

EMEUNNEWS



ACR Highlight Topics

Rheumatoid Arthritis
Ankylosing Spondylitis
SLE

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THE NEWSLETTER OF

EMEUNET

THE EMERGING EULAR NETWORK

ACR Highlight Topics

Vasculitis
Imaging
Basic Science

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UPCOMING EVENTS

- » 4th EULAR/EUSTAR Course on Scleroderma
January 27-30, 2011
- » 4th Course on Musculoskeletal Sonoanatomy
February 17-19, 2011
- » EWRR 2011
March 3-6, 2011
- » WIRM 2011
World Immune Regulation Meeting V - DAVOS
March 24-27, 2011
- » Keystone Symposia
<http://www.keystone-symposia.org/default.cfm>
- » 8th European Lupus Meeting, Porto
April 6-9, 2011

EMEUNET EVENTS

Please watch out for an EMEUNET meeting around EULAR 2011 and for EMEUNET activities during the EULAR congress. People interested will be welcome to attend. Details will soon be posted on our website.

LINKS OF INTEREST

- » EMEUNET Website
www.eular.org/emeunet.cfm
- » EULAR Online Course on Rheumatic Diseases
www.eular-online-course.org
- » EULAR Online Course on Connective Tissue Diseases
www.eular-ctd-online-course.org

Layout / Impressum

Hans Ulrich Scherer
Leiden University,
The Netherlands

Highlights from ACR 2010

In this edition of EMEUNNEWS we present a “Best Of” this year’s ACR: We compiled what we found to be the most interesting presentations on rheumatoid arthritis, ankylosing spondylitis, systemic lupus erythematosus, vasculitis, imaging and basic science for you to review.

Highlights in

RHEUMATOID ARTHRITIS I

Daniel Aletaha, Maya Buch, Isabel Castrejon, Jackie Nam

New RA remission criteria for clinical trials, as formulated by a joint ACR/EULAR/OMERACT initiative, were presented by Drs. Boers, Felson and Smolen: At any timepoint a patient must satisfy all of the following: TJC, SJC, CRP (mg/dL) and patient global health all 1 or have an SDAI 3.3. In clinical practice, a variant without serological inflammation markers may be used, omitting CRP and using the CDAI cutpoint for remission: 2.8. This approach is substantiated by new analyses of data from the ASPIRE, ERA, PREMIER, and TEMPO-trials, showing that clinical rather

than serologic measures of inflammation determine radiographic progression (AB 2258, Aletaha et al.)

Early Rheumatoid Arthritis (ERA)

Wallin et al. reported that after good initial response to MTX monotherapy, excellent clinical outcomes were observed at follow-up, but radiological progression was not completely prevented (AB 1393). Most patients responding to MTX in the initial 4 months (during the pre-randomization phase of the SWEFOT trial) stayed on MTX over a 2-year course, and showed very good control of disease activity, but they continued to have at least little radiographic progression. The authors conclude that even if early response to MTX is a good predictor for continued disease sup-

pression, close monitoring and especially the evaluation of joint damage progression is crucial. In the IMPROVED study on induction therapy with MTX and prednisone (De Boer et al., AB 1396), patients with RA or undifferentiated arthritis (UA) had comparable clinical and functional outcomes after initial treatment with combined MTX and glucocorticoids (60mg/day, tapered in 7 weeks). When analyzing predictors of remission, ACPA positivity was afflicted with a 3-fold increased likelihood of achieving remission in UA-, but not in RA patients. These findings indicate that ACPA negative UA patients are at higher risk of suboptimal outcome and that the treatment approach to ACPA negative UA still needs to be optimized. Two-year results from the TEAR trial (AB 1368, Moreland et al.) showed

that in aggressive ERA, radiographic outcomes did not differ significantly between initial combination of MTX+ETA, or MTX+SSZ+HCQ, and a step-up from MTX to respective combination therapies. In updated results of DAS-steered treatment in the BeSt study, presented by Dirven et al. (AB 334), all four treatment arms led to similar clinical and radiological outcomes after 7 years, but patients treated with IFX+MTX had better functional results, as well as the lowest drop-out rates and the highest current use of IFX. These data emphasize that a disease-activity-steered therapy leads to stable outcomes also in the long-term perspective, regardless of the therapeutic sequence. Sub-analyses of the BeSt trial, reported by vd. Broek et al. (AB 663) suggested that ACPA status might be an import-

ant factor in treatment decisions. When comparing ACPA positive vs. negative patients, treatment response, as well as the chance of remission, was similar, but persistent drug-free remission was less frequent and rates of significant radiographic progression higher in ACPA positive patients. Connell et al. reported results of another emerging molecule for RA treatment, applied in an ERA population: In their presentation of an open label RCT-extension, the authors found tasocitinib to be effective and tolerated when administered either as long-term monotherapy or on background MTX (AB 2171). With ACR20 response rates at month 24 being 81.8% and 77.8% for MTX and non-MTX patients, respectively, the authors concluded that tasocitinib demonstrated sustained efficacy.

Welcome to our new EMEUNET members

Since our first EMEUNET Newsletter in August 2010, many young people involved in European Rheumatology have expressed interest in EMEUNET and its activities. Here, we would like to welcome them to the growing EMEUNET community:

Alexandra Tuczai - Hungary; Christian Dejaco - Austria; Umut Kalyoncu - Turkey; Concepcion Castillo-Gallego - Spain; Adriana Maria Kakehasi - Brazil; Walter Alberto Si-fuentes Giraldo - Spain; Alejandra Begazo Cruz - Spain; Alessandra Vacca - Italy; Alessia Alunno - Italy; Ana Maria Gherge -

Romania; Anca Emanuela Musetescu - Romania; Anna MOLTO - Spain; Anna Södergren - Sweden; Bimba Franziska Hoyer - Germany; Carlos Montilla - Spain; Ancuta Codrina - Romania; Cristina Pamfil - Romania; David Spoerl - Switzerland; Diane van der Woude - The Netherlands; Elena

Bartoloni Bocci - Italy; Elien Mahler; Figen Yargucu Zihni - Turkey; Francesca Nacci - Italy; Inmaculada de la Torre Ortega - Spain; Juan Antonio Martinez Lopez - Spain; Lisa van Baarsen - The Netherlands; Mariana Peixoto G. U. e Silva de Souza - Brazil; Michaela Köhm - Germany; Nata-

lia Palmou Fontana - Spain; Omer Karadag - Turkey; Rogier Thurlings - The Netherlands; Wietske Kievit - The Netherlands; Sheraz Butt - Denmark; Borbala Pazar - Switzerland

Spread the word, folks!

Highlights in VASCULITIS

Gulen Hatemi RTX is effective, but not superior to iv. CYP. Jones et al. (AB 678) presented outcomes of a protocolised RTX regimen (1g x 2 followed by 1g x 1 every 6 months for 2 years) when compared to non-protocolised use (1g x 2 or 375mg/m² x 4), repeated only if relapses occurred, in refractory ANCA associated vasculitis patients. Relapse rates at the end of 2 years were 22% in protocolised and 71% in non-protocolised use (p<0.001), serious infection rates were similar. The authors concluded that protocolised treatment is safe and effective in refractory ANCA associated vasculitis. An observational study of RTX with conventional treatment in mixed cryoglobulinemia (De Vita et al., AB 2201) showed that average survival time on RTX was 529.1±40.5 days, compared to 76.9±24.2 days on conventional treatment (p<0.0001). The use of RTX in ANCA associated vasculitis as first-line induction therapy vs. only in certain situations - such as CYP-contraindication or major fertility concerns, was also discussed controversially in the vasculitis group meeting prior to the conference.

Highlights in SYSTEMIC LUPUS ERYTHEMATOSUS (SLE)

Monika Schoels that Aspirin response is impaired in SLE patients. The authors measured serum concentrations of TxB2 in 34 SLE patients and 36 sex and age-matched controls and showed that aspirin resistance was significantly higher in SLE patients. Aspirin resistant patients were also more likely to have diabetes, hypertension, a history of smoking, and higher BMI (AB 2123). In a small study with 12 months follow-up, Ezeonyeji et al. (AB 1153) described induction therapy with rituximab and azathioprine in newly diagnosed SLE to be a safe, effective, and steroid sparing regimen. Several presentations (AB 1146, 1454, 1456, 1848, 1172) reported the latest results of the BLISS-52 and BLISS-76 studies on belimumab (BEL), a BlyS-specific inhibitor: Stohl et al. showed that BEL significantly reduced autoantibodies, normalized low complement and reduced selected B-cell populations in seropositive SLE. Two abstracts (Furie et al. and Manzi et al.) outlined clinical efficacy data at week 52, reporting significantly greater response rates vs. placebo, and significant improvement in central nervous system, vascular, musculoskeletal, immunologic and dermal domains of SLEDAI. Also, BEL improved fatigue and SF-36 physical & mental scores (Strand et al.). Safety results showed comparable rates of serious and severe infections in BEL and placebo. The rate of malignancy, excluding non-melanoma skin cancers, was not elevated (Wallace et al.). Two studies tackled under-treatment in SLE: Hersh et al. (AB 484) described underuse of HCQ as documented by National Ambulatory and National Hospital Ambulatory Medical Care Surveys that was particularly evident in patients who are not regularly seen by a rheumatologist. Broder and coll. (AB 1179) suggested that in patients with end-stage-renal disease on dialysis active disease may often be unrecognized and undertreated. In patients that were seen frequently by their rheumatologist, mortality rates were significantly lower. Also, patients treated with prednisone alone had higher mortality rates than those who received DMARDs (AZA, HCQ, or MMF).

Highlights in IMAGING

Peter Mandl found strong and significant correlations between MRI and radiographic scores at baseline, whereas correlations between changes in radiographic scores and changes in MRI synovitis, bone edema, and bone erosion scores during follow-up were inconsistent and weak. Østergaard et al. (AB 1369) reported on the development and validation of an MRI joint space narrowing score: This system showed good intra- and inter-reader agreements and may, after further validation in longitudinal data sets, improve the usefulness of MRI in RA trials by allowing the quantification of cartilage damage. Schmidt et al. investigated the utility of diagnostic ultrasonography (US) in RA patients and the association with clinical and radiographic outcomes (AB 1114): In patients from the GO-BEFORE (MTX-naive) and GO-FORWARD (MTX-inadequate responder) trials, the authors measured structural damage by RAMRIS (MRI) and the vdH-Sharp score (radiography). They thus indicating the potential inclusion of US into PMR classification criteria. Bandinelli et al. presented a study that highlights the significance of performing thorough US and XR investigations in early PsA (AB 1962): The authors describe enthesal and synovial US and sacroiliac XR modifications to be present early in a high percentage of patients. Also, they investigated correlations of entheses with Glasgow Ultrasound Enthesitis Scoring System (GUESS) and Power Doppler signal (PD, a semiquantitative system), for peripheral joints with presence/absence of PD, and for sacroiliac joints with the New York score (NYS): GUESS and PD of entheses correlated with the presence of lower limb psoriasis but not with PASI, PD signal of entheses correlated with ESR. GUESS was higher in patients positive for the CW6 haplotype. Synovitis and sacroiliitis did not correlate with familiarity, psoriasis, ESR/CRP, or HLA.

Highlights in ANKYLOSING SPONDYLITIS

Pedro Machado frequently in spine-vertebral units and in sacroiliac joint-quadrants with active lesions at baseline and subsequent resolution, compared with sites without inflammation or with persistent inflammation. The AS Disease Activity Score (ASDAS) has now established clinically relevant cut-off values for disease activity states and improvement scores; these cut-offs were shown to have external validity and a very good performance compared to existing criteria (Machado et al., AB 1922, van der Heijde et al., AB 518 & 1927, Baraliakos et al., AB 526). Two interesting studies focused on the relationship between inflammation and fat lesions: Chiowchanwisawakit et al. (AB 667) reported that new vertebral corners (VC) fat lesions occur more frequently at sites of prior inflammation, especially after inflammation has resolved following institution of TNFi, while existing VC fat lesions are more likely to resolve with TNFi. Song et al. (AB 669) showed that new fat infiltration occurs more

Highlights in RHEUMATOID ARTHRITIS II

Daniel Aletaha, Maya Buch, Isabel Castrejón, Jackie Nam

Tumor Necrosis Factor Inhibitors (TNFi)

Three interesting abstracts (AB 421, 1381, 640) highlighted risks and benefits of TNFi: Galloway et al. investigated RA patients included in the British Society for Rheumatology Biologics Register and found that varicella zoster virus infections are increased in patients receiving TNFi. The adjusted hazard ratio for herpes zoster was 2.2. A similar pattern of risk was seen for each anti-TNF therapy (ADA, ETA, or IFX), with no statistical difference between ETA and the monoclonal antibodies. Data

on TNFi therapy during elective orthopedic and hand surgery revealed that the overall risk for surgical site infections (SSI) in patients on ADA, ETA or IFX during a follow-up of 2 years was not raised depending on whether or not TNFi therapy was continued during and after surgery. Alas, in sub-analyses, patients undergoing foot surgery did have higher SSI if TNFi was continued (Pettersson et al.). Chou et al. presented results demonstrating that TNF may be an important component in the pathogenesis of Alzheimer's dementia. The authors investigated >40,000 RA patients with 7 years follow-up and found that TNFi reduces the incidence of Alzheimer's disease.

After TNFi failure

In a meta-regression analysis, Benedict et al. assessed the comparative effectiveness of biologic therapies in RA (AB 2266) by estimating the probability of clinical response for abatacept, adalimumab, anakinra, etanercept, golimumab, infliximab, rituximab, and tocilizumab, all in combination with MTX. The authors conclude that for patients failing their first TNFi, a second agent of this group should also be considered an appropriate treatment option before switching to a non-TNF biologic therapy. Roll et al. investigated change in peripheral memory B-cell subsets of RA patients receiving monthly tocilizumab (AB 745): After immunophenotyping B-

cells of 16 RA patients and 21 healthy controls, they found that post TCZ, both memory cell subsets IgA and IgG were significantly reduced at week 24 compared to baseline. Also, there was a significant reduction in IgA expressing B-cells at wk. 12. While IL-6 is known to induce B-cell differentiation, this data suggests TCZ may exert some of its action by B-cell reduction and hence reduce hyperactivity. Ferracioli et al. (AB 1098) presented data to identify possible biomarker-predictors for response to B-cell depletion in seropositive RA patients: EULAR good response to RTX after 6 months was closely correlated with: baseline lymphocyte count<1875/uL, RF-IgG levels>52.1 IU/ml, plas-

ma BAFF levels<1011 pg/ml, and the absence of current steroid therapy. Raterman et al. showed that rituximab alters the HDL particle from a pro-inflammatory into an anti-inflammatory property in good responding RA patients (AB 332): the authors observed changes in HDL composition from baseline to 6 months in responders and non-responders to RTX therapy. Their results demonstrate that in addition to quantitative change in lipid profile with inflammatory reduction, HDL composition becomes less inflammatory with a less atherogenic phenotype.

Preclinical RA

In patients who donated

blood prior to onset of clinical RA, vd. Stadt et al. investigated the development of the ACPA repertoire (AB 1091). They tested patterns of auto-antigen response for reactivity to 5 distinct citrullinated peptides (2 fibrinogen, 1 vimentin, 1 -enolase, 1 cyclic citrullinated peptide). ACPA epitope spreading preceded clinical disease by several years with the number of peptides and median antibody titers increasing over time before disease onset.

Highlights in BASIC SCIENCE

Caroline Ospelt

Akhtar et al. gave a good example on how microRNAs fine-tune the expression of effector proteins in inflammation and open a novel treatment possibility by modulating miR expression in inflammatory disease: MicroRNA-199a* mediated regulation of cyclooxygenase-2 (COX-2) expression in human OA chondrocytes (AB 633): The authors investigated in vitro assays with cultured healthy and OA chondrocytes, and the regulation of COX expression after IL-1 stimulation by microRNAs in chondrocytes. They found that levels of miR-199a* are decreased in OA cartilage vs. healthy cartilage. In vitro, overexpression of miR-199a* inhibits IL-1 induced expression of COX-2. Wang et al. found that down-regulation of microRNA-152 induces aberrant DNA methylation in scleroderma endothelial cells by targeting DNA methyltransferase 1 (AB 1352). Looking at the expression of microRNAs in microvas-

cular endothelial cells (MVEC) and their influence on DNA methylation in healthy and scleroderma (SSc) MVECs, they discovered that transfection of SSc microRNA pool into healthy MVECs induced a down-regulation of the DNA methyltransferase 1 (DNMT1). Particularly, levels of miR-152 are down-regulated in SSc MVECs, leading to an increase of DNMT1. Sheleff et al. presented results on citrullination of extracellular matrix proteins that inhibits synovial fibroblast invasion and migration (AB 1421). In contrast to many studies analyzing antibodies against citrullinated proteins in RA, this study looked at the physiological function of citrullination in inflammation, suggesting that extracellular matrix proteins might be citrullinated to protect the cartilage from invasion by synovial fibroblasts. In human synovial fibroblasts from RA and OA patients, synovial fibroblast invasion into Matrigel coated with untreated or citrullinated fibronectin was investigated:

The authors found that citrullination blocked adhesion, migration and invasion of synovial fibroblasts into Matrigel. Furthermore, citrullination inhibited phosphorylation of FAK and paxillin. Willemze et al. (AB 2114) investigated gene-environment interaction between HLA-SE and smoking and found the association of autoantibodies against citrullinated fibrinogen, vimentin, enolase and myelin basic protein with HLA-SE status and smoking to play an important role in shaping the reactivity of the ACPA response to several citrullinated autoantigens. The authors corroborate the strong association between smoking and ACPA positive disease and show that this connection is not based on reactions to a specific citrullinated antigen, but extends to all measured citrullinated antigens.

WHO WE ARE

Structure & Organization

EMEUNET STEERING GROUP

Maya Buch (UK), Laure Gossec (F), Daniel Aletaha (A)

The steering group (the current trio comprising the founders of EMEUNET) assumes overall responsibility for the running of EMEUNET. Subgroups of the working group (see right side) update the steering group on progress/activities when appropriate. Decisions on including new members to the working group are undertaken by the steering group.

EMEUNET WORKING GROUP

This group undertakes the organisational role to facilitate the wider aims of EMEUNET and to represent the EMEUNET community. A particular focus will be addressing young European rheumatologist's issues. The working group members should therefore provide good regional representation, with a maximum of 2 persons from any one country; although each 44 member countries need not be specifically represented. The group currently comprises 27 members from 17 countries (see website). A maximum of 35 members has been agreed upon.

EMEUNET NETWORK / COMMUNITY

This is the fundamental basis of EMEUNET – i.e. the development of a pan-European/International network of young rheumatologists and rheumatology-based researchers. Membership of EMEUNET provides access to regular newsletters, opportunities and activities geared towards the young rheumatologist/rheumatology researcher. Any interested persons may complete the contact form (available on the website) and submit to emeunet@eular.org.

Abbreviations

AB abstract, ABA abatacept, ADA adalimumab, Ana anakinra, AZA azathioprine, BMI body mass index, CDAI clinical disease activity index, CRP C-reactive protein, CYP cyclophosphamide, ETA etanercept, GOL goli-

mumab, HCQ Hydroxychloroquine, IFX infliximab, MMF Mycophenolate Mofetil, MTX methotrexate, OA osteoarthritis, PMR polymyalgia rheumatic, PsA psoriatic arthritis, RTX rituximab, SDAI simplified disease activity index, SJC swollen joint count, TCZ tocilizumab, TJC

tender joint count, TNFi tumor necrosis factor inhibitor, US ultrasound, vdH-S van der Heijde modified Sharp score