MicroRNAs in rheumatic diseases

Micro-RNA (miRNA) are small noncoding RNAs that regulate the gene expression at a posttranslational level. Alterations in the expression pattern of miRNAs may lead to diseased states including cancer or autoimmune diseases. Thus, miRNAs do not only represent potential molecular targets but may also be used as diagnostic tools.

miRNA in rheumatoid arthritis (RA)
Trenkmann et al. (OP0017) demonstrated that in RA synovial fibroblasts the miR-17-92 cluster is induced by TNFa via the NF-kB pathway and that by repressing TNFAIP3 miR-18a represents a positive regulator of NF-kB signalling. The overexpression of miR-18 increased the production of inflammatory cytokines and matrix degrading enzymes, thus aggravating the activated phenotype of RASF.

Filkova et al. (SAT0105) analyzed the profile of circulating miRNA before and after treatment in patients with early RA (ERA) and established RA, their association with clinical activity and response to therapy. miR-223 was found to correlate with the disease activity in treatment naïve patients with early RA and was significantly downregulated after MTX. Although further confirmation is needed, in those patients, miR-223 might represent a promising future biomarker.

miRNA in lupus nephritis (LN)
Costa Reis et al. (THU0289) identified a distinct miRNA signature (miR-16, miR-26a, miR-30b, miR-451, miR-494) in pediatric patients with lupus nephritis. These miRNAs are predicted to regulate the expression of genes implicated in the pathogenesis of nephritis and/or tissue inflammation. Future studies will address their role in SLE pathogenesis and their potential function as LN biomarkers.

Krasoudaki et al. (SAT0006) also found a distinct miRNA signature in renal biopsies of adult patients with LN. Moreover, their study suggests a potential role for miR-422a that was substantially upregulated in LN and of which the levels correlated with the disease activity in a lupus mouse model. miR-422a was found to directly downregulate kallikrein 4. Kallikreins are known to play an important role in regulating inflammation, apoptosis, coagulation and fibrosis in the kidneys.

miRNA in systemic sclerosis (SSc)
Vettori et al. (AB0837) found that most miRNA down-regulated in cultured SSc fibroblasts are detectable in SSc serum samples and display a similar expression profile. Moreover, they showed that different miRNA were associated with distinct SSc features. Of note, miR-29a and miR-186 were independently associated with FVC <80% in multivariate analysis, and might be considered as candidate biomarkers for fibrotic lung involvement in SSc patients.

EULAR 2012 Highlights
Basic research
Rheumatoid arthritis
Psoriatic Arthritis
Axial Spondyloarthritis

Newsletter Topic: EULAR 2012 Highlights!
In this edition of EMEUNES, we would like to draw your attention to what we believe has been the most interesting presentations at this year’s EULAR
At this year's EULAR, as in most of the recent meetings, fine specificities of anti-citrullinated peptide antibodies (ACPAs) were a major topic. Carl Turesson from the Lund University in Malmö, Sweden presented a study in which ACPA epitope spreading over time was analyzed (OP0084). Around 5 years before onset of RA, ACPAs were detectable in 50% of the analyzed patients and were most frequently directed against citrullinated vimentin and citrullinated alpha-enolase peptide 1 (CEP1). The shorter the time between analysis and diagnosis, the more ACPA specificities could be found, indicating that relevant spreading of ACPA epitopes occurs already before clinical symptoms of RA appear.

Similar results were presented by Brink et al (OP0085). In their pre-RA cohort, the first ACPAs, directed against citrullinated fibrinogen (Fib α36-50), were already detected around 10 years before disease onset. They could also show that over time not only the repertoire of specificities, but also the concentration of specific ACPAs increased. The highest concentrations before onset of RA were found for ACPAs targeting fibrinogen (Fib β36-52), α-enolase and CCP1.

Finally, Willemze et al from Leiden, Netherlands, connected ACPA avidity to disease severity (AB0152). Similar to ACPA specificities also ACPA avidity was highly variable. Interestingly, lower avidity of ACPAs was associated with more severe joint destruction. Also, low avidity ACPAs were more potent in activating the complement system and less restricted in binding to several citrullinated antigens.

Two studies presented data on the pathogenic role of ACPAs in RA. The first study by Harre et al from Erlangen, Germany showed that ACPAs against mutated citrullinated vimentin (MCV) strongly bound to osteoclasts and induced osteoclastogenesis in vitro (OP0019). Also, in a mouse model, transfer of anti-MCV antibodies induced release of TNF from osteoclast precursors and osteoclastogenesis. Thus this study provides a link between formation of ACPAs and bone loss. The second study was presented by Perez-Sanchez et al from Cordoba, Spain (SAT0044). They found an association between ACPAs, numbers of neutrophils and levels of IL-2 and IL-17A. In vitro incubation of cells with ACPAs led to increased peroxide production in neutrophils and production of pro-inflammatory cytokines and chemokines in monocytes. Thus, the authors suggest a causative role for ACPAs in oxidative stress and inflammation in cells of RA patients.

Standards of care in RA

Lahiri et al. (OP0046) proposed a prediction score using demographic and lifestyle factors. Lifestyle data were obtained from a prospective population-based study. Individuals who developed inflammatory polyarthritis (IP) were identified by linkage with the Norfolk Arthritis Register. A Cox proportional hazards model was developed and a score was assigned to each risk factor based on the β-coefficients from the model. A total of 25,455 participants aged 40-79 years were followed (342,916 person-years), 184 developed IP. The 10-year cumulative incidence of IP was 0.37% in men, 0.67% in women. For men, every 10 pack-years of smoking, being obese and having diabetes mellitus scored positively, whereas drinking up to 3 units of alcohol per day, and being of a higher occupational class scored negatively. For women, smoking status was a better predictor than pack-years smoked and additional positive scores were assigned for having 2 or more children, whereas negative scores were assigned for every 6 months of breastfeeding.
Antibodies: Anti-TNF and B-cell therapies

**RA II (biologics: anti-TNF and B-cell therapies)**

Isabel Castrejon, MD, is a rheumatologist working as clinical research fellow in the Division of Rheumatology, Hospital for Joint Diseases, NY (Prof. T. Pincus). Areas of interest include outcomes research in RA & SLE.

**Anti-TNF therapies**

Stranfeld et al. (OP0144) reported the criterion validity of a score RABBIT risk score- which enables the calculation of the risk of serious infections in patients with rheumatoid arthritis (RA) treated either with TNF inhibitors or conventional DMARDs. There was a very good agreement between observed and expected rates of serious infections in a cohort of patients enrolled in the German biologics register RABBIT. Kuroda et al. (OP0146) evaluated the safety and survival rates of anti-TNF and anti-interleukin-6 biologic agents in RA patients with reactive AA amyloidosis. Survival rate was significantly higher in the biologic group than in the non-biologic group (p=0.001) and more patients in the non-biologic group required initiation on hemodialysis. Keystone et al (FR0157) compared remission rates among RA patients initiating Etanercept therapy in routine clinical practice settings (RADIUS II, a prospective observational study) with remission rates in the Trial of Etanercept and Methotrexate (TEMPO). Generally, more patients with lower baseline CDAI scores achieved remission by year 3 in routine clinical care and the RCT. There was a slightly higher percentage of CDAI remission in TEMPO (39% if Initiation of ETN monotherapy and 54% ETN added to established MTX) compared to RADIUS II (35%), may be explained in part by a better compliance.

**B-cell therapies**

Dougados et al. (THU0087) evaluated the efficacy and the safety profile of 2 dose regimen of rituximab (RTX) in patients who had a EULAR response 6 months after a first cycle of 2 infusions of RTX 1g and who required subsequent therapy. In case of a EULAR response after a first cycle of 2 infusions of RTX 1g, retreatment with a RTX 1g single infusion provides similar clinical outcomes compared with 2 x 1g infusions. Vollenhoven et al (THU0120) investigated the long-term safety of rituximab (RTX) in RA patients. The analysis included data from 3595 patients with up to 10-year follow-up. Infusion-related reaction was the most frequent adverse event (AEs). Rates of AEs, serious AEs and infections were comparable across populations and generally remained stable over time and multiple courses. Overall serious infection rates in the rituximab all exposure and >5 year sub-population were 3.80 events/100 pt-yrs and 2.76 events/100 pt-yrs, respectively, both rates being comparable to the placebo population (3.79 events/100 pt-yrs). RTX has a consistent safety profile and remains well tolerated over time and multiple treatment courses.

**RA III (other biologics and new drugs beyond biologics)**

Cécile Gaujoux-Viala (1979) MD, PhD – France. She is a fellow at the graduate school BioSE, currently occupies a half-time clinical position and half-time research and teaching position at Paris 6 University and Salpetriere Hospital in Paris. Her main interest area focuses on outcome assessment, epidemiology and treatment of rheumatic diseases.

Sarilumab is a fully human monoclonal antibody directed against IL-6R. 306 adults with active, moderate-to-severe RA despite MTX therapy were randomized to different dose regimen or placebo. In this phase 2 study, sarilumab 150 mg qw, in combination with MTX, was efficacious on signs and symptoms (OP0025). Sarilumab is an anti-IL-6 monoclonal antibody. In this phase 2 study of multiple subcutaneous doses of LY in 260 patients with RA naïve to biologic therapy and 188 inadequate responders TNF, significant differences vs. placebo were seen for DAS-28 CRP reductions in both populations at all LY doses, with a rapid onset of efficacy within 1 week after the first dose and with increasing magnitude of reductions with increasing doses. The safety profile was comparable to other biologic therapies (OP0021).

NNC0109-0012 is a novel human monoclonal IgG4 antibody which binds to and neutralises the activity of IL-20. In this trial (n=67), NNC0109-0012, administered at 3 mg/kg s.c. once-weekly for 12 weeks in combination with MTX significantly reduced disease activity, improved ACR20/50/70 responses in RF- and anti-CCP-positive patients, and showed a favorable safety profile as compared to placebo (LB004). LY2439821 (LY) is an anti-IL-17 monoclonal antibody. In a phase 2 study of multiple subcutaneous doses of LY in 260 patients with RA naïve to biologic therapy and 188 inadequate responders TNF, significant differences vs. placebo were seen for DAS-28 CRP reductions in both populations at all LY doses, with a rapid onset of efficacy within 1 week after the first dose and with increasing magnitude of reductions with increasing doses. The safety profile was comparable to other biologic therapies (OP0021).

GLPG0634 is an orally-available, selective inhibitor of JAK1. These double-blind, placebo-controlled trial in 36 patients with active RA and insufficient response to MTX is the first to demonstrate that selective inhibition of JAK1 is efficacious and safe for the treatment of RA within 4 weeks. No anemia and no effect on LDL/lipid were observed (OP0263).
PsA assessment: Whether axial PsA and AS with psoriasis are the same disease or not is still debated. Castillo-Gallego et al (SAT0289) presented data concerning spinal involvement in PsA. Spinal MRI involvement was scored by the Leeds scoring system for bone marrow oedema: HLAB27 may play a key role in the axial disease as the extent and severity of the disease in HLAB27 positive PsA patients were comparable to the AS patients, with similar MRI scores, whereas HLAB27 negative PsA patients had lower MRI scores compared to PsA HLAB27 positive and AS patients.

However, Fernández-Sueiro et al (SAT0302) found no significant differences in demographics, metrology (with exception of the occiput-wall distance), inflammation, function and structural damage in axial PsA according to the presence of HLAB27: 52 HLAB27 negative vs 16 HLAB27 positive axial PsA patients.

Enthesitis is another common feature both in PsA and AS but its assessment is not always easy nor reliable. Poggenborg et al (OP0165) presented the results of a study where Whole Body MRI (WBMRI) was used to assess enthesis in AS, PsA and healthy subjects and compared to clinical assessment. Inflammation was most likely seen in the great trochanter and the Achilles tendon, but no association was found between the enthesis on WBMRI and the tender enthesis according to 7 enthesis index.

Improving remission in PsA: It is well known that concomitant methotrexate (MTX) improves efficacy of TNF-alpha inhibitors (TNFi) in rheumatoid arthritis, its role in PsA remains unclear: Fagerli et al (OP160) aimed to investigate if PsA patients receiving concomitant MTX have better responses and drug survival to the 1st TNFi, compared to those receiving no concomitant DMARD; responses were similar in both groups at 3 months, but an improved 3-year drug survival was observed in the combination group.

Obesity prevalence is increased in PsA patients, increasing cardiovascular risk of these patients, but more recently related to more active forms of disease with lower response to treatment. Di Minno et al (OP-162) aimed to evaluate whether the presence of obesity impacted on the achievement of the Minimal Disease Activity (MDA) in subjects with PsA: obesity was associated with a higher risk of not achieving MDA (HR: 4.90) at 12 months, and moreover, among the patients that achieved MDA, the presence of obesity was associated with a poor probability of sustained MDA at 24-months (HR:2.04). However, in another study, Di Minno (OP 163) gives some hope for our obese patients, and compared the response to a first TNFi in obese patients divided in two groups (hypocaloric diet vs self-managed diet): patients following a successful hypocaloric diet presented with significant higher rates of MDA at 6 months, confirming the importance of a weight control in psoriatic patients.

Kiltz et al (OP0251) aimed at developing a measure to assess the burden of AS, the AS Health Index, based on the Comprehensive International Classification of Function Core Set for AS. The phases of development of the index were presented. The item pool for this index started with 251 items and has been successfully reduced to 66 items, still covering much of the ICF Core Set for AS. This draft version will be tested in a second survey to create a first version of the ASAS Health Index. The final measure can be used in clinical trials and cohort studies as a new composite index that captures relevant information on the health status of the patients.

A study from Kroon et al. (THU0261) showed that patients with elevated acute phase reactants benefit most from continuous NSAID treatment, as they have a slower radiographic progression. Therefore, prioritizing patients with elevated acute phase reactants for continuous NSAID-treatment may improve the benefit-risk-ratio of NSAID-treatment in AS.

A possible role of some biomarkers in the progression of syndesmophytes was described by Poddubnyy et al (OP0096) who found that, among patients with syndesmophytes and high CRP at baseline, those with progression in 2 years (new syndesmophyte or growth of an existing one) had higher levels of MMP3, BMP-2, PIINP and VEGF, and lower levels of OPG).

Ciruela et al. (OP0096) reported a dependence of the known cross-sectional association between smoking and BASDAI or ASDAS on the HLA-B27 status, with only HLA-B27 positive patients having an increased disease activity with smoking. Nevertheless, the same authors found that smoking does not seem to change the long-term evolution of BASDAI and ASDAS.

Two RCTs investigating the effect of anti-IL6 drugs (sarilumab and tocilizumab) in patients with AS were presented (Sieper et al.OP0169, Sieper et al. OP0166).

In both studies, the primary endpoint was not met, which means that as of now (i.e. with the current trial designs we have) these drugs do not seem to play a role in the treatment of AS.

In a post-hoc analysis of GO-RAISE, van der Heijde et al. (OP0170) showed that achieving ASDAS inactive disease or major improvement in patients with AS after treatment with golimumab is associated with improvements in HRQoL and productivity and a trend towards regaining employability was observed for patients with clinical improvements. This study also reinforces the validity of the ASDAS for assessment of response to therapy.
patients with lupus erythematosus.

SLE & APS

Cristina Pamfil, MD, is a rheumatology clinical research fellow, currently completing a PhD at the University of Crete Heraklion, under the supervision of Professor Dimitrios Boumpas. Her major research interest is systemic lupus erythematosus.

The joint EULAR/ERA-EDTA recommendations for the management of adult and pediatric lupus nephritis (LN) were presented by Bertssias et al (OP0064). The authors gave mycophenolate mofetil (MMF) a definite position in the LN armamentarium: in patients with Class III and Class IV (±V) LN, MMF or low-dose intravenous cyclophosphamide (CY) in combination with glucocorticoids are recommended. For MMF or CY failures, the authors recommend switching to the other, or to rituximab. The presence of APS may increase the mortality risk of patients with SLE, mainly by arterial thrombotic events that occur late in the disease course (THU0170). In a large prospective study, conducted by the Johns Hopkins group, hydroxychloroquine was shown to be protective against thrombosis, particularly in patients with positive antiphospholipid antibodies (HR 0.6, p=0.0080). Inversely, prednisone use (>20 mg/day, HR 4.2, p=0.0001) was found to be a significant independent predictor of thrombotic events (SAT0222). Although rituximab (RTX) failed to meet the primary efficacy end point in two RCTs, uncontrolled observations continue to support its efficacy in some patients. Bang et al presented a multicenter retrospective analysis on the effectiveness and safety of RTX in Korean patients with refractory SLE. Complete or partial remission occurred in 65%, 90%, 100%, 67%, and 67% of patients with renal, hematologic, arthritis, myositis, and other manifestations at 6 months, suggesting that RTX is efficient, and may exhibit a prolonged effect in controlling disease activity (AB0631). Vollenhoven et al estimated the proportion of patients receiving off-label treatment with RTX in 30 European countries to be between 0.5-1.3% of the lupus population. The data may reflect the indication in patients in whom established therapeutic options have been exhausted, and, perhaps, the lack of access to therapy [SAT0199]. In a study reported by Furie et al, abatacept, a modulator of T-cell costimulation, failed to show benefit in class III and IV LN, when administered as add-on therapy on a background of MMF and steroids (SAT0185). However, targeting plasma cells in refractory SLE showed promising results. Voll et al reported that, bortezomib, a proteasome inhibitor approved for the treatment of multiple myeloma, was effective in a case series or SLE patients with refractory disease (SAT0203). Regarding lupus in “little folks”, Tang and co-workers identified childhood-onset SLE as an independent risk factor for deterioration of bone microarchitecture and mechanical properties, stressing the importance of early use of steroid-sparing therapies (SAT0210).

OTHER CONNECTIVE TISSUE DISEASES

Jan Sznaijd, MD – internal medicine specialist and rheumatology fellow working in Allergy and Immunology Clinic at Jagiellonian University in Krakow, Poland. His main interests focus on ANCA associated vasculitis and SLE.

The results of TEARS (OP0065), French RCT comparing rituximab (RTX) with placebo in 122 patients with active primary Sjogren syndrome (pSS) with mostly systemic manifestations did not show statistically significant difference in primary outcome, which was defined as improvement of at least a 30 mm on 2 of 4 VAS scores evaluating dryness, pain, fatigue and global disease activity. However data from the AIR registry (OP066) give some hope for the future as improvement according to the clinician and CS sparing effect was observed in 45 out of 78 refractory pSS pts (54%) with systemic involvement treated with RTX. Promising results of treating mouth dryness with rebamipide, an anti-ulcer, gastro-protective drug, were reported by Abou-Rayya et al (THU0166). Same authors showed its efficacy also in treating oral ulcers due to Bechcet disease (OP1083). Japanese authors in a retrospective study confirmed the efficacy of tacrolimus added to conventional therapy in refractory pts with interstitial lung disease complicating PM/DM however cautious interpretation is warranted due to observational nature of the study (THU0231). A core set of indications for right heart catheterization in pts with suspicion of PAH related to systemic sclerosis (SSc) comprising clinical, echocardiographic and pulmonary function domains has been proposed by group of experts from the EPOSS group (OP0226). Long-awaited first results of ASTIS trial (LB0002) evaluating efficacy of autologous HSCT in comparison with cyclophosphamide in patients with poor prognosis dSSc showed fewer deaths in transplant arm however treatment related mortality through day 100 was high (10%). N. Rasmussen presented the 2012 update of the Chapel Hill Consensus Conference definitions of vasculitic diseases (SP0065). The original list of 10 vasculitides was extended to include 27 diseases, some were renamed to avoid eponymous names or in order to reflect their pathogenesis better. New EULAR/ACR diagnostic and classification criteria of systemic vasculitids (DCVAS) are in the process of development (AB0757) and participation of new centers in this international project is still welcome. Very preliminary results of MYCYC trial comparing cyclophosphamide (CYC) with mycophenolate (MMF) for remission induction in ANCA associated vasculitis (AAV) were presented during WIN session and MMF appeared not inferior to CYC in this regard. A systematic review of the efficacy and safety of anti-TNF drugs in AAV (AB076) did not show their superiority if added to standard treatment besides possible corticosteroid sparing effect, however only 2 RCTs were included in this analysis. The retrospective study from Italy (THU0209) confirmed the efficacy of aTNF drugs for refractory Takayasu arteritis in native but not revascularized lesions.
Nakagomi et al (OP 0133) reported about the importance of depiction of synovitis by using ultrasound in patients with rheumatoid arthritis on the improvement of the accuracy of the 2010 ACR/ EULAR classification criteria. Overall, 117 pts with musculoskeletal symptoms <3 years underwent ultrasound (US) on 38 joint regions and received routine care from expert rheumatologists blinded to the ultrasound findings. Joints with any positive signal on grey-scale or power-doppler ultrasound were defined as having US-synovitis; joints with swelling or tenderness were defined as having clinical (CL)-synovitis. Pts classified as RA when joint assessment was replaced with US-synovitis were defined as US-RA; Pts classified as RA without US assessment were defined as having CL-RA. When US-synovitis was applied, sensitivity and specificity of the classification criteria to predict MTX-requirement within the first year of classification improved from 71.4 to 81.6% and from 68.2% to 79.3%, respectively.

In another study in RA, cut-offs for determining a MRI inflammatory activity acceptable state (remission status) but also sub-groups of patients at risk for radiographic progression were defined (Haarvaldshom et al, OP0274). A total of 213 patients in clinical remission and 81 with low disease activity (LDA [DAS28-CRP <3.2]) from 6 cohorts were included. Synovitis as quantified by the RAMRIS was a significant predictor for future radiographic progression. A cut-off value of 5 was defined as clinically relevant. Furthermore, patients with a RAMRIS synovitis score of >6 and RF+ were more at risk to develop vs. those with a RAMRIS score of ≤5.

Finally, in the BeSt Study, the rate of radiographic progression during the first treatment year with biologics was found predictive for the status of disability (measured by HAQ) after 8 years of treatment despite relatively equal suppression of DAS in patients with ≥ 5 points SHS) or without rapid radiographic progression (van den Broek et al, FRIO059).

In SpA, the negative effect of smoking in predicting radiographic progression was confirmed by an analysis of the dose dependence of smoke. In 210 pts with axSpA, tobacco smoking had a clear dose-dependent effect on radiographic spinal progression in axSpA, with the highest progression risk in patients who smoke >10 cigarettes per day (Poddubny et al, OP0097).

In an experimental study of P. van Lent et al. (OP0014) a single intraarticular injection of ADSCs (adipose derived stem cells) into the knee joints of mice with collagenase-induced osteoarthritis gave protection of synovial activation, cartilage destruction and osteophyte formation, probably by inhibiting the activated phenotype of synovial macrophages. In a randomized placebo-controlled trial from Abou-Raya et al. (FRIO299) methotrexate-treated patients with osteoarthritis (25mg/week oral methotrexate) achieved significantly greater reduction in pain and better physical function compared to the placebo group. Whittoek et al. (OP0033) reported radiographic follow-up data of a one-year open-label extension study of treatment with adalimumab in erosive osteoarthritis of the IP joints. The first double-blind placebo controlled RCT confirmed the efficacy and safety of adalimumab in 60 patients with erosive osteoarthritis of the interphalangeal finger joints during 52 weeks. 50 patients were included in the extension phase of the trial. Follow-up radiographic data confirm the potency of adalimumab to delay the radiographic progression in EOA. Abou-Raya et al. (OP0129) showed in a randomized double-blind placebo-controlled trial that low dose oral glucocorticoids (7.5mg daily) had both a short term and a longer sustained effect resulting in less knee pain, better physical function, and attenuation of systemic inflammation in older patients with knee osteoarthritis. In a randomized, double-blind, placebo-controlled pilot study by Lindsey et al. (FRIO304), intraarticular infliximab (INF) 100 mg showed significant improvement (assessed by WOMAC score). Baseline synovial cellularity and CRP also correlated with improvement. Rahela et al. (FRIO306) conducted a randomized, controlled study with 181 patients with knee osteoarthritis, where the physical exercise program improved both functional status and quality of life in patients with knee osteoarthritis by increasing range of motion and muscular strength and by reducing pain. Baptista et al. (THU0341) showed in a RCT that art therapy can be used in the treatment of fibromyalgia, leading to a reduction in pain and improvements in degree of depression and quality of life. Bettoni et al. assessed the efficacy and safety of whole Body Cryotherapy, which was significantly superior (P <0.05) to the treatment with only antioxidants and analgesics in reducing pain (THU0347). In a retrospective study by Metyas et al (THU 0355) the superiority of combination pharmacotherapy (pregabalin in combination with duloxetine or milnacipran) versus monotherapy with any of the above drugs was shown.
Many gout patients are not well controlled with current urate lowering therapies (ULTs); the search for new, safe and effective ULTs is therefore ongoing. BCX4208 is the first of a new class of drugs that inhibits purine nucleoside phosphorylase (PNP), located a step above xantine oxidase in the metabolic pathway of uric acid. A short (12 weeks) dose-ranging RCT assessed the use of BCX4208 as add-on therapy to allopurinol (300mg/d) in 278 patients with serum uric acid above target 6mg/dL. Most of the BCX4208 doses (5, 20 and 40mg/d; but not 10mg/d) improved the percentage of patients achieving the target sUA<6mg/dL: from 18% (placebo) to 39-49% (BCX4208, several doses) (Becker et al, FRI0367). BCX4208 was generally well tolerated with no clear increase in the rate or severity of adverse events or infections even though 15 patients withdrew from the study due to decrease in CD4+ cell count <350cells/mL (Hollister et al, FRI0380).

Event though a relationship between hyperuricemia or gout and cardiovascular disease has been described in several studies, it is still unclear if this association is causal. Rothenbacher et al (OP0100) presented a study of 1056 patients with stable coronary heart disease (229 with gout; 827 without gout) followed up for 8 years. 151 patients presented a cardiovascular event (myocardial infarction or stroke). Incidence correlated with increased serum uric acid and CRP but not to the presence of gout. On the other hand, Perez-Ruiz et al (OP0102) presented the prospective follow-up of a well-characterized cohort of 706 patients with gout. Standardized mortality ratios showed an increase in mortality (SMR 2.37), with a marked increase in women. The presence of subcutaneous tophi and a high baseline serum urate (≥8.74mg/dL) were independently associated with a higher risk of mortality. In a study using the Taiwan national health insurance database, Kuo et al (OP0103) evaluated the factors associated with incidental end stage renal disease. After adjustment for well-known risk factors like diabetes, hypertension, age, gout emerged as an independent risk factor (HR 1.57), especially in patients over 45 years old.

In a study by Sehgal et al. (OP0043), 4.3 million patients over the age of 65 with osteoporotic hip fractures were studied via the Nationwide Inpatient Sample. Results showed that 67.3% of hip fractures occurred in the extreme elderly, increasing from 172,209 in 1993 to 180,428 in 2008, despite the fact that hip fracture prevalence decreased from 2,236 to 1,600 per 1,000 person-years in the same period. With the extreme elderly predicted to comprise 25% of the total US population by 2050, this study calls for more aggressive measures to be introduced to enable osteoporosis to be more effectively prevented, diagnosed and treated. The open-label, active-treatment, 3-year results from the FREEDOM extension study were presented by Chapurlat et al (SAT0342): Denosumab treatment for 3 years in the cross-over group produced FREEDOM observations, and in the 6-year (long-term) group, Denosumab continued to significantly increase BMD, maintained reduced bone turnover and remained well tolerated; fracture incidence remained low. Using intravital multiphoton microscopy in 3-GFP mice, Kikuta et al (OP0040) identified different populations of live osteoclasts on the bone surface, from "static - bone resorptive" to "moving - non resorptive"; RANKL not only promoted the differentiation of osteoclasts but also regulated the bone-resorptive function of fully differentiated mature osteoclasts; RANKL-bearing Th17 cells were shown to control bone resorption of mature osteoclasts, demonstrating novel actions of Th17 cells that may have therapeutic implications in Th17-mediated inflammatory diseases. In a double-blind, placebo-controlled, randomized, ascending multiple dose study with AMG-785 (a sclerostin antibody), 48 healthy men and postmenopausal women (36 AMG-785, 12 placebo) aged 45-80 years (mean 59 years) with a lumbar spine or total hip DXA T-score ≤–1.0 and ≥–2.5 were enrolled (Padhi et al, OP0044). Multiple doses of AMG-785 significantly increased the bone formation marker PINP, decreased the bone resorption marker sCTX, increased lumbar spine BMD and were well tolerated, supporting the continued clinical investigation of sclerostin inhibition as a potential therapeutic strategy for conditions that would benefit from increased bone formation. Payet et al (FRI0375) described the clinical characteristics of a population of 54 adult patients with osteogenesis imperfecta. In this cohort of patients, 72.2% had vitamin D insufficiency and 50% had vitamin D deficiency. Just over half of the patients had vitamin D supplementation. This study shows that vitamin D insufficiency/deficiency is common in osteogenesis imperfecta and that systematic vitamin D screening and supplementation may be advisable in patients with this disease.
EMEUNET members were invited to collaborate.

Rheumatology/Immunology Working Party

Trials and Research (EUSTAR) group, and

Information Network

European Musculoskeletal Conditions Surveillance and

following organizations, networks and specialty groups:

opportunities were discussed by representatives of the

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ESCCA, and the committee welcomes more research

activities of the ESCCA include elaborating guidelines

for management of musculoskeletal conditions;

recommendations for conducting clinical trials; and

developing criteria for classification, diagnosis,

outcomes and response in rheumatology. There are

currently 5 new project proposals under review at the

ESCCA, and the committee welcomes more research

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European Musculoskeletal Conditions Surveillance and

Information Network (EUMUSC), EULAR Scleroderma

Trials and Research (EUSTAR) group, and

Rheumatology/Immunology Working Party (RIWP). The

EMEUNET members were invited to collaborate.

ESCC A - EULAR SC for Clinical Affairs

Elena Myasoedova, MD, PhD is an Assistant Professor at the Department of Internal Medicine and Rheumatology in Ivanovo State Medical Academy (Russian Federation) and a Research collaborator at the Dpt of Health Sciences Research at Mayo Clinic (USA). Her major research interest is epidemiology of rheumatic diseases and their co-morbidities, especially cardiovascular disease.

The EULAR Standing Committee for Clinical Affairs (ESCCA, Chairman: Dr. Daniel Aletaha) is currently the largest of the EULAR committees working on a vast and continuously growing spectrum of clinical research projects encompassing a wide variety of rheumatic diseases. During the Business meeting of the ESCCA at the EULAR 2012 the results of ongoing initiatives and further work were discussed. Extensive research activities of the ESCCA include elaborating guidelines for management of musculoskeletal conditions; recommendations for conducting clinical trials; and developing criteria for classification, diagnosis, outcomes and response in rheumatology. There are currently 5 new project proposals under review at the ESCCA, and the committee welcomes more research applications. Validation and implementation of the recommendations in rheumatology research and practice have been recognized among the current priorities. The EULAR website was suggested as a platform for the presentation of recommendations endorsed by EULAR committees to ensure better access, dissemination and implementation of the recommendations. A variety of collaboration opportunities were discussed by representatives of the following organizations, networks and specialty groups: European Musculoskeletal Conditions Surveillance and Information Network (EUMUSC), EULAR Scleroderma Trials and Research (EUSTAR) group, and Rheumatology/Immunology Working Party (RIWP). The EMEUNET members were invited to collaborate.

E U LAR 2012 Highlights!

Reports from the EULAR Standing Committees

ESECT - EULAR SC for Education and Training

by Sofia Ramiro, contributor also for the EULAR Highlights for Axial Spondyloarthritis

The ESCET business meeting at EULAR 2012 was attended by 30 participants. Dimitrios Boumpas, Chair of ESCET, summarized the EULAR initiatives to which the Education committee has contributed during the past year: EULAR courses (online, ultrasound and other courses), the “What is New (WIN)” course (first edition to take place in November), the Fellow’s Day (preceding the WIN course and targeting fellows, this year replacing the Postgraduate Course) and a new EULAR educational DVD: Principles of the Musculoskeletal History and Examination. Future initiatives include courses for allied health professionals & patients and a summer rheumatology school (targeting medical students in their final year). The Postgraduate Course and its future format will be revisited. EULAR has broadened its educational output, and has summarized it in a brochure that will be updated each year.

EMEUNET currently has 5 observers in ESCET (Sofia Ramiro, Peter Mandl, Laure Gossec, Jan Sznadaj and Gyorgy Nagy). We aim to continue our active participation and contribute to the implementation of new initiatives in education, especially to those targeting young rheumatologists. EMEUNET has contributed 8 proposals for the EULAR 2013 Fellows’ sessions. We also presented the results of a mentoring survey (also presented in a fellows’ session) and another ongoing project on the similarities and differences in rheumatology training across Europe.

SCEHSR – Standing Committee on Epidemiology and Health Services Research

by Pedro Machado, contributor also or the EULAR Highlights for Osteoporosis & Metabolic Bone Disease

The standing committee (SC), chaired by Prof. Loreto Carmona, discussed a number of major activities under various stages of progress:

1. EULAR 2017 strategic plan: the 5-year EULAR strategic plan and potential tactical objectives were discussed.
2. European Musculoskeletal Conditions Surveillance and Information Network (eumusc.net): the SCEHSR closely collaborates with the eumusc.net project funded by the European Union and EULAR. The project will also link with an international World Bank initiative updating data used in the Global Burden of Disease project.
3. Study group on longitudinal observational drug studies in European Rheumatology: this study group is being formed.
4. SCEHSR is taking a more active role in bringing the European registers together.
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8. SCEHSR is taking a more active role in bringing the European registers together.
During EULAR I had the opportunity to attend the ESCIR as an EUMEUNET observer. At this meeting which was chaired by Georg Schett, different study group reported updates on their particular progresses. Maurizio Cutolo represented the Neuroendocrine Immunology group (NEIRD) with an update on projects on “sexhormones, pregnancy and rheumatic diseases”, “Circadian rhythms and rheumatic diseases” “Glucocorticoids and rheumatic diseases” and “VitD and rheumatic diseases”. There will be a new EULAR compendium of NEIRD. Christian Jorgensen on behalf of the Study Group on gene and cell therapy for Rheumatic Diseases (SGGCT) reported on MSC therapy in knee OA. EULAR study group on animal models for rheumatic diseases (SGAM) was represented by Florence Apparailly and reported on a standardization workshop to establish SOP guidelines. So far SOPs for 4 animal models have been established. Constantino Pitzalis of the EULAR Synovitis study group presented the “Pathobiology of Early Arthritis Cohort (PEAC) and demonstrated the feasibility of US guided synovial biopsies with the clinical utility at individual patient level for possible future patient targeted trials. Finally Karim Raza reported on the Study group for Risk Factors for RA and how to standardize terminology on individuals at risk to final RA diagnosis.

The meeting was led by (now) past chairman professor Mikkel Østergaard and chairperson professor Maria-Antonietta D'Agostino. All participants introduced themselves, and professor Østergaard explained the role of the committee as well as the difference between representatives of the various national societies and the co-opted members. Then followed a summary of main activities during the last period from 2011 to 2012. So far three different tasks forces are working on different EULAR recommendations in imaging, which will soon be finished; the 1st one is delayed due to change of fellows and lead epidemiologist. There was also information about the Imaging project, where key persons are Dr. Walter Grassi and Dr. Emilio Filippucci. The project website can be found at http://www.irheum.eu/

The chairperson also highlighted the different educational activities of the committee, including a broad presence at EULAR 2012 sessions with imaging related topics, as well as a strong focus on US courses - including a "teach the teacher"-session before EULAR. In addition, several new proposals were discussed, especially regarding the possibility of defining criteria for establishing “EULAR Centers of Excellence for Imaging”. The committee will continue to work on this project.
The selection of presentations for this newsletter is totally personal, limited and consecutively very incomplete. The edition of this newsletter has no type of financial support.

http://emeunet.eular.org
emeunet@eular.org