Dear Reader,

We are happy to present the 15th issue of the EMEUNET-EULAR ‘Press Review’ newsletter. 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 August 2021 and November 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.

Unfortunately, for this edition both Twitter Journal Club and EMEUNET’s Choice Paper voting are missing. Both initiatives will be back in the next issue. Meanwhile, you can access the previous editions in our Twitter Journal Club (@EULAR_JC) account and on our YouTube channel.

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, Diego Benavent, Maria Sokolova, Anastasia Madenidou, Giacomo Cafaro, David Simon and Tsvetoslav Georgiev on behalf of the EMEUNET and EULAR EMEUNET Journal Club team
In the study by Kong et al (doi: 10.1136/annrheumdis-2021-220832), the authors investigated efficacy and safety of tofacitinib (TOF) in Takayasu arteritis in a prospective cohort of 53 patients with active disease. One group received TOF and the other methotrexate (MTX), in both groups, patients received glucocorticoids. TOF was superior to methotrexate in inducing complete remission and reducing inflammatory markers after 6 (complete remission in 85.19% versus 61.54%) and 12 months of treatment (88.46% vs 56.52%). Patients on TOF were able to taper glucocorticoids somewhat faster. There were more treatment-naive patients in the MTX group than in TOF group, otherwise the groups were similar in clinical and demographic characteristics. No differences in imaging progression was observed between the groups, though the authors do not specify which modalities were used. No new safety concerns were issued. Platzer et al (doi: 10.1136/annrheumdis-2021-220331) investigated trajectories of radiographic progression in rheumatoid arthritis (RA). In total, 1887 patients with 7738 X-rays were included in cluster analysis. Four distinct clusters were identified: with stable radiographic score over 2 years (86%), with relentless progression (5.8%), with decreasing score (6.9%); and one with going up and down (1.4%). In the multivariable decision tree model with information available at the baseline, radiographic SHS score and CRP were leading factors for clustering (the biggest cluster of non-progressors was randomly down sampled to the second largest cluster). This study emphasize that most patients stay in stable radiographic state with the use of modern treatment options and confirms the baseline radiographic damage and inflammation to be the risk factors for progressive disease, though also a big proportion of patients with high inflammation show no progression. Therefore, the authors emphasize the necessity of the new biomarkers that would explain these discrepancies. Nasonov et al (doi: 10.1136/annrheumdis-2021-219876) published the results of the CREDO1, a phase III study of olokizumab (OKZ), a monoclonal antibody against interleukin (IL)-6, in combination with MTX for the treatment of active biologic-naïve (other than TNF-inhibitor discontinuation for the reasons other than inefficacy) RA. In the multicenter 24-week double-blinded placebo-controlled study, 428 patients were randomized 1:1:1 to receive OKZ 64 mg subcutaneously once every 2 weeks, or 64 mg every 4 weeks, or placebo plus MTX. OKZ was superior to placebo with methotrexate with ACR20 response rates of 63.6% and 70.4% with 2- and 4-weeks regimens, respectively. All secondary endpoints were met: of DAS28-CRP <3.2 and significant improvements in physical function assessed with HAQ-DI at week 12; ACR50 response and percentage of subjects with CDAI ≤2.8 (remission) at week 24. Antidrug antibodies without neutralizing activity were registered in 4.4% subjects. Adverse events were more frequent with OKZ, the main ones being infections.
Heckert et al (doi: 10.1136/annrheumdis-2021-220882) showed that arthritis in rheumatoid arthritis (RA) patients tends to recur at the same sites during the disease course. 508 patients with newly diagnosed RA from the BeSt study with a follow up of 6-10 years and 24-40 study visits were included. In 46% of the joints swollen at baseline, inflammation reoccurred at least once during the follow-up. Arthritis at baseline was associated with its reoccurrence at the same site with the odds ratio (OR) of 2.37 (95% CI 2.3-2.43). This study is the first one to investigate whether the inflammation occurs consequentially at the same sites and indicates the need for the understanding of the underlying pathogenic events. In the study by Achilleas et al (doi: 10.1136/annrheumdis-2021-220458) the authors describe polyfunctional T cell subsets in the synovial tissue of RA at-risk individuals (n=20) and RA patients (n=118). Synovial-tissue RNA sequencing analysis revealed enrichment in T-cell activation and differentiation pathways that pre-date the onset of RA. Cluster analysis revealed the accumulation of highly polyfunctional CD4+ CD8dim T-cells in the synovial tissue of individuals at-risk and RA patients, but not of healthy controls. Therefore, the authors suggest that there is a “switch” from the protective T cells to pathogenic polyfunctional T cells taking place during the course of RA development. Furie et al (doi: 10.1136/annrheumdis-2021-220920) published the results of the randomized, double-blinded, placebo-controlled trial NOBILITY of B-cell depleting type II anti-CD20 agent obinutuzumab (that has a distinct mode of binding to CD20) in combination with standard treatment modalities for the treatment of proliferative lupus nephritis. 125 patients with lupus nephritis receiving mycophenolate and corticosteroids were randomized to obinutuzumab 1000 mg or placebo and followed through week 104. Achievement of complete renal response was greater with obinutuzumab at week 104 (41% vs 23%; p=0.026) and improvement of renal response parameters was observed. The drug was well tolerated with no new safety concerns. Meer et al (doi: 10.1136/annrheumdis-2021-220761) investigated whether the use of biological agents in patients with psoriasis can prevent the development of psoriatic arthritis (PsA). They investigated 193,709 patients with psoriasis without PsA. Of those, 14,569 were receiving biologic agents and 20,321 were on cumulative oral or phototherapy. The cumulative incidence of PsA was 9.75 per 1000 person-years and 77.26 among those receiving biologic agents; 61.99 among oral therapy users, 26.11 among phototherapy users and 5.85 among those without prescription. Adjusted hazard ratio (HR) for biologic users was 4.48 with respect to other treatments or no treatment. Hence, on the contrary to the hypothesis, the use of biologics was associated with increased risk of PsA. However, this might be biased through confounding factors, such as indication and propathic bias.
Giaglis et al (doi: 10.1136/rmdopen-2021-002010) investigated whether the mitochondrial (mt) DNA is useful in the diagnosis and monitoring of systemic lupus erythematosus (SLE). MtDNA and chromosomal nuclear (n) DNA was quantified by PCR in the plasma of 103 consecutive patients with SLE and 56 healthy controls. A cut-off set at 1.8×10^7 mtDNA copies identified patients with SLE with 87.4% sensitivity and 94.6% specificity; the AUC was 0.95 (p<0.0001). MtDNA levels correlated with Systemic Lupus Erythematosus Disease Activity Index (SLEDAI) on multivariable analysis (p=0.004). In 33 SLE patients with follow-up data, the changes of mtDNA, but not those of nDNA concentrations, correlated with the changes of the SLEDAI (r=0.55, p=0.001). Lauper et al (doi: https://doi.org/10.1136/rmdopen-2021-001818) evaluated the analysis and reporting of observational studies in rheumatology. The authors performed a systematic literature review searching for articles comparing drug effectiveness in observational studies, published from 2008 till 2019 (n= 211 articles). Ten percent of studies did not adjust for confounding factors, 9% did not explain how they chose covariates for adjustment, 21% used bivariate screening and/or 18% used stepwise selection procedures. Only 33% studies reported the number of patients lost to follow-up and 25% acknowledged attrition (drop-out or treatment cessation). Most studies did not report the number of missing data on covariates (83%), and when addressed, 49% used complete case (CC) and 11% last observation carried forward (LOCF). Date of publication did not influence the results. Law-Wan et al (doi: 10.1136/rmdopen-2021-001882) aimed to identify predictors of response to TNF inhibitors (TNFi) in rheumatoid arthritis. Individual patient data of 11,617 patients from 29 randomised controlled trials (RCTs) evaluating the efficacy of a TNFi versus placebo or conventional therapy were analysed. High mass index increased the odds of EULAR non-response in 6 months (OR 0.52 vs 0.36 for non-obese, p=0.01). A multivariable regression analysis of 7,457 patients showed that patients treated by TNFi had a final DAS28(CRP) decreased by 0.02 for each year of disease duration (p<0.001), and a 0.21 decrease for patients with a baseline DAS28(CRP)>5.1 (p<0.001). McInnes et al (doi: 10.1136/rmdopen-2021-001838) reported the 56-week efficacy and safety of upadacitinib in patients from the SELECT-PsA 1 study. Patients with psoriatic arthritis (PsA) received upadacitinib 15 mg or 30 mg once daily, adalimumab 40 mg every other week for 56 weeks or placebo through week 24 switched thereafter to upadacitinib 15 mg or 30 mg until week 56. ACR20/50/70, PASI75/90/100 and inhibition of radiographic progression were maintained with upadacitinib through week 56 and were numerically higher than with adalimumab. Efficacy results in patients who switched from placebo to upadacitinib were comparable to those observed in patients originally randomised to upadacitinib.
McInnes et al (doi: 10.1002/art.42010) investigated in the DISCOVER-3 trial the long-term efficacy (over 100 weeks) and safety of guselkumab in patients with active psoriatic arthritis (PsA) (≥5 swollen and ≥5 tender joints; CRP ≥ 0.6 mg/dL). Of 739 randomized and treated patients, 652 (88%) completed treatment. In all groups of patients treated with guselkumab, ACR20 (68%-76%), ACR50 (48%-56%), ACR70 (30%-36%) response rates and regression rates of enthesitis (62%-70%) and dactylitis (72%-83%) had durable improvement in arthritis signs/symptoms and extra-articular manifestations. 8% (5.8/100 patient-years) and 3% (1.9/100 patient-years) of 731 guselkumab-treated patients had a serious adverse event or serious infection, respectively; one death occurred. Saag et al (doi: 10.1002/art.41981) assessed in a randomized, double-blind, placebo-controlled phase 2 study changes in bone turnover and bone mineral density in 82 rheumatoid arthritis (RA) patients on glucocorticoid after discontinuing denosumab for 12 months. After denosumab discontinuation, CTX returned to baseline and was not significantly different from placebo after discontinuation. The median percentage changes in P1NP from baseline for denosumab 60 mg at 6 and 12 months after discontinuation were -0.16%/15.3%, respectively (P = 0.062 and 0.017 versus placebo); the corresponding changes for denosumab 180 mg were 9.0%/75.8% (P = 0.018 and 0.002). Compared to placebo, lumbar spine and total hip bone mineral density increased in subjects receiving denosumab and returned to baseline after 12 months. Perez et al (doi: 10.1002/art.41961) assessed in premenopausal women with long-standing RA the relationship between parameters of systemic and localized bone involvement using high-resolution peripheral quantitative computed tomography at the distal radius (DR) and tibia (DT). Bone erosions were found in 75% of patients, and were associated with a lower cortical volumetric bone mineral density (DR: 980±72 versus 1021±47 mgHA/cm³, p = 0.03; DT: 979±47 versus 1003±34 mgHA/cm³, p = 0.04) and higher cortical porosity (DR: 2.8±2.5 versus 1.8±1.6%, p = 0.04; DT: 3.7±1.6 versus 2.7±1.6%, p = 0.01). Zhao et al (doi: 10.1002/art.41958) investigated the generation of HLA-DR+CD90+ synovial fibroblasts and their function by using human materials in RA patients and bioinformatic analyses of mass cytometry and transcriptomics patient datasets. Enriched and activated FcyRIIIA(CD16)+ NK cells in synovia from active RA were found, while CD16 recognized immune complexes in synovial fluid, potentially contributing to NK cell activation. JAK inhibition prevented HLA-DR induction and blocked pro-inflammatory signals to T cells. Rosenthal et al (doi: 10.1002/art.41946) investigated the effect of biological treatments for psoriasis on the incidence of PsA in a cohort of 1326 cases. Multivariable Cox regression showed that the control group had a significantly higher risk for PsA compared to the biological treatment group (adjusted HR=1.39; 95%CI: 1.03-1.87).
assessed the rate of atherosclerosis progression over a 3-year period between 74 patients with Antiphospholipid syndrome (APS), 58 with diabetes mellitus (DM) and 73 healthy controls (HC). APS patients exhibited a 3.3-fold higher risk of new atherosclerotic plaque formation compared with HC (p=0.031), similar to that in DM (odds ratio [OR]=3.45, p=0.028). In APS patients, the risk of plaque development was independently associated with the presence of traditional cardiovascular risk factors (OR = 2.31, p=0.008). Lorenzin et al (doi: 10.1093/rheumatology/keab728)
evaluated the influence of psoriasis on spinal/pelvic radiographic progression and MRI features in early-stage axial spondyloarthritis (axSpA) in the Italian SPACE cohort. 88 patients had axSpA (84.1% non-radiographic; 15.9% radiographic); 36.4% had psoriasis. The latter patient group was older; was less HLA-B27 positive. Psoriasis was a predictor of increased spinal progression (odds ratio = 0.18; 95% CI: 0.04, 0.78). Verstappen et al (doi: 10.1093/rheumatology/keab880)
assessed the analgesia prescribing in English National Health Service-managed patients with inflammatory arthritis. Opioid prescribing in cases fell between 2000–2015 but remained common with 45.4% (95% confidence interval [CI] 42.4%, 48.4%) and 32.9% (95% CI 29.8%, 36.0%) receiving at least 1 and ≥3 opioid prescriptions, respectively in 2015. NSAID prescription prevalence fell from 53.7% (95% CI 49.6%, 57.8%) in 2000, to 25.0% (95% CI 22.4%, 27.7%) in 2015. Across years, analgesia prescribing was commoner in RA than PsA/axial SpA, and 1.7–2.0 times higher in cases than controls. Zhang et al (doi: 10.1093/rheumatology/keab610)
investigated the phenotype, function and clinical significance of ILCs in 67 IgG4-related disease (IgG4-RD) patients and 44 age- and sex-matched healthy controls. Frequency of circulating pan ILCs in IgG4-RD patients was lower than in HCs. ILC2s were higher in IgG4-RD compared with HCs, whereas ILC1s were lower in IgG4-RD. Circulating ILC2s correlated positively with Treg cells and the surface expression of CD154, PD-1 and CXCR5 in ILC2s correlated positively with CD19+ B cells, serum IgG4 levels and serum IgE, respectively.
Alexander Jr et al (doi: 10.1186/s13075-021-02610-y) investigated the use of matrix metalloproteinase-generated neoeptite of CRP (CRPM) as a biomarker of inflammation and radiographic severity in patients with knee osteoarthritis (OA). Participants with symptomatic osteoarthritis (n=25) of at least one knee underwent knee radiographic imaging and radionuclide etarfolatide imaging to quantify inflammation of the knees and other appendicular joints. CRPM was associated with synovitis of the knee (p=0.017), synovitis of multiple joints (p=0.008), MMP-generated neoeptite of type III collagen in serum (p<0.0001), and macrophage marker CD163 in serum (p=0.009) and synovial fluid (p=0.03). Ikawa et al (doi: 10.1186/s13075-021-02667-9) investigated the potential role of CCL20/CCR6 in systemic sclerosis (SSc) vasculopathy and the contribution of Friend leukemia virus integration 1 (FLI1) deficiency to this process. CCL20 expression was significantly elevated in dermal fibroblasts of patients with early diffuse cutaneous SSc, while CCR6 was significantly up-regulated in dermal small vessels of SSc patients. In human dermal microvascular endothelial cells, FLI1 small interfering (si) RNA induced the expression of CCR6, but not CCL20. Vascular permeability was attenuated by CCR6 siRNA treatment, and CCR6 siRNA suppressed the angiogenic activity of human dermal microvascular endothelial cells assayed by in vitro tube formation. Faustini et al (doi: 10.1186/s13075-021-02589-6) aimed to identify the risk factors for Anti-drug antibodies (ADAs) in systemic lupus erythematosus (SLE) and ANCA-associated vasculitis (AAV). After first rituximab cycle, no AAV patients were ADA-positive compared to 37.8% of the SLE patients. ADA-positive SLE individuals were younger (34.0 (25.9–40.8) vs 44.3 (32.7–56.3) years, p = 0.002) and with more active disease (SLEDAI-2 K 14.0 (10.0–18.5) vs. 8.0 (6.0–14), p = 0.0017) and shorter disease duration (4.14 (1.18–10.08) vs 9.19 (5.71–16.93), p = 0.0097) compared to ADA-negative SLE. ADAs primarily occurred in nephritis patients, were associated with anti-dsDNA positivity, but were not influenced by concomitant use of corticosteroids, cyclophosphamide or previous treatments. Lechtenboehmer et al (doi: 10.1186/s13075-021-02654-0) assessed the association between conventional synthetic (cs) and biological (b) disease-modifying antirheumatic drugs (DMARDs) and radiographic distal interphalangeal-(DIP) OA in patients with rheumatoid arthritis (RA) (n= 2234). Cox analyses demonstrated that bDMARD monotherapy had an increased risk of radiographic DIP OA progression compared to csDMARD treatment (adjusted HR 1.34 [95% CI 1.07–1.69]). The risk was not significant in csDMARD/bDMARD combination therapy (HR 1.12 [95% CI 0.96–1.31]), absent in past DMARD use (HR 0.96 [95% CI 0.66–1.41]), and significantly lower among never DMARD users (HR 0.54 [95% CI 0.33–0.90]). In 894 patients without initial DIP OA, the risk of developing OA did not differ between the treatment groups (0.89 [95% CI 0.56–1.43]).

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Perrucio et al (doi: 10.1002/acr.24826) analyzed a profile of cardiovascular disease (CVD) risk factors by sex in 6098 individuals with and without osteoarthritis (OA). Nearly a third of the 3049 OA respondents were in the highest risk category versus one-fifth of non-OA. Compared to non-OA, OA was associated with worse CVD risk quartiles with increasing risk thresholds among females with multisite OA but not males. Messier et al (doi: 10.1002/acr.24765) analyzed whether long-term 1.5-year diet (D) and exercise (E), alone or in combination (D+E), have sustainable effects for older adults with knee OA 3.5-years after the interventions end. A secondary analysis of patients (n = 94) who completed the IDEA trial (1.5 year) showed that weight regain in D+E and D was 5.9 kg (7%) and 3.1 kg (4%), respectively, with a 1 kg (1%) weight loss in E. Compared to baseline, weight and knee pain were significantly lower in each group at 5-year follow-up. Cheah et al (doi: 10.1002/acr.24767) identified specific clinical features associated with slow colonic transit (SCT) in 48 out of 100 patients with systemic sclerosis (SSc). SSc patients with gastrointestinal symptoms were prospectively enrolled and completed a scintigraphy-based whole gut transit study. SCT was positively associated with female sex (OR 12.61, 95% CI 1.56-101.90), telangiectasia (OR 4.00, 95% CI 1.32-12.10), anti-centromere antibodies (OR 3.25, 95% CI 1.25-8.44), smoking (OR 2.56, 95% CI 1.06-6.21), and a Medsger severity score of ≥3 (OR 3.94, 95% CI 1.16-15.36) and negatively with restriction on pulmonary function tests (OR 0.23, 95% CI 0.09-0.63). Mikuls et al (doi: 10.1002/acr.24769) quantified vehicle control as a metric of automobile driving performance in patients with rheumatoid arthritis (RA). Typical driving habits were linked to RA disease status, disease activity, and functional status in RA drivers (n=33), across 1,292 driving hours, and controls (n=23). Evidence of significant statistical interaction between disease status and road type (p<0.001) was found. On residential roads, RA patients showed lower braking/accelerating variability than controls, while increased steering variability was associated with moderate/high disease activity on highways/interstate roads (p=0.04). The alterations were more pronounced in drivers with a higher disease activity. Chernis et al (doi: 10.1002/acr.24812) studied clinical, demographic, and socioeconomic factors that predict modified health assessment questionnaire (mHAQ) scores over time in 388 SSc patients from an early disease cohort with mean disease duration of 2.5 and mean follow-up time of 3.9 years. Lower income and education status, older age, and more severe skin disease were predictors of higher longitudinal mHAQ, which on the other hand predicted higher mortality (HR 1.29, 95% CI 1.09-1.52).
Garvey et al (doi:10.1016/j.semarthrit.2021.09.006) analyzed trends in the incidence and use of diagnostic modalities for giant cell arteritis (GCA) in a population-based cohort over the past seven decades and explored survival trends. Three time frames (1950–1979, 1980–1999, and 2000–2019) were compared and standardized mortality ratios (95% CI) were 1.03 (0.79, 1.32), 1.11 (0.91, 1.34), and 0.82 (0.64, 1.04), respectively. The proportion of patients diagnosed using temporal artery biopsy decreased over time (89%, 86%, and 72%) while the patients with a clinical diagnosis of GCA increased (11%, 14%, and 17%).

Jeon et al (doi: 10.1016/j.semarthrit.2021.07.004) compared the risk of serious infections (SIs) between tocilizumab (TCZ) and tumor necrosis factor inhibitor (TNFi) treatment in Korean patients with rheumatoid arthritis (RA). A total of 8794 patients were included who initiated TNFi or TCZ treatment between January 2013 and June 2018. No increased risk of SIs was reported in TCZ group versus TNFi (HR, 1.00; 95%CI, 0.90–1.11). However, TCZ was associated with a higher risk of skin and subcutaneous tissue infections (HR, 1.26; 95%CI, 1.02–1.54) but a lower risk of urological and gynecological infections (HR, 0.65; 95%CI, 0.49–0.87) compared to TNFi.

Alibaz-Oner et al (doi: 10.1016/j.semarthrit.2021.09.010) compared the treatment outcomes of TNFi (n = 88) and TCZ (n = 23) in patients with Takayasu arteritis refractory to conventional immunosuppression. Complete/partial remission rates between TCZ and TNFi were similar. Both groups were also similar in terms of glucocorticoids (GCs) dose decrease (<4 mg) or discontinuation (TNFi vs TCZ: 78% vs 59%, p = 0.125) and drug survival rate (56% vs 57%, p = 0.22). TNFi and TCZ did not differ in rate surgery need and mortality. Dormuth et al (doi: 10.1016/j.semarthrit.2021.08.002) evaluated the impact of concomitant use of conventional synthetic DMARDs (csDMARDs) on adherence, switching and dose of biologic DMARDs (bDMARDs) in RA patients. This population-based cohort study included 20,221 patients with RA starting bDMARDs. Concomitant treatment with csDMARDs was linked to a small increase in bDMARD dose compared to the mean dose over the first three months (mean change: 0.56%, 95%CI 0.14-0.97). It was however not associated with reduced discontinuation of bDMARD treatment (HR 0.9, 95%CI 0.79-1.02) or reduced switching of bDMARDs (HR 0.95, 95%CI 0.80-1.11).

Jung et al (doi: 10.1016/j.semarthrit.2021.07.015) examined the association between facet joint ankylosis and functional impairment in 126 patients with radiographic axial spondyloarthritis (r-AxSpA). Facet joint ankylosis score correlated positively with ASDAS, mSASSS and the syndesmophyte score. Facet joint ankylosis was significantly associated with decreased lumbar motion and BASFI in patients with r-AxSpA.
**Bowman et al (doi: 10.1016/S0140-6736(21)02251-0)** analyzed the safety and efficacy of different subcutaneous doses of ianalumab (VAY736) in patients with moderate to severe **primary Sjögren's syndrome (pSS)**. In this phase 2b dose-finding trial, 190 patients were randomly assigned to 4 groups (placebo n=49, ianalumab 5 mg n=47, 50 mg n=47, 300 mg n=47). The EULAR Sjögren's Syndrome Disease Activity Index (ESSDAI) score decreased from baseline in all ianalumab groups, with the maximal ESSDAI score change from baseline in the ianalumab 300 mg group: −1.92 points (95% CI, −4.15-0.32). **Izadi et al (doi: 10.1001/jamanetworkopen.2021.19400)** analyzed whether there are socioeconomic disparities in functional status among U.S. national cohort of 83,965 individuals with **rheumatoid arthritis** seen in rheumatology practices. The probability of functional decline was 14.1% (95% CI, 12.5%-15.7%) in the highest socioeconomic status (SES) quintile and 18.9% (95% CI, 17.1%-20.7%) in the lowest SES quintile. The association between SES and functional decline was partially mediated (7%; 95% CI, 4%-22%) by disease activity. **Da Costa et al (doi: 10.1136/bmj.n2321)** evaluated the effectiveness and safety of different preparations and doses of non-steroidal anti-inflammatory drugs (NSAIDs), opioids, and paracetamol for **knee and hip osteoarthritis** in a systematic review and network meta-analysis of 192 randomised trials. Five oral NSAIDs (diclofenac 150 mg/day, etoricoxib 60 and 90 mg/day, and rofecoxib 25 and 50 mg/day) showed ≥99% probability of more pronounced treatment effects than the minimal clinically relevant reduction in pain. The risk of dropouts due to adverse events was 18.5%, 0%, and 83.3% for oral NSAIDs, topical NSAIDs, and opioids, respectively. **Beaton et al (doi: 10.1056/NEJMoa2102074)** conducted a randomized, controlled trial of secondary antibiotic prophylaxis in Ugandan children and adolescents 5 to 17 years of age with latent rheumatic heart disease. 916 participants were randomly assigned to receive either injections of penicillin G benzathine (also known as benzathine benzylpenicillin) every 4 weeks for 2 years or no prophylaxis, 818 were included in the modified intention-to-treat analysis. A total of 3 participants (0.8%) in the prophylaxis group had echocardiographic progression at 2 years, as compared with 33 (8.2%) in the control group (risk difference, −7.5%; 95%CI -10.2 to -4.7)
Ulloa et al (doi: 10.3899/jrheum.210363) investigated whether there is an association between schizophrenia genetic susceptibility loci and neuropsychiatric systemic lupus erythematosus features in childhood-onset (c) systemic lupus erythematosus (SLE). They included 513 patients with cSLE with median age of 13.8 years (11.2-15.6). The authors did not observe any associations with the schizophrenia susceptibility loci. Sun et al (doi: 10.3899/jrheum.210677) used Danish nationwide registries to select 1923 patients with granulomatosis with polyangiitis (GPA) which were matched with 7124 subjects from the general population to investigate the 10-year risk of heart failure (HF). The median patient follow-up was 6.4 years. The authors found the absolute 10-year risk of HF to be 6.8% (95%CI, 5.5-8.2%) for GPA patients and 5.9% (5.3-6.6%) for the background population and concluded that in the long-term, there was no increased risk for patients with GPA. However, in the first year after the diagnosis, the risk of HF among GPA patients was higher (hazard ratio (HR) of 3.6 (95%CI 2.28-5.67)) compared to general population. The risk of atrial fibrillation and ischemic stroke were also considerably increased in the first year (HR of 6.5 and 3.24, respectively). Eun et al (doi: 10.1016/j.joca.2021.10.012) aimed to investigate the connection between female reproductive factors and osteoarthritis (OA). They included 1,134,680 postmenopausal women from the Korean national health examinations database from 2009 and investigated the frequency of total replacement arthroplasty of the knee (TKRA) and hip (THRA). During a mean follow-up of 8.2 years, 1,610 incident THRA cases and 60,670 incident TKRA cases occurred. Later age at menarche, longer breastfeeding, hormonal-replacement therapy and oral contraceptives use were associated with increased risk of TKRA for severe knee OA, while later age at menopause and longer reproductive span were associated with decreased risk. The associations with THRA was not prominent. Matza et al (doi: 10.1016/S2665-9913(21)00359-3) conducted a prospective, open-label, single-arm single-center study at the Massachusetts General Hospital, Boston to assess efficacy and safety of abatacept for the treatment of IgG4-related disease (IgG4-RD). Ten patients older than 18 years of age were enrolled to receive 125 mg of abatacept subcutaneously weekly through week 24. Concurrent glucocorticoid treatment was permitted but had to be discontinued by week 4. Baseline organ involvement was diverse, with a median of five organs (IQR 3–5) affected at the time of enrolment. The primary endpoint was complete remission of IgG4-RD at 24 weeks, defined by an IgG4-RD responder index of 0, a prednisone dose of 0 mg/day beyond week 4, and no recurrence of disease activity. At 24 weeks, only three (30%) participants were in complete remission. Higher baseline proportions of unswitched memory B cells were associated with responsiveness to abatacept, which might indicate that certain patient populations might be eligible for the treatment.
COVID-19

August 2021 to November 2021

Giacomo Cafaro

Giacomo is consultant rheumatologist and PhD candidate at the Rheumatology Unit of the University of Perugia, Italy. He was PARTNER fellow at the Institute of Infection, Immunity and Inflammation at the University of Glasgow, working on stromal immunology in tendinopathy and PsA. His main research interests are T cell biology in autoimmune diseases, psoriatic arthritis, Sjögren’s syndrome and ultrasound in rheumatology. Giacomo is a member of the Newsletter Subcommittee.

Raiker et al. (doi: 10.1016/j.semarthrit.2021.08.010) investigated the outcomes of COVID-19 in patients with rheumatoid arthritis (RA) compared to the general population. 9,730 and 656,979 patients were enrolled in each group and compared by propensity score matching. RA patients showed and increased risk of venous thromboembolism (RR: 1.18, 1.01 to 1.38) and sepsis (RR: 1.27, 1.12 to 1.43) compared to the general population. Among RA patients, black race, glucocorticoid use and male sex were associated with more severe disease, such as hospitalization, mechanical ventilation and ICU admission. Hospitalization was also more frequent in patients treated with rituximab (RR: 1.78, 1.24 to 2.54) and IL-6 inhibitors (RR: 1.50, 1.00 to 2.25). Yuki et al. (doi: 10.1002/acr.24824) investigated the response to an inactivated SARS-CoV-2 vaccination schedule by a cohort of systemic lupus erythematosus (SLE) patients compared to a group of healthy controls (HC). Among SLE patients, the seroconversion rate was 26.5% and 70.2% after 1st and 2nd dose, respectively, while HC showed a seroconversion rate of 45.2% and 98.1% (p= 0.012 and <0.001). Similarly, mean antibody titres were significantly higher in HC compared to SLE patients (p<0.001). Treatment with prednisone and mycophenolate mofetil were independently associated to the absence of neutralizing antibodies in SLE. Felten et al. (doi: 10.1136/annrheumdis-2021-220549) performed a retrospective analysis of all patients receiving intravenous treatment with rituximab, infliximab, tocilizumab and abatacept for rheumatoid arthritis (RA) and spondyloarthritis (SpA), including psoriatic arthritis (PsA), enrolled from seven sites in France and evaluated the incidence of severe COVID-19 infection leading to hospitalization through a Bayesian analysis. Of the 1116 patients, 10 cases of severe disease occurred, 9 in patients being treated with rituximab (2.3%) and 1 in a patients treated with infliximab (0.2%). At multivariate analysis treatment with rituximab was independently associated with severe COVID-19 (OR 4.4, 1.8 to 11.1). Papagoras et al. (doi: 10.1136/annrheumdis-2021-221539) analyzed the outcomes of COVID-19 infection in a cohort of patients with inflammatory arthritis, connective tissue diseases and vasculitis, comparing unvaccinated patients with fully vaccinated or partially vaccinated subjects. The groups were similar in terms of demographics, disease distribution, disease activity and ongoing treatment. The main outcome of the study was a significantly higher rate of hospitalization among unvaccinated patients compared to fully vaccinated ones (29.3% and 10.3%, respectively, p = 0.0377). Simon et al. (doi: 10.1136/annrheumdis-2021-221554) evaluated the effect of a 3rd COVID-19 vaccine dose in patients with immune-mediated inflammatory diseases (IMID) who had not responded to a 2-dose vaccination schedule. The 3rd vaccine dose was responsible for a seroconversion rate of 49.2% (p<0.0001) and a significant increase in the rate of subjects with neutralizing antibodies (p<0.0001). This significant effect, however, was mostly due to the patients not being treated with rituximab. In fact, among the rituximab-treated subjects, only 18.2% seroconverted and 21.9% had neutralizing antibodies after a 3rd dose, further confirming the significant negative effect of B-cell targeted therapies on vaccination response.
Mehta et al. (doi: 10.1136/rmdopen-2021-001746) performed a meta-analysis clinical trials on the use of colchicine in COVID-19. 6 randomized controlled studies were selected, involving 16,148 patients. They found that colchicine did not show any significant effect on mortality (risk difference 0.0, -0.01 to 0.01), ventilatory support (risk ratio 0.67, 0.38 to 1.21), ICU admission (RR 0.49, 0.19 to 1.25), length of hospital stay (RR -1.17, -3.02 to 0.67). Serious adverse events were not different but patients in the treatment arm showed a higher frequency of diarrhea (RR 1.92, 1.62 to 2.29). Regierer et al. (doi: 10.1136/rmdopen-2021-001896) investigated the outcomes of COVID-19 in a cohort of 2,274 patients enrolled in the COVID-19-RMD registry. The results confirmed a higher risk of severe disease in older patients and in patients with comorbidities, as also seen in subjects with no rheumatic diseases. Additionally, psoriatic arthritis was associated with a lower risk of severe disease, compared to rheumatoid arthritis (RA) (OR 0.5, 0.3 to 0.7). Compared to methotrexate, treatment with mycophenolate mofetil, azathioprine, cyclophosphamide and cyclosporine was independently associated with severe disease (OR 2.2, 1.3 to 3.9), along with JAK inhibitors (OR 1.8, 1.1 to 2.7) and rituximab (OR 5.4, 3.3 to 8.8). On the contrary, treatment with TNF inhibitors was independently associated to a less severe disease (OR 0.6, 0.4 to 0.9). Moreover, active disease or glucocorticoid treatment were independent predictors of severe disease. Janssen et al. (doi: 10.1136/rmdopen-2021-001906), performed a follow-up to the CHIC study, investigating the outcomes at 3 and 6 months in patients with COVID-19-associated hyperinflammatory state, comparing those being treated with steroids and steroids + short term tocilizumab. Modified Medical Research Council dyspnoea scale, Hospital Anxiety and Depression Scale, Trauma Screening Questionnaire, EuroQol 5-dimensions and EuroQol visual analogue scale did not show any difference. Similarly, no difference was found in terms of pulmonary and exercise function tests, which continued to improve form 3 to 6 months in both arms, thus confirming the short-term benefits of tocilizumab are not hampered in the medium term. Schioppo et al. (doi: 10.1093/rheumatology/keab611) analyzed the clinical features of 51 systemic lupus erythematosus (SLE) patients who developed COVID-19 and found that 17.6% had asymptomatic infection and 9.8% developed interstitial pneumonia. 3 SLE flares were detected post-infection. The presence of major organ involvement, including renal disease and ongoing glucocorticoid treatment were associated with asymptomatic disease (p=0.021 and p=0.018, respectively). These results may be the consequence of more aggressive immunosuppression in case of more severe SLE. Iancovici et al. (doi: 10.1093/rheumatology/keab879) investigated the humoral response to COVID-19 mRNA vaccine BNT162b2 in RA patients treated with JAK inhibitors compared to healthy subjects (HC). The levels of anti-spike IgG were significantly lower in RA compared to HC (775 mg/ml and 1261 mg/ml, respectively (p=0.042). Accordingly, plasma samples from RA patients showed lower neutralization activity compared to HC (p=0.018 for NT50 and 0.027 for NT80). B cells from RA subjects tend to respond less to an in vitro stimulus by Spike protein compared to HC.
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:**
  - EULAR recommendations for the management and vaccination of people with rheumatic and musculoskeletal diseases in the context of SARS-CoV-2: the November 2021 update

- **EULAR suggested read:**
  - EULAR 2021 updated viewpoints on SARS-CoV-2 vaccination in patients with RMDs: a guidance to answer patients’ questions
  - Safety of vaccination against SARS-CoV-2 in people with rheumatic and musculoskeletal diseases: results from the EULAR Coronavirus Vaccine (COVAX) physician-reported registry
  - EULAR COVID-19 registry: lessons learnt and future consideration
  - Factors associated with COVID-19-related death in people with rheumatic diseases: results from the COVID-19 Global Rheumatology Alliance physician-reported registry
  - Characteristics associated with hospitalization for COVID-19 in people with rheumatic disease: data from the COVID-19 Global Rheumatology Alliance physician-reported registry
  - EULAR calls on Governments in Europe to recognize the most vulnerable during COVID-19

- **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.
UPCOMING EDUCATIONAL EVENTS

APRIL 2022

British Society for Rheumatology Annual Conference
- When and Where: 25-27 Apr 2022, Glasgow, UK (Hybrid Event)
- Website: https://www.rheumatology.org.uk/events-learning/conferences/annual-conference

66th Japan College of Rheumatology Annual Conference
- When and Where: 25-27 Apr 2022, Yokohama, Japan

MAY 2022

4th Digital Rheumatology Day
- When and Where: 6-7 May 2022, Berlin, Germany
- Website: https://digitalrheumatology.org/4th-digital-rheumatology-day/

European Workshop for Rheumatology Research (EWRR)
- When and Where: 5-8 May, Vienna, Austria
- Website: https://www.meduniwien.ac.at/web/ueber-uns/events/2022/european-workshop-for-rheumatology-research/

European Calcified Tissues Society Congress 2022
- When and Where: 7-10 May, Helsinki, Finland
- Website: https://www.ects2022.org/

17th International Congress on Antiphospholipid Antibodies
- When and Where: 11-14 May, Cordoba, Argentine (hybrid meeting)
- Website: https://icapa2022.com/

Australian Rheumatology Association Annual Scientific Meeting
- When and Where: 20-22 May 2022, Perth, Australia (Hybrid Event)
- Website: https://www.araconference.com/
EULAR 2022 will be an extraordinary year for EULAR, marking not only our first-ever hybrid congress but also our 75th anniversary! We look forward to welcoming you on-site in Copenhagen or virtually. Read the welcome message from the EULAR President, Prof. Annamaria Iagnocco.

The EULAR 2022 Scientific Programme is now online!

The EULAR 2022 Scientific Programme will start on Wednesday, 1 June 2022. Go to programme.

EULAR 2022 Congress will be held both virtually and onsite in Copenhagen, offering our first-ever hybrid congress experience. Registration is now open!

EULAR 2022 Congress
June 1-4, 2022
Join us in Copenhagen or online.
The 4th “Digital Rheumatology Day” will take place in Berlin, Germany on May 6-7, 2022.

The event will be hybrid – live and virtual.

Topics this year will be (all with a focus on rheumatology):
- New digital solutions and user preferences
- New Apps and digital therapies in the field
- AI & self-learning systems
- Telemonitoring & PRO’s
- Digital biomarkers
- Analysing the online health community
- Pitching Event for providers and developers of digital care solutions that can improve quality of care in rheumatology
- Workshops on AI, LinkedIn and Twitter and DIGAs

Preliminary program is available online!
Registration is now open:
https://digitalrheumatology.org/4th-digital-rheumatology-day/
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

### 11th 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**: 17.10.2022; **Registration will open in June 2022**
- **Available for**: 1 year + 1 year extension

### 12th 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**: 17.10.2022; **Registration will open in June 2022**
- **Available for**: 1 year + 1 year extension

### 17th 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. The expected learning time per week is calculated around 2 1/2 hours but very flexible for the learners who can enter the learning system at any time and have available free of charge an extra year if needed.

Knowledge and skills are targeted to suit a level of knowledge appropriate for the final years of training as a rheumatologist.

- **Fee**: 150 EUR
- **Start**: 17.10.2022; **Registration will open in June 2022**
- **Available for**: 2 years + 1 year extension
14th 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**: 17.10.2022; **Registration will open in June 2022**
➢ **Available for**: 1 year + 1 year extension

2nd 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**: 17.10.2022; **Registration will open in June 2022**
➢ **Available for**: 1 year + 1 year extension

4th 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**: 17.10.2022; **Registration will open in June 2022**
➢ **Available for**: 1 year + 1 year extension

5th 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**: 17.10.2022; **Registration will open in June 2022**
➢ **Available for**: 1 year + 1 year extension
**EULAR ONLINE COURSES AND MODULES**

8th 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:** 17.10.2022; **Registration will open in June 2022**
- **Available for:** 1 year + 1 year extension

9th 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:** 17.10.2022; **Registration will open in June 2022**
- **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)
EMEUNET Research Speed-Dating
at #EULAR2022

The EMEUNET Research Speed-Dating is an organized networking activity during the EULAR 2022 conference in which young rheumatologists and researchers interact in a series of short one-on-one conversations to determine if there is mutual interest for research collaborations. The EMEUNET research Speed-Dating will provide an opportunity for participants to explore collaboration interests in a cursory way, forming the basis for further and more profound interaction.

Location: EULAR 2022 Congress Venue
Time & Date: Thursday 2nd of June at 12 pm

Application requirements

Before applying, do ensure that you have prepared the following application documents:

- Completed application form
- CV
- Motivation letter
- Proof of nomination by National Society for the EULAR Congress bursary (If applicable)

For more information and registration, access through the EULAR website.
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/
The European Alliance of Associations for Rheumatology (EULAR) is very concerned about the situation in Ukraine, and it condemns Russia's unacceptable act of aggression towards the country. As hospitals are being attacked and access to medical aid is interrupted, EULAR wants to respond to this humanitarian crisis and particularly support the Ukrainian people with rheumatic and musculoskeletal diseases (RMDs), who need urgent treatment and assistance.

Together with EMEUNET, EULAR has developed a support programme for young Ukrainian rheumatologists, enabling them to take up their profession, maintain and further develop their skills, and provide care to a range of patients, including particularly displaced Ukrainian RMD patients. Across Europe, Ukrainian rheumatologists or rheumatologists in training can apply for this programme, sponsoring their employment in one of EULAR’s various partner hospitals or institutes. EULAR will fund up to 20 such positions, allowing for a stable income for a Ukrainian physician who had to flee their country, and securing medical treatment for Ukrainian refugees with RMDs. EULAR will provide € 500,000 for this purpose.

What: Funding programme for displaced Ukrainian physicians
Who can apply: Hospitals or medical institutions (employers) in countries with many displaced Ukrainian refugees
Target group: Ukrainian rheumatologists, focus on rheumatologists in training
How much: 20,000 – 30,000 EUR/year

Please send your application to eular@eular.org.
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:

- Anchor
- Apple Podcasts
- Breaker
- Google Podcasts
- Overcast
- Pocket Casts
- Radio Public
- Spotify

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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