to receive biological DMARDs, while those ≥70 years more often received only glucocorticoid treatment.
COVID-19

April 2021 to August 2021

Féline Kroon

Féline is a rheumatologist-in-training at Zuyderland Medical Center in Heerlen (The Netherlands). She did her PhD on treatment and outcome measurement in hand osteoarthritis at the Leiden University Medical Center in Leiden. She is a member of the OMERACT Technical Advisory Group, and currently also fellow in a EULAR recommendations task force. Féline is a member of the Newsletter Sub-Committee and EMEUNET Country Liaison for The Netherlands.

Sparks et al. (doi:10.1136/annrheumdis-2021-220418) investigated COVID-19 severity in 2869 rheumatoid arthritis (RA) patients treated with biologic or targeted synthetic disease-modifying antirheumatic drug (b/tsDMARDs) from the Global Rheumatology Alliance COVID-19 database. Rituximab (OR 4.15, 95%CI 3.16 to 5.44) and Janus kinase inhibitors (JAKi) (OR 2.06, 95%CI 1.60 to 2.65) were associated with worse COVID-19 severity, while abatacept or interleukin-6 inhibitors (IL6i) were not. England et al. (doi:10.1002/art.41800) conducted a matched cohort study using the national Veterans Affairs database to compare the risk of COVID-19 and COVID-19 hospitalisation or death in RA versus non-RA patients (n=33,886 each; 84.5% male, mean age 67.8 years). They found a higher risk of COVID-19 (HR 1.25, 95%CI 1.13 to 1.39) and COVID-19 hospitalization or death (HR 1.35, 95%CI 1.10 to 1.66) in RA patients. Associated risk factors were DMARD or glucocorticoid use, Afro-American or Hispanic ethnicity and several underlying chronic conditions. Garrido-Cumberera et al. (doi:10.1136/rmdopen-2020-001546) aimed at assessing the impact of the COVID-19 pandemic on 1800 patients with 15 different rheumatic diseases (RMDs). Patients reported disruption in access to healthcare services (e.g., 58.4% had their rheumatology appointment cancelled), poorer lifestyle habits (e.g., 45.6% unable to continue exercising), and negative effects on physical and mental health (including elevated pain (75.6%), high self-reported disease activity (mean VAS pain 5.3±2.7), as well as 57.3% and 45.9% at risk of anxiety or depression, respectively. Furer et al. (doi:10.1136/annrheumdis-2021-220647) studied efficacy, safety and disease activity in 686 patients with inflammatory RMDs and 121 healthy controls six weeks after two-dose SARS-CoV-2-mRNA vaccination regimen. They reported lower seropositivity rates (86% vs 100%, p<0.0001) and S1/S2 IgG levels (132.9±91.7 vs 218.6±82.06 BAU/mL, p<0.0001) in patients versus controls. Particularly rituximab, as well as older age, glucocorticoids, mycophenolate and abatacept were important risk factors of poorer response. Postvaccination disease activity generally remained stable. Connolly et al. (doi:10.1002/art.41924) studied risk of disease flare one month after two-dose SARS-CoV-2-mRNA vaccination regimen in 1377 RMD patients, of whom 11% reported flare requiring treatment and none reported severe flares. Risk factors were previous SARS-CoV-2 infection (incident rate ratio (IRR) 2.09, p=0.02), flare in six months preceding vaccination (IRR 1.95, p<0.001), and immunomodulatory therapy (IRR 1.95, p<0.001). Boekel et al. (doi:10.1016/S2665-9913(21)00222-8) addressed the effect of immunosuppressive drugs on antibody development following SARS-CoV-2 vaccination in 632 older patients with RMDs compared to 289 healthy controls (mean age 63±11). They report lower seroconversion after first vaccination among patients without previous SARS-CoV-2 infection versus controls (49% vs 73%, OR 0.33, 95%CI 0.23-0.48), associated with methotrexate or anti-CD20 use. After second vaccination, seroconversion exceeded 80%, except in those treated with anti-CD20 (43%).
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

The EULAR viewpoint “EULAR COVID-19 registry: lessons learnt and future considerations” was published in the Annals of Rheumatic Diseases. The authors discuss what can be learnt from the ongoing pandemic in the context of rheumatology and what can be improved to be prepared to care for the patients under similar circumstances in the future.
UPCOMING EDUCATIONAL EVENTS

NOVEMBER 2021

ACR Convergence 2021
- When and Where: 05 – 09 Nov 2021, Virtual Event
- Website: https://www.rheumatology.org/Annual-Meeting

The Royal Society of Medicine: Vasculitis: From cell to service
- When and Where: 17 – 18 Nov 2021, Virtual Event
- Website: https://www.rsm.ac.uk/events/nephrology/2021-22/neq51/

VIB Translational Immunology Meeting
- When and Where: 22 – 23 Nov 2021, Ghent, Belgium
- Website: https://www.vibconferences.be/events/translational-immunology

7th Qatar Musculoskeletal Ultrasound Course - Level: Basic and Intermediate
- When and Where: 25 – 27 Nov 2021, Hybrid Event (Doha, Qatar + Online)
- Website: https://www.hamad.qa/EN/All-Events/7Qmusc/Pages/default.aspx

British Society for Immunology Annual Congress
- When and Where: 28 Nov – 1 Dec 2021, Hybrid Event (Edinburgh, UK + Online)
- Website: https://www.bsicongress.com

DECEMBER 2021

PRINTO Egypt Pediatric and Adolescent Rheumatology Conference
- When and Where: 01 – 03 Dec 2021, Cairo, Egypt
- Website: http://www.printoegypt.org/index.html

Central European Congress of Rheumatology
- When and Where: 02 – 04 Dec 2021, Bratislava, Slovakia
- Website: http://cecr2020.sk/

7th International Musculoskeletal UltraSound Course
- When and Where: 09 – 11 Dec 2021, Athens, Greece
- Website: https://event.concopco.com/cms/mitoscourse2021
EULAR has developed e-learning opportunities with the newest updates in the field of rheumatology. 99 modules are available, covering different areas of rheumatology.

- **Fee**: 25 EUR for each module
- **Start**: no deadline / any time
- **Available for**: 1 year after booking

10th EULAR Online Introductory Ultrasound Course
The course, covering 7 modules, is designed for approx. 7 months of training, the expected learning time per week is around 2 1/2 hours. Upon passing the examination, a EULAR certificate will be issued.

- **Fee**: 150 EUR
- **Start**: 14.10.2021; **Registration deadline**: 30.11.2021
- **Available for**: 1 year + 1 year extension

10th EULAR Online Course on Systemic Sclerosis
The Course consists of 10 modules dealing with physiopathology, clinical aspects and management of SS. All modules are developed by EUSTAR.

- **Fee**: 150 EUR
- **Start**: 14.10.2021; **Registration deadline**: 30.11.2021
- **Available for**: 1 year + 1 year extension

16th EULAR Online Course on Rheumatic Diseases
The course is managed by a scientific course committee controlling the structure and content of the course and performing regular quality control and advancement. The full version covers the entire field of rheumatology and consists of 55 illustrated modules (of which some are optional), each one covering a specific topic. Each module corresponds to approximately 5 - 8 hours of study for the student, totalling around 275 - 440 hours of educational training. Knowledge and skills are targeted to suit a level of knowledge appropriate for the final years of training as a rheumatologist. It will finish with an online examination and upon passing, with a EULAR Certificate.

- **Fee**: 150 EUR
- **Start**: 14.10.2021; **Registration deadline**: 30.11.2021
- **Available for**: 2 years + 1 year extension
EULAR ONLINE COURSES AND MODULES

13th EULAR Online Course on Connective Tissue Diseases
The Course consists of 16 modules which deal with immunology and systemic auto-immune diseases, such as SLE, scleroderma, and vasculitis.
- **Fee:** 150 EUR
- **Start:** 14.10.2021; **Registration deadline:** 30.11.2021
- **Available for:** 1 year + 1 year extension

1st EULAR Online Course on Patient Education for Physicians and Health Professionals
The Course consists of 4 modules (approx. 6 hours each). The learning objectives are: understand the problematics of chronic rheumatic diseases, understand issues of patient education, develop attitudes in the relationship with the patient, elaborate a program of patient education, perform an educational diagnosis, design and animate educational workshops evaluate a program and among different learning objectives. Upon passing the examination a EULAR certificate will be issued.
- **Fee:** 150 EUR
- **Start:** 14.10.2021; **Registration deadline:** 30.11.2021
- **Available for:** 1 year + 1 year extension

3rd EULAR Online Course for Systemic Lupus Erythematosus
The Course consists of 12 modules covering the recent updates in diagnosing and managing SLE, as well as the recent updates to management guidelines.
- **Fee:** 150 EUR
- **Start:** 14.10.2021; **Registration deadline:** 30.11.2021
- **Available for:** 1 year + 1 year extension

4th EULAR Online Course on Imaging in RMDs
The Course covers 3 modules. The learner level is aimed primarily at Section Residents and Fellows in Training as well as Rheumatologists. It aims to educate rheumatologists and future rheumatologists on how to interpret imaging examinations in chronic inflammatory RMDs and to use the imaging results to guide their daily treatment.
- **Fee:** 150 EUR
- **Start:** 14.10.2021; **Registration deadline:** 30.11.2021
- **Available for:** 1 year + 1 year extension
7th EULAR Online Course for Health Professionals in Rheumatology

The course consists of a total of 8 modules. Care is given to integrate the multidisciplinary perspective of the treatment of rheumatic diseases.

- **Fee:** 150 EUR
- **Start:** 14.10.2021; **Registration deadline:** 30.11.2021
- **Available for:** 1 year + 1 year extension

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8th EULAR/PRES Online Course in Paediatric Rheumatology

The 11-module course represents a joint effort of EULAR and the Paediatric Rheumatology European Society (PRES), offering a deep insight of all the aspects related to rheumatic diseases in children and adolescents including their impact on the growing body and the differential diagnosis with other paediatric disorders.

- **Fee:** 150 EUR
- **Start:** 14.10.2021; **Registration deadline:** 30.11.2021
- **Available for:** 1 year + 1 year extension
By 2023, EULAR will be the leading provider of education in rheumatic and musculoskeletal diseases (RMDs).

**EULAR School of Rheumatology**

- **EULAR Online courses:**
  - RMD: EULAR Course on Rheumatic Diseases
  - US: EULAR Online Introductory Ultrasound Course
  - IMG: EULAR Online Course on Imaging in RMDs
  - PAED: EULAR / PRES Online Course in Paediatric Rheumatology
  - HPR: EULAR Online Course for Health Professionals in Rheumatology
  - SSc: EULAR Online Course on Systemic Sclerosis

- **The EULAR Educational Cooperation with National Societies (EULAR ECONS)**

- **5th EULAR Immunology Course** 18.03 – 19.03.2022
The EULAR Research Center

How does it work?

1. Select your support area and describe your needs in a short online form
2. Get matched with an experienced scientist
3. Obtain up to 10 hours of free consultation
4. Share your feedback upon service completion

Support Areas

- Basic/Translational Research (using patient/human materials, e.g. cells, serum...or Dedicated animal models of RMDs to address bedside-to-bench research questions)
- Clinical Research
- Epidemiology and Public Health
- Health Services Research
- Implementation Science

The EULAR Research Consultation Service is offered through the EULAR Research Centre. The service is available for researchers based in EULAR-affiliated countries.
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 database includes a detailed description of each instrument, including the instrument itself (and validated language versions, if available), useful references, a description of the population(s)/setting(s) where it has been validated, recommendations and rules for use, guideline for interpretation of the results in clinical practice or in research, information on the most relevant psychometric properties of each instrument. Instruments are categorized by disease or by topic.

Also, guidelines for interpretation of results in both practice and research settings are provided. 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/
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!

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

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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.

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