A. Pathophysiologie

Give and Take: Evidence for Transfer of Mitochondria via Nanotubes in Fibroblast-Like Synoviocytes 01

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Background Fibroblast-like synoviocytes (FLS) are primarily responsible for the formation of the synovium. Its multicellularity requires cell-to-cell communication as well as the homotypic exchange of materials between cells to confer specialized functions critical to joint homeostasis. Using a 3D model of the synovium, we analyzed FLS capacity for exchange of cytoplasmic content, with special interest in the cell-to-cell transfer of mitochondria via nanotubes.

Methods Human FLS were prepared from synovial tissues obtained as discarded specimens following joint arthroplasty. Cells were cultured in spherical matrigel micromasses with an average size of 2 mm Ø. Data was acquired by confocal live cell imaging. Analysis of the resulting 4D movies was done with Imaris® software.

Results To examine the general possibility for intercellular cytoplasmatic transfer, we labelled 50 % of FLS with red cell tracker dye and loaded the other 50 % with green non-degradable microspheres. Additionally, we were able to capture evidence that FLS in-spheres. Furthermore, we repeated similar experiments with labelled mitochondria. We found that the transfer rate for these organelles is similar to the one for microspheres. Moreover, we observed intracellular mitochondrial transfer, with special interest in the transfer of mitochondria.

Conclusions Our experiments suggest transfer of cytoplasmic cargo, including particles as large as mitochondria, between FLS. Organelle transfer between cells along nanotube connections seems to be an important feature for concerted cellular communication within the synovial tissue. It begs the question, if cells can still be seen as individuals, or if their networking is so intertwined that individuality can rather be found on the level of the tissue. However, this cellular behaviour may also be a mechanism for the spreading of disease. Further studies will demonstrate the significance of directed cargo exchange for cellular cooperation and the function of the normal as well as the diseased synovium.

Premature Senescence of Naïve T-Cells in Sjögren's Syndrome and Systemic Lupus Erythematosus 02

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Aim To study the possible occurrence of early thymic involution and premature senescence of naïve CD4+ T-cells in patients with Sjögren’s syndrome (SjS) and systemic lupus erythematosus (SLE).

Methods Prospective, cross-sectional study on 16 SjS patients (median age 62.7 [31.9–75.9], 65.4 % female), 9 SLE patients (40.0 [34.1–54.3], 77.8 %) and 50 healthy controls (HCs). HCs were split into two age-matched control groups (15 HC assigned to both control groups): 26 HCSjS (54.5 [36.3–71.4], 93.8 %; p = 0.170) and 39 HCSLE (38.3 [23.3–54.8], 69.2 %; p = 0.296). Prevalence of memory (CD45RO+) and activated (intracellular Ki67+) CD4+ T-cells was assessed by flow cytometry according to standard surface and intracellular staining protocols. Naïve (CD45RA+) CD4+ T-cells were isolated by MACS technology. Telomere length and T-cell receptor excision circles (TREC) were measured by real-time PCR. Telomere length was chosen as parameter for cellular senescence and TRECs for the evaluation of thymic function. Telomerase activity was analyzed according to the Telomeric Repeat Amplification Protocols (TRAP).

Results A decline in thymic output as indicated by the number of TREC in naïve CD4+ T-cells was observed in SjS patients compared to HCSjS (2 [10.45] vs 132 [0.15,544], p = 0.000). Similar results were observed for the comparison of SLE and HCSLE (93 [7–1477] vs 132 (0–15544), p = 0.031).

The prevalences of memory CD4+ T-cells was increased in SjS patients compared to HCSjS (8.57 % of total lymphocytes [2.77–12.78] vs 5.81 % [0.14–14.75], p = 0.013) while no difference was found between SLE patients and HCSLE (4.68 % [0.85–13.36] vs 4.07 % [0.02–11.91], p = 0.321). The number of activated Ki67+ CD4+ + cells was low in all groups.

To test if the reduction in thymic output leads to a higher need for peripheral proliferation we performed telomere length as well as telomerase activity analysis. We observed significantly impaired telomerase activity and Telomerase activity analysis. We observed significantly impaired telomerase activity in both, SjS (1.37 [–0.02–92.05]) and SLE patients (0.50 [–12.13–8.54]) compared to their respective control groups (HCSjS 18.33 [–2.98–60.76], p = 0.001; HCSLE 5.21 [–2.98–60.76], p = 0.003).

Telomere length was not different in either of the disease-groups compared to HCs (SLE 6.43 [5.47–6.56] vs HCSLE 6.30 [5.32–8.87], p = 0.361), apart from a slight trend toward shorter telomeres in the SjS cohort (6.00 [5.40–6.60] vs HCSjS 6.28 [5.32–8.67], p = 0.104).

Summary/Conclusion These data indicate a premature decline in thymic output as well as impaired enzymatic function of telomerase in naïve CD4+ T-cells of SjS and SLE patients.

MicroRNA-146a Controls Local Bone Destruction by Regulating Fibroblast-Induced Osteoclastogenesis in Inflammatory Arthritis 03

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Aim MicroRNA (MiR-) 146a plays an important role in the regulation of the innate immune response and has been shown to suppress cancer development in myeloid cells. Although in late stages of arthritis elevated expression of miR-146a in synovial tissue of rheumatoid arthritis patients was detected, the level of this miRNA was found to be down regulated in early disease, but its role in the development of inflammatory arthritis is still elusive. The aim of this study was to clarify the function of miR-146a in arthritis.
Methods To induce arthritis we used the chronic inflammatory hTNFtg disease model, therefore we crossed miR-146a-deficient into hTNFtg mice. Disease severity was assessed clinically and histologically. Blood of arthritis animals was analyzed by flow cytometry. Serum cytokine levels were measured by Elisa. Synovial fibroblasts were isolated from metatarsal bones. Proliferation of fibroblasts was analyzed histologically and by 3[H]thymidine incorporation. RNA expression levels were measured by qPCR.

Results When we crossed miR-146a−/− into hTNFtg mice, histological examination revealed a significant increase in synovial inflammation and even more striking than a twofold increase in local bone destruction, due to increased generation of osteoclasts in the tarsal joints in miR-146a−/− hTNFtg mice compared to hTNFtg mice. Interestingly, systemic bone loss was comparable in hTNFtg compared to miR-146a−/− hTNFtg mice, suggesting an important local role of miR-146a. Indeed, we detected increased levels of IL-1β, TRAF6, a major target of miR-146a, and RANKL, in addition the expression level of OPG was decreased locally in the paws of miR-146a−/− hTNFtg compared to hTNFtg mice. By performing bone marrow transplants we could indeed show a pivotal role for miR-146a in mesenchymal cells in controlling local osteoclast generation and bone destruction. Analysis of important mesenchymal cells in arthritis, the synovial fibroblasts exhibited enhanced proliferation if miR-146a is missing, in vitro and in vivo. Moreover stimulation of these cells with IL-1β, a prominent cytokine in arthritis which was also shown to be negatively regulated by miR-146a, led to increased expression of RANKL and TRAF6 in miR-146a-deficient synovial fibroblasts.

Summary/Conclusion These data demonstrate an important mitigating role of the miR-146a in inflammatory arthritis, most importantly in local bone destruction, by controlling mesenchymal expression of osteoclastogenic factors. This shows an important anti-inflammatory role of miR-146a, which might possibly be exploited for therapeutic purposes.

Finger Joints Are Not Little Knees – A Gene Expression Study on Cultured Chondrocytes from Pip and Knee Joints 04


Purpose Osteoarthritis (OA) of the hand is a common disease resulting in pain and impaired function. The pathogenesis of hand OA (HOA) is elusive and models to study it have not been described. Chondrocyte culture has been essential to understand cartilage degeneration, which is a hallmark of OA. We investigated the feasibility of human chondrocyte culture derived from proximal interphalangeal (PIP) finger joints.

Methods Hyaline cartilage of the proximal interphalangeal (PIP) joint was obtained from 31 cadavers using two different protocols. Cultured chondrocytes were monitored for contamination, viability, and expression of chondrocyte-specific genes. Chondrocytes derived from knee joints of the cadavers and patients undergoing surgery for total knee replacement were cultured under identical conditions. Gene expression comparing chondrocytes from PIP and knee joints was carried out using Affymetrix Genechip Human 2.0 ST arrays. The resulting differentially expressed genes were validated by real-time PCR and immunohistochemistry.

Results Chondrocytes harvested up to 236 hours after death of the donors were viable. Compared to chondrocytes of the knee chondrocytes derived from PIP joints exhibited a specific gene expression pattern. Genes involved in developmental processes including the WNT pathway were differentially expressed. Real-time PCR and immunohistochemistry confirmed these results.

Conclusions These findings suggest that our knowledge on chondrocyte biology derived mainly from knee and hip joints may not apply to chondrocytes of the PIP joints and some of the distinctive features of HOA may be caused by the specific properties of PIP chondrocytes. Chondrocyte culture of PIP cartilage is a novel tool to study cartilage degeneration in HOA.
Methods Mice with a T-cell-specific deletion of HDAC1 (HDAC1 cKO) were generated by using the CD4Cre/LoxP system. At week 8 of age arthritis was induced in wild-type (WT) and HDAC1 cKO mice by immunizing with chicken collagen II (CII) emulsified in complete Freund’s adjuvant. After 21 days mice received a booster injection of CII. Two times a week the animals were scored for paw swelling and grip strength. Anti-CII antibody levels were determined by ELISA. Various cell subsets, including Th cells, where detected in the blood, the spleen and the draining lymph node by FACS analysis. After 10 weeks mice were sacrificed and paraffin sections of the affected joints were analyzed for histomorphologic signs of inflammation, cartilage and bone destruction.

Results Hundred percent of the animals developed serum anti-CII antibodies (IgM and IgG) whereby the antibody levels were similar between the HDAC1 cKO and the WT mice. Furthermore, no differences in the production of pathogenic IgG2c antibody were observed. Enhanced percentages of Th1 and Th7 cells among HDAC1-null CD4+ T-cells were detected after immunization in the HDAC1 cKO mice. Nonetheless and unexpectedly, these mice did not develop any signs of disease at the clinical level while WT mice developed pronounced paw swelling and loss of grip strength. In accordance with the clinical data, histological analysis revealed no signs of inflammation, no bone erosion and no appearance of osteoclasts in the joints of HDAC1 cKO mice. Since there were no HDAC1 cKO CD4+ T-cells in the joints, this might suggest an impaired migratory capacity of CD4+ T-cells in these mice.

Conclusion Our data show the importance of HDAC1 as a key immune regulator in the pathogenesis of T-cell-driven collagen-induced arthritis. Therefore it might be considered as an interesting novel therapeutic target in RA.

The Impact of Rituximab on Leukocyte Subsets in Patients with Rheumatoid Arthritis (RA) 07

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Objective To use in vivo multimodal [18F]FDG PET-CT imaging for the assessment and monitoring of systemic inflammatory processes and its colocalized bone destructions before and after TNF blockade in human tumour necrosis factor transgenic (hTNFtg) mice, an established mouse model of chronic inflammatory, erosive polyarthritis.

Methods Eight-week-old hTNFtg mice were treated with anti-TNF antibodies (Infliximab, i.p., 3x times per week, 10 mg/kg body weight) for 4 weeks. Before and after the treatment period isofluran-anesthetized hTNFtg mice and their wt littermates were used for [18F]FDG PET-CT scans using an Inveon small animal PET/CT/SPECT multimodality system (Siemens Medical Solutions). Mice received [18F] FDG (~25 MBq) by intra-orbital injections for static PET scans (45 min post injection) followed by whole-body and high resolution leg CT scans (800 kV, 500 mA, 800 ms, 360 projections, FOV whole-body: 10 cm or legs: 4 cm, Feldkamp, Ramp filter). PET reconstructions were conducted with OSEM3D/MAP, FBP algorithm using the Inveon Acquisition Workplace software. Quantitative [18F]FDG standard uptake values (SUV; radioactivity concentration in VOI MBq/l per injected dose [MBq]/weight of the animal [g]) were calculated using PMOD software. Joints were subsequently isolated, fixed in 7% formaldehyde for 24h and stored in 70% ethanol for ex vivo high resolution μCT imaging (Scanco μCT 35, energy: 55 kVp; 145 µA, 8 W; resolution µCT imaging (Scanco μCT 35, energy: 55 kVp; 145 µA, 8 W; VO/F diameter 12.3). Synovial inflammation, bone and cartilage degradation were assessed in hematoxylin-eosin (H&E), tartrate-resistant acid phosphatase (TRAP) and toluidine-blue (TB) stained paraffin-embedded joint sections.

Resolution of Systemic Inflammatory Processes and Regeneration of Inflammation-Driven Bone Damage upon TNF Blockade as Monitored by In Vivo Multimodal [18F]FDG PET-CT Imaging in Experimental Arthritis 09

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The Impact of Rituximab on Leukocyte Subsets in Patients with Rheumatoid Arthritis (RA) 08

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Objective To use in vivo multimodal [18F]FDG (fluoro-D-glucose) positron emission tomography/computed tomography (PET-CT) imaging for the assessment and monitoring of systemic inflammatory processes and its colocalized bone destructions before and after TNF blockade in human tumour necrosis factor transgenic (hTNFtg) mice, an established mouse model of chronic inflammatory, erosive polyarthritis.

Methods Eight-week-old hTNFtg mice were treated with anti-TNF antibodies (Infliximab, i.p., 3x times per week, 10 mg/kg body weight) for 4 weeks. Before and after the treatment period isofluran-anesthetized hTNFtg mice and their wt littermates were used for [18F]FDG PET-CT scans using an Inveon small animal PET/CT/SPECT multimodality system (Siemens Medical Solutions). Mice received [18F] FDG (~25 MBq) by intra-orbital injections for static PET scans (45 min post injection) followed by whole-body and high resolution leg CT scans (800 kV, 500 mA, 800 ms, 360 projections, FOV whole-body: 10 cm or legs: 4 cm, Feldkamp, Ramp filter). PET reconstructions were conducted with OSEM3D/MAP, FBP algorithm using the Inveon Acquisition Workplace software. Quantity [18F]FDG standard uptake values (SUV; radioactivity concentration in VOI MBq/l per injected dose [MBq]/weight of the animal [g]) were calculated using PMOD software. Joints were subsequently isolated, fixed in 7% formaldehyde for 24h and stored in 70% ethanol for ex vivo high resolution μCT imaging (Scanco μCT 35, energy: 55 kVp; 145 µA, 8 W; FOV/diameter 12.3). Synovial inflammation, bone and cartilage degradation were assessed in hematoxylin-eosin (H&E), tartrate-resistant acid phosphatase (TRAP) and toluidine-blue (TB) stained paraffin-embedded joint sections.
Results To explore reversibility of inflammatory, erosive arthritis upon therapeutic intervention, we investigated an anti-TNF α treatment at a progressed stage of disease in hTNFtg mice showing established clinical signs of increased paw swelling, decreased grip strength as well as progressed histopathological features such as synovitis, pannus formation, subchondral bone erosions and cartilage proteoglycan loss. Before therapeutic intervention, we observed an increased accumulation of [18F]FDG in various joints of hTNFtg mice including knees, ankles, shoulders, wrists as well as axial joints compared to wild littermates. Four weeks after anti-TNF α treatment we found a significant decrease in [18F]FDG SUVs in both small and large joints in the same individuals. Comparison of repeated in vivo CT images before and after the treatment also demonstrated reversed, intact bone architecture indicating bone regeneration in anti-TNF α-treated hTNFtg animals. In contrast, placebo-treated hTNFtg animals showed significantly increased [18F]FDG SUVs in knees and shoulders, in particular, and more constant [18F]FDG SUVs in ankle joints. Moreover, we found severe progressive bone destructions in all articular joints in placebo-treated animals as shown by repeated in vivo CTs. Therapeutic effects of TNF blockade on inflammatory, erosive arthritis were also confirmed by histological sections and ex vivo μCT analysis.

Conclusion In vivo small animal multimodal [18F]FDG PET-CT imaging provides an objective, non-invasive imaging tool for the longitudinal monitoring of (I) progressive systemic inflammatory processes and structural bone damage in various joints, which cannot be generally addressed with standard clinical measurements, and (II) reversibility of ongoing inflammatory processes and regeneration of localized bone damage during therapeutic intervention in the same animals.

In Vitro Silencing of hnRNP-A2/B1 in Synovial Fibroblasts Reveals Involvement in Regulation of Several Signal Transduction Pathways

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Background and Objectives The heterogeneous nuclear ribonucleoprotein (hnRNP) A2/B1 is involved in post-transcriptional regulation of gene expression. It has been shown to be highly upregulated in synovial tissue of patients with rheumatoid arthritis (RA). In addition, autoantibodies and T-cells directed against hnRNP α and β have been identified in RA patients. Recently, it was shown that silencing of hnRNP-A2/B1 in two animal models of RA, namely collagen-induced arthritis (CIA) and K/BxN serum transfer arthritis, led to reduction of arthritis severity [Herman et al. Arthritis Rheumatol 2015]. To further elucidate the role of hnRNP-A2/B1 in RA, we sought of analyzing the signalling pathways affected by silencing of hnRNP-A2/B1 in human fibroblast-like synoviocytes (FLS).

Materials and Methods siRNA-mediated silencing of hnRNP-A2/B1 in FLS was achieved by lipofectamine-based transfection. After three days, successful reduction of hnRNP-A2/B1 expression was analyzed by real-time quantitative polymerase chain reaction (RT-qPCR). The role of hnRNP-A2/B1 in FLS was investigated by activating cells with TNFα. Proteome Profiler Arrays were used to analyze cytokine production and phosphorylation of various signal transduction molecules. Interleukin (IL)-6 and IL-8 secretion was assayed using the enzyme-linked immunosorbent assay (ELISA).

Results Silencing of hnRNP-A2/B1 led to a reduction of phosphorylation of AKT and mammalian target of rapamycin (mTOR) in TNFα-stimulated cells and a slight reduction in phosphorylation of p70 S6 kinase, which is a downstream signalling component of mTOR. Moreover, down-regulation of hnRNP-A2/B1 led to reduced levels of phosphorylated MAPK14 (p38α), and a reduction of MSK2 phosphorylation. Analysis of supernatants revealed reduced levels of CCL5 (RANTES), CXCL10 (IP-10), CCL20 (MIP-3α) and Serpine E1, phosphorylation. Analysis of supernatants revealed reduced levels of TNF-α stimulated cells and a slight reduction in phosphorylation of AKT and mammalian target of rapamycin (mTOR).

Conclusions hnRNP-A2/B1 seems to play an important role in regulation of several signalling pathways, mainly the mTOR pathway, which is involved in translation and cell growth. Further analyses will be needed to fully understand the role of hnRNP-A2/B1 in signalling pathways operative in FLS and other inflammatory cell types involved in the pathogenesis of RA.

3D Synovial Organoid Culture Reveals Cellular Mechanisms of Tissue Formation and Inflammatory Remodelling

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Introduction The synovial membrane is a distinctly organized structure with two layers: a densely packed lining layer that sits on top of a more loosely organized sublining layer. During the course of arthritis, the synovium becomes hyperplastic and demonstrates thickening of the lining layer and cellular condensation at the sublining layer. Using a three-dimensional synovial organ culture system, we explore cellular mechanisms of synovial tissue formation and inflammatory remodelling.

Methods Fibroblast-like synoviocytes (FLS) derived from patients with rheumatoid arthritis (RA) were cultured in 3D Matrigel microcarriers. To mimic synovial inflammation, microcarriers were challenged with TNF. For histological analyses, microcarriers were embedded in paraffin, sections were stained with haematoxylin and eosin; reticular fibres were dyed using the Gomori silver staining technique. Ki67 labelling was performed to identify proliferating cells. Two-photon laser scanning microscopy was used to measure lining layer thickness during the culture period and to visualize newly formed collagenous fibres (Second Harmonic Generation [SHG]). 3D confocal micrographs were analyzed using Imaris® Bitplane software. mRNA levels for various genes expressed in FLS were determined by qPCR.

Results Synovial microcarriers demonstrated thickening of the lining layer over time. When stimulated with TNF, hyperplasia of the lining layer and cellular aggregation at the sublining layer was observed. In order to identify the origin of cells contributing to the thickening of the lining layer, proliferation studies were conducted. Intriguingly, in the early phase of the culture period, the percentage of proliferating cells in the lining layer was higher when compared to the sublining layer. This proliferative activity, however, was no longer present in the late phase, after the lining layer was established (mature phase). In the presence of TNF, an increased number of proliferating cells at the lining layer was maintained for an extended period of time, consistent with higher rates of cellular proliferation at the synovial lining in sections of RA synovial tissues when compared to OA synovial tissues. During the course of lining/sublining layer maturation, mRNA expression levels of genes of interest were measured. qPCR data indicated that MMP1, MMP3, and IL-6 are differentially expressed during the early phase (one week old) and the mature phase (four weeks old) of the culture period. By contrast, lubricin, cadherin-11, CCL20, and STAT1 gene expression did not show a significant difference.

Conclusions The three-dimensional FLS microcarriers culture reveals spontaneous formation of a tissue structure that strikingly resembles the lining/sublining architecture of the in-vivo synovial tissue. This process involves FLS proliferation as well as expression of genes that allow for tissue remodelling. In inflammatory conditions similar cellular programs are re-activated resulting in synovial lining hyperplasia and a pannus-like condensed mass of cells.

Resident Non-Classical Monocytes Are Critically Important for Tissue Destruction in Arthritis

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Introduction Bone destruction in rheumatoid arthritis is mediated by osteoclasts, which are derived from precursor cells of the myeloid lineage. Although there is much known about mature osteoclasts, the
identity of osteoclast precursor populations during arthritis is poorly understood. Blood monocytes can be subdivided in classical inflammatory monocytes (CD11b+Ly6ChighCCR2+) and non-classical resident monocytes (CD11b+Ly6C-/lowCCR2−) and especially classical monocytes have been implicated in mediating tissue damage in autoimmune immunity. 

**Methods**

HTNFTg mice were clinically scored once per week for grip strength and swelling. In addition, blood was collected every other week starting on week 4. Mice were sacrificed at week 10 - blood, spleen and bone marrow were collected for flow cytometry analysis. K/BxN arthritis was induced in wild-type mice, blood and spleen were collected 14 days after disease induction. HTNFTg/CCR2− and HTNFTg mice were analyzed histologically. Different monocyte subsets were FACS-sorted and cultured in the presence of RANKL and MCSF to induce osteoclasts. RNA sequencing of RANKL-stimulated osteoclast precursor cells was performed.

Here we show that HTNFTg mice lacking CCR2, which lack circulating classical inflammatory monocytes, show enhanced local bone erosion and osteoclast generation in chronic TNF-driven arthritis. When we correlated the number of the two monocyte subsets in blood with histological signs of joint destruction the number of inflammatory monocytes did not correlate at all with those parameters. In contrast, the number of non-classical monocytes in blood significantly correlated with the extent of tissue damage in both HTNFTg arthritis and also K/BxN serum transfer arthritis. Histological examination revealed that while all infiltrating monocytes express CD11b, only a small fraction of these cells express Ly6C, suggesting that the synovial infiltrate predominantly consists of Ly6C+/low monocytes. Upon sorting resident and from blood, we demonstrate that resident Ly6C+/low monocytes are more potent to form osteoclasts ex vivo than classical Ly6C+ high monocytes. Genome-wide transcriptome profiling revealed increased expression of genes which are required for pre-osteoclast fusion in RANKL-stimulated resident Ly6C+/low monocytes. 

**Conclusion**

Non classical resident monocytes possess particular osteoclastogenic potential and their numbers in blood correlate with histological parameters of joint destruction in two different models of inflammatory arthritis. Therefore these cells may provide a biomarker for erosive inflammatory arthritis and even a possible target for therapeutically intervention.

**B. KINDERRHEUMATOLOGIE**

**Assoziierte Autoimmunerkrankungen bei Patienten mit Juveniler Idiopathischer Arthritis**

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**Zusammenfassung/Schlussfolgerung**

In unserer Studie zeigte sich eine häufige Assoziation der JIA mit Autoimmunthyreoiditis, Zöliakie und Polyartikulärer Psoriasisarthritis. Die Prävalenz von Zöliakie, Autoimmunthyreoiditis und Polyartikulärer Psoriasisarthritis in der Allgemeinbevölkerung wurde mit 0,3%, 0,0% und 0,1% angegeben. In der Patientengruppe zeigte sich eine signifikant höhere Prävalenz von Autoimmunthyreoiditis (14,3%), Zöliakie (1,2%) und Polyartikulärer Psoriasisarthritis (2,2%) als in der Allgemeinbevölkerung. Die Prävalenz von Autoimmunthyreoiditis und Zöliakie war signifikant höher als in der Vergleichsgruppe (p = 0,001 und p = 0,005). Die Prävalenz von Polyartikulärer Psoriasisarthritis war nicht signifikant höher als in der Vergleichsgruppe (p = 0,23).

**Ergebnisse**

115 Patienten mit JIA wurden in einem Tertiärrzentrum über einen Zeitraum von 2 Jahren untersucht. Bei allen Patienten erfolgte ein Schilddrüssenscreening mit Bestimmung der Schilddrüsenfunction (bTSH, FT3, FT4) und Antikörper gegen Thyreoglobulin (TgA) und Thyreoperoxidase (TPOA), ein Zöliakiescreening mit Bestimmung der Gewebs-Transglutaminase-AK (TG) sowie die Bestimmung von Glukose in Serum und Harn. Bei Patienten mit erhöhtem bTSH, erniedrigten FT3-, FT4-Werten und/oder TPOA und/oder TgA erfolgte eine Schilddrüsensonographie. Eine subklinische Hypothyroese wurde definiert als erhöhtes bTSH > 4,0 µIU/l bei normalen FT3-, FT4-Werten. Eine manifeste Hypothyroese wurde definiert als erhöhtes bTSH bei erniedrigten FT3-, FT4-Werten und eine AIT als erhöhte TgA und TPOA bei gleichzeitig erhöhtem bTSH und/oder typischem Sonographiebefund. Bei wiederholt positiven TTG-AK erfolgte eine Dünndarmbiopsie zur histologischen Bestätigung der Verdachtsdiagnose Zöliakie. Bei erhöhten Glukose-Werten erfolgten die Bestimmung von Nüchternglukose (NGL), HbA1c, einer oralen Glukosetoleranztest (OGTT) sowie die Bestimmung von Antikörpern gegen Gluten (IgA), Inselzellen (IA-2) und Glutamat-Decarboxylase (GAD).

**Ergebnisse**

115 Patienten (w: 84, m: 31, mittleres Alter ± SD: 10,4 ± 4,0) wurden untersucht. Darunter systemische JIA: 9,6%; Polyarthritiden (PA) Rheumaaktor (RF) positiv: 3,5%; PA RF negativ: 10,4%; Oligoarthritis: 65,2%; Enthesitis-assoziierte Arthritis: 9,6%; Psoriasisarthritis: 61,0.

14 Patienten (12,2%) hatten eine subklinische Hypothyroese. Kein Patient litt an einer manifesten Hypothyroese. Bei 7 (6,1%) wurde die Diagnose AIT gestellt. Verglichen mit der Prävalenz in der pädiatrischen Normalbevölkerung (< 1 €) besteht ein über 6-fach erhöhtes Erkrankungsrisiko.

6 von 115 Patienten (5,2%) hatten CD-spezifische AK. Bei 5 (4,4%) wurde die Diagnose CD in der Dünndarmbiopsie bestätigt. Verglichen mit der Prävalenz in der Normalbevölkerung (0,3%) besteht ein 15-fach erhöhtes Erkrankungsrisiko. Bei 4 von 115 (3,5%) Patienten besteht ein T1D. Bei 2 von 115 Patienten wurde der T1D der JIA diagnostiziert. Bei den übrigen 2,7 bzw. 4,1 Jahre danach. Verglichen mit der Prävalenz in der pädiatrischen Normalbevölkerung (0,15%) bedeutet dies ein 23-fach erhöhtes Risiko, an T1D zu erkranken.

**Sichere Zusammenfassung/Schlussfolgerung**

In unserer Studie zeigte sich eine häufige Assoziation der JIA mit Autoimmunthyreoiditis, Zölik
Ultrasound Verified Inflammation and Structural Abnormalities in Patients with Hemochromatosis with and without Associated Arthropathy

C. Dejacq1, A. Stadlmayr1, V. Trimmel1, C. Dutten1, R. Husici1, E. Krones1, S. Zhandieh5, Emma Husar-Memmer5, G. Zollner3, J. Hermann3, J. Oberndorf and Vienna. HH arthropathy (HH-A) was defined as the presence of hand pain (VAS > 10 mm and/or ≥ 1 tender joint) plus ≥ 1 radiographic finding compatible with HH-A. Thirty-eight patients with hand osteoarthritis (HOA), according to ACR criteria were studied for comparison [mean age, 60.1 ± 9.8 years, 89.5 % female]. Clinical examination was performed at 68 joints, and we retrieved data on hand function, pain and overall health status (all using a VAS), morning stiffness, ferritin levels and phlebotomy. Ultrasound was conducted at 40 joints (hand joints, hips, knees, ankles) by one rheumatologist blinded to clinical data using an ESAOTE Tivisce ultrasound device. Synovial hypertrophy and/or joint effusion (SH/E), Power Doppler (PD), osteoarthropathies and erosions were subjectively graded from 0 to 3 in accordance with prior publications.

Results Twenty-six (52.0 %) HH patients were classified as HH-A. Mean age [57.1 ± 13.0 years] vs 57.6 ± 9.7 years], median disease duration [7.5 (3.2–22.8) vs 10.3 (0.8–27.6) years], median ferritin levels [83.6 (23–1060) vs 66.1 ng/ml (14–853)] as well as median duration [6.0 (0–23) vs 6.0 (0–26) years] and number of phlebotomies/year [3 (0–5) vs 2.5 (0–12)] were comparable between HH patients without arthropathy (HH-WA) and HH-A patients. Patients with HH-A and HOA had a similar number of tender [4 (0–29) vs 3 (0–40)] and swollen joints [0 (0–7) vs 0 (0–6)], and similar scores for hand function [39.5 (0–100) vs 47.0 (0–92) mm] and hand pain [3.0 (0–72) vs 23.0 (0–86) mm]. These findings were absent/low in HH-WA patients by definition. Using ultrasound, we observed ≥ 1 erosion in 10 (41.7 %) HH-WA patients, 12 (46.2 %) HH-A, and 21 (55.3) HOA patients (p > 0.2). Similarly, ≥ 1 osteophyte was observed in 23 (95.8 %), 26 (100 %) and 38 (100 %) patients, respectively (p > 0.2). median osteophyte score, however, was higher in HH-A than in HH-WA patients [19 (0–53) vs 30 (3–69), p = 0.019] and comparable between HH-A and HOA [36 (8–68)]. SH/E were observed in a high portion of HH-WA, HH-A and HOA patients [20 (83.3 %), 25 (96.2 %) and 38 (100 %), respectively] whereas PD-findings were more common in the HH-A [n = 21 (80.8 %)] and the HOA [n = 31 (81.6 %)] than in the HH-WA group [n = 12 (50.0 %), p < 0.05]. Also, SH/E scores were comparable between the three groups [HH-WA: 6.5 (0–25), HH-A 9 (0–32) and HOA 11.5 (1–30)] whereas PD-scores were higher in HH-A [2.5 (0–17)] and HOA [2 (0–17)] than in HH-WA cases [0.5 (0–9), p < 0.05]. In HH-A patients, there was a weak correlation between PD-score and hand function (0.23, p = 0.031), whereas the other clinical parameters were unrelated to ultrasound results.

Summary/Conclusion A high prevalence of ultrasound verified inflammatory and structural lesions were found in patients with hereditary hemochromatosis. Higher PD scores were observed in patients with arthropathy, and these were related to limited hand function.
Results

Summary Safety: SAEs: 7 serious adverse events (SAEs). In each of the two groups one suspected serious adverse reaction (SSAR) with relationship to a study drug was reported: ALT elevation in Arm A; Urinary tract infection in Arm B.

AEs: The most frequent adverse events were: 44 infections and infestations; 41 investigations; 24 blood and lymphatic system disorders; 20 gastrointestinal disorders. No death occurred during the entire study.

Summary Efficacy: Primary Endpoint: Change in DAS28 from week 12 (time of randomization) to week 24 was slightly positive in Arm A (n = 32) and slightly negative in Arm B (n = 33): ITT population: 0.17 ± 0.83 vs –0.16 ± 1.13; 95-% confidence interval for the difference [–0.16; 0.82]. The null hypothesis that there is no difference in DAS28 change from week 12 to week 24 between the two treatment groups could not be rejected (p = 0.19).

Secondary Endpoints: No significant differences; most of the secondary endpoints showed a minimal tendency towards better results in the placebo group.

Summary/Conclusion

Tocilizumab showed a positive effect on disease activity in mildly to moderately diseased RA patients.

The study results give no indication that the combination of tocilizumab with methotrexate induces a better outcome (measured as a change in DAS28 score within 12 treatment weeks) in comparison to tocilizumab monotherapy in patients corresponding to those in the study.

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Efficacy and Safety of Baricitinib in Patients with Active Rheumatoid Arthritis and Inadequate Response to Tumour Necrosis Factor Inhibitors: Summary Results from the 24-Week Phase 3 RA-BEACON Study

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Aim Baricitinib (BARI), an oral JAKI/JAK2 inhibitor, improved disease activity with an acceptable safety profile in the phase 3 RA-BEACON study of patients with moderate to severe active rheumatoid arthritis (RA) and inadequate response (IR) to tumour necrosis factor inhibitors (TNFIs). A summary of efficacy and safety data up to week (wk) 24 in patients with IR/intolerance to ≥ 1 TNFI is presented.

Methods 527 patients with active RA despite previous use of ≥ 1 TNFI for ≥ 3 months were randomised 1:1:1 to receive placebo (PBO) or BARI (2 or 4 mg, QD). Primary endpoint was ACR20 at wk12 (BARI 4mg vs PBO). Subgroup efficacy by prior biologic use, safety, and changes in total lymphocyte count (TLC) and natural killer (NK)-cells are reported. DAS28 and CDAI improvements at wk4 were used for predicting Low Disease Activity (LDA)/remission at wk12.

Results 57% of patients had received ≥ 2 bDMARDs (biologic disease-modifying antirheumatic drugs) and 38% ≥ 1 non-TNFIs bDMARD. ACR20 at wk12 was higher with BARI 4 mg vs PBO (55% vs 27%, p < 0.001). Improvements in ACR20/50/70 and DAS28-CRP occurred with BARI 4 mg (1 prior TNFI) at wk12/24; improvements in CDAI, SDAI, and HAQ-DI were observed at wk24. A decrease ≥ 0.6 in DAS28 and ≥ 6 in CDAI at wk4 was observed in 79% and 80% of patients on BARI 4 mg, respectively, and was associated with LDA/remission at wk12 and wk24. More treatment-emergent adverse events occurred with BARI 2 and 4 mg vs PBO (71%, 77%, 64%) including infections (44%, 40%, 31%), although severe infections occurred comparably. In patients on BARI 4 mg, no opportunistic infections were seen, two patients developed non-melanoma skin cancer, TLC changes in BARI groups were similar vs PBO at wk12 and wk24. There was an increase in T-cells, B-cells and NK-cells at wk4, followed by decreases in T-cells, NK-cells, and an increase in B-cells at wk12 and wk24 for BARI groups (all TLC changes within normal range; NK-cell decrease was not associated with increased infection).

Summary/Conclusion In RA patients, regardless of number of prior biologics used, BARI showed rapid and sustained clinical improvements at wk4 through wk24 with an acceptable safety profile. Early clinical response at wk4 might predict later LDA/remission. The Good, the Bad and the Ugly – Refractory Rheumatoid Arthritis and Inadequate Response to Tumour Necrosis Factor Inhibitors

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Aim As seen in a previous analysis, the prevalence of anemia in rheumatoid arthritis (RA) patients is decreasing due to increased awareness and early therapeutic intervention (from between 30 and 66% to around 12% in our cohort) [1]. In a study cohort which was designed to evaluate iron metabolism in chronic inflammation, we further analyzed the characteristics and underlying pathophysiology of anemia in RA patients. Therefore, we investigated the type of anemia in RA outpatients at our tertiary centre and evaluated the iron state in monocytes. We also investigated the impact of disease activity on anemia prevalence and of therapy strategies on persistence of anemia [2–4].

Methods We analyzed RA outpatients. Laboratory parameters, disease activity (CDAI, DAS28) and drug therapy were collected. 354 patients were classified based on biochemical parameters for inflammation and iron deficiency. Anemia was defined as hemoglobin < 120 mg/dl in women, and < 130 mg/dl in men. Iron deficiency anemia (IDA) was defined as ferritin < 30 μg/l and C-reactive protein (CRP) < 0.5 mg/dl; anemia of chronic disease (ACD) as ferritin > 100 μg/l and CRP > 0.5 mg/dl. Their combination (IDA/ACD) as ferritin < 100 μg/l and CRP > 0.5 mg/dl; Patients with anemia not fulfilling these criteria were defined as “other”; we also classified patients with abnormal iron state without anemia as iron-deficient (ID) without anemia (ferritin < 30 μg/l and ACD typical without anemia (ferritin > 100 plus CRP > 0.5 mg/dl). Iron parameters on monocytes were measured by polymerase chain reaction (PCR) in 88 RA patients with or without anemia. Kruskal Wallis test and Mann–Whitney test was performed to compare subgroups, Spearman-Rank Analysis was applied to analyze correlations.

Results 268 female (75.9%) and 85 (24.1%) male patients were analyzed (n = 353). In male patients 28.4% were anemic and 12.8% had an atypical iron status. In female patients the prevalence of anemia was 25.5% and 15.1% had an atypical iron state. As expected hemoglobin (Hb) levels were lower in female RA patients (p < 0.001) than
in male patients whereas ferritin and CRP-levels (p = 0.005) were significantly higher in men reflecting the higher prevalence of ACD in the male patient group (8.6 vs 3.9 %).

Comparing the PCR-results with the serological iron parameters, in ACD and ADA/ACD there was a significant correlation between transferrin receptor saturation (p = 0.01) and ferroportin mRNA expression on monocytes (p = 0.01).

There were no significant differences in treatment regimen on the prevalence or type of anemia except for corticosteroid use (p = 0.006) which was more frequent in the ACD and ADA/ACD group. Patients using corticosteroids had in nearly 50 % an abnormal iron status, patients without corticosteroids only in 25 %.

Summary/Conclusions In this study cohort with was designed to evaluate the causes of anemia and dysregulation of iron metabolism in RA-patients we could show a higher prevalence of anemia then in a previous analysis. This may be due to a selection bias; patients with anemia were more often included to the database.

The characterization of anemia in RA patients showed a different distribution among pathophysiological types (IDA 27.0 %, ACD 19.1 %, IDA/ACD 29.2 %, other 24.7 %) [5] than previously described [4]. The correlation between higher disease activity, anemia and the need of corticosteroids were shown. The association between iron parameters on monocytes, clinical and laboratory findings and treatment strategies in RA-patients has to be further investigated.

References:

**Resultate** Die Korrelationsanalyse nach Pearson ergab eine signifikante lineare Korrelation von Serum C3 (p = 0,001) mit dem PASDAS bei 36 untersuchten Patienten in einem Beobachtungszeitraum von 24 Wochen. Als korrelierende Variablen zeigten sich die globale Patientenselbsteinschätzung, die globale Arzteinschätzung, die Anzahl geschwollener Gelenke, der Psoriasis-Hautbefall, der physische Komponenten Score des SF-36, die BSG und das CRP. Die Untersuchung jedes individuellen Beobachtungszeitpunktes zeigte lediglich eine signifikante Korrelation von C3 und dem PASDAS zur Woche 12, jedoch keine zur Baseline sowie zur Woche 24 (Tab. 1).

**Zusammenfassung/Schlussfolgerung** In dieser Pilotstudie konnte ein signifikanter Zusammenhang von Serum C3 mit dem PASDAS beobachtet werden. Im Hinblick auf individuelle Variablen der Krankheitsaktivität zeigten sich die globale Patientenselbsteinschätzung, die globale Arzteinschätzung, die Anzahl geschwollener Gelenke, der Psoriasis Hautbefall, der physische Komponenten Score des SF-36, die BSG und das CRP als signifikant. Diese Resultate rechtfertigen weitere Untersuchungen, um die Verwendbarkeit und den Stellenwert des Komponent-C3-Serumspiegels in der Krankheitsaktivitätsbestimmung bei PsA-Patienten zu bestätigen.

**Die Bestimmung von Anti-Drug-Antikörper bei Patienten unter Anti-TNF-Therapie ist überflüssig**

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**Ziel** Es ist vor allem von Patienten mit rheumatoider Arthritis (RA) bekannt, dass sie Arzt und Patient in der Beurteilung der Krankheitsaktivität unterscheiden [1, 2]. Mit Daten aus dem österreichischen Biologikaregister BioReg (www.bioreg.at) wurde überprüft, wie Patienten und Ärzte bei den 3 dokumentierten Krankheitsgruppen (RA, PsA und SpA) die Krankheitsaktivität einschätzen.

**Methoden** Im Biologikaregister BioReg werden etwa im Abstand von 6 Monaten Kontrollvisiten dokumentiert. Für die vorliegende Fragestellung wurden die Daten der ersten 4 Jahre (= Einschluss, Baseline [BL] und 8 Kontrollvisiten [V]) ausgewertet. Die globale Einschätzung des Gesundheitszustandes und der Krankheitsaktivität durch Arzt (EGA) und Patient (PGA) erfolgt durch Anwendung einer VAS-Skala von 0 bis 100 mm.

**Ergebnisse** VAS (Median Werte von BL: V1; V2; V3; V4; V5) von Patienten mit RA zeigten Unterschiede zwischen PGA (30; 20; 22; 20; 20) und EGA (15; 7; 10; 10) ebenso wie jene von Patienten mit SpA (PGA 39; 30; 26; 30; 20; 20 und EGA 20; 10; 10; 10; 10) und PSA (PGA 30; 20; 12; 20; 20 und EGA 20; 10; 5; 10; 10). Medi-anwerte von Entzündungswerten (BSG in mm/1st Stunde und CRP

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**Tabelle 1: Korschbaumer A, et al. Korrelationsanalyse nach Pearson von C3 und C4 mit PASDAS und individuellen Krankheitsmanifestationen der PsA (n = 71).**

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<tr>
<th></th>
<th>Serum C3</th>
<th>Serum C4</th>
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<tr>
<td></td>
<td>p</td>
<td>r</td>
</tr>
<tr>
<td>PASDAS</td>
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<td>Schmerz (VAS)</td>
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</tr>
<tr>
<td>Evaluator Global (VAS)</td>
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<td>Schmerzhafte Gelenke (0–68)</td>
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<td>Geschwollene Gelenke (0–66)</td>
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<td>BSG</td>
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<tr>
<td>CRP</td>
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<tr>
<td>SF-36 PCS*</td>
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<td>–0,253</td>
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**Guter Therapieerfolg auf Biologika, aber Patienten und Ärzte erteilen verschieden. Daten aus dem österreichischen Biologikaregister BioReg**

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in mg/l) waren immer im Normbereich (BSG und CRP bei RA 5; 12; 14; 12; 14 und 2.0; 2.0; 2.2; 2.0; 2.0; 2.0; bei SPA: 7; 7; 7; 8; 7; 7 und 1.5; 0; 1.5; 2.0; 1.4; 1.4; 1.0; 1.0; 1.0). Zusammensetzung/Schlussfolgerung Wie für RA mehrfach beschrieben, belegen auch die Daten aus BioReg, dass nicht nur bei RA, sondern auch bei SPA und PsA Ärzte die Krankheitsaktivität niedriger einschätzen als Betroffene. Wir nehmen an, dass Ärzte sich vorwiegend auf Zeichen einer floriden Entzündung konzentrieren und weniger auf allgemeines Wohlbefinden. Diese Vermutung wird auch durch die normalen Werte von BSG und CRP unterstützt.

Literatur:

Anmerkung:
– BioReg ist ein von pharmazeutischen Unternehmen unterstützter und nicht auf Profit ausgerichteter Verein.

BioReg: Prospektives Register zur Langzeitbeobachtung der Therapie von entzündlich rheumatischen Erkrankungen mit Biologika


Ergebnisse Die Verteilung der verschriebenen Biologika ist ähnlich wie im deutschen Biologikaregister RABBIT.

Die meisten Biologika zur Behandlung der RA sind in Kombination mit MTX zugelassen und werden auch als Kombinationstherapie allgemein empfohlen. Dennoch werden in Österreich mehr als ein Drittel der RA Patienten mit einem Biologikum in Monotherapie behandelt und der Anteil der RA Patienten unter einem Biologikum in Monotherapie nimmt mit Therapiedauer zu [1].

Die Aufzeichnungen in BioReg bestätigen, dass die Behandlungen der RA mit Biologika in Österreich auch gut vertragen werden und erfolgreich sind. Ein Jahr nach Beginn einer Biologikabehandlung war bei RA Patienten, die bereits unter Biologikatherapie standen und die, die erst mit Therapiebeginn in das Register einge- schlossen wurden, keine Unterschiede in Bezug auf Krankheitsaktivität nachweisbar [2].


Literatur:
Cardiovascular Risk Factors in Individuals with Inflammatory Back Pain: A Cross-Sectional Analysis

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Aim: While there is substantial evidence that there are plenty of cardiovascular (CV) risk factors associated with several rheumatologic diseases like rheumatoid arthritis and psoriatic arthritis, there is lack of evidence concerning inflammatory back pain (IBP). The aim of this study is to identify associated CV risk factors using the national and health and nutrition examination survey (NHANES) from the US center for disease control. Aim of the present study was to analyze CV risk factors in individuals fulfilling the Berlin 8a criteria compared to the general population.

Methods: This analysis was a cross sectional analysis of 3607 males and females aged 19–50 yrs who participated at the NHANES in 2009 and 2010. 406 of these individuals fulfilled the IBP Berlin criteria 8a. Blood levels of triglycerides, cholesterol, LDL, HDL, creatinine, hemoglobin, c-reactive protein, fasting glucose, insulin, uric acid, glycohemoglobin and hemoglobin as well as smoking status, weight, waist circumference, diabetes and blood pressure were taken and underwent statistical analysis. Statistical analysis was adjusted for the complex study design. All calculations have been performed using Stata 13 IC.

Results: Participants fulfilling the Berlin 8a criteria were more frequently smokers (OR 2.59, 95-% CI 1.92–3.20, p < 0.0001). Furthermore, waist circumference (mean 99.05 cm, 95-% CI 96.55–101.54 vs mean 94.93 cm, 95-% CI 93.88–95.98, p < 0.006) and diastolic blood pressure (mean 71.30 mmHg, 95-% CI 69.13–73.46 vs mean 69.39 mmHg, 95-% CI 68.03–70.75, p < 0.04) showed significant differences in IBP. Serum cholesterol (mean 194.63 mg/dl, 95-% CI 190.03–199.23 vs mean 189.67 mg/dl, 95-% CI 187.92–191.44, p < 0.03) and CRP (mean 0.46 mg/dl, 95-% CI 0.38–0.55 vs mean 0.33 mg/dl, 95-% CI 0.30–0.37 p < 0.0002) showed also higher levels in those individuals. There was a strong correlation in using NSAIDS and suffering from IBP (OR 85.47, 95-% CI 66.77–120.22, p < 0.0001). Of interest, women were more likely to fulfill the Berlin 8a criteria.

Summary/Conclusion: IBP is associated with several cardiovascular risk factors. It seems that as with RA smoking is strongly associated with IBP. Additionally, other cardiovascular risk factors as waist circumference, high serum cholesterol or CRP are associated with IBD.

Towards Harmonized Data Collection in Rheumatoid Arthritis (RA): The EULAR Task Force for Standardising a Minimum Data Collection for RA Observational Research

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Aim: Collaborative research is compromised by heterogeneity of data collection in observational rheumatoid arthritis (RA) databases. Therefore a EULAR taskforce has been convened to develop a minimum core dataset (MCD) of data items (i.e. “what to collect”) and instruments for data collection (i.e. “how to collect”) to (1) harmonize future data collection, (2) act as a common data model to which existing databases can be mapped, (3) serve as a template for standardized data collection for RA research in routine clinical practice.

Methods: The task force comprised a study steering committee, a task force working group and a pan-European expert panel. The project involved a multi-step process: (1) a hierarchical literature review to identify data items and instruments of existing RA cohorts and registers, (2) an online survey to capture information on perceived importance of extracted items and instruments for possible inclusion, (3) two face-to-face (F2F) meetings of the working group with discussion and voting on content (items) and structure (instruments) of the MCD. The voting of the F2F meetings were confirmed and consolidated by a ratification survey and work performed by the steering group between the two F2F meetings.

Results: Published articles from 67 different European registers and cohorts were included for data extraction. The number of patients recruited in each register ranged from 130 to more than 50,000. A total of 40 different items and 125 instruments were identified in literature, 7 items felt to be missing were added by the steering group. A total of 90 experts from 28 different European countries, including patients (18%), health professionals (18%), physicians (55%) and researchers or other experts (10%) participated in the online survey. 27/47 (57%) items were regarded to be important for inclusion in a MCD by > 80% of responders. At the first F2F meeting 22/47 items were voted to be included, 24/47 to be excluded in a MCD, for 2 items no consensus was reached. Ratification survey and second F2F meeting revealed consensus to include 21/47 items and their instruments. Remaining work in the task force pertains to instruments for two items (“glucocorticoids” and “comorbidities”).

Summary/Conclusion: Based on the multistep process, a first draft of a MCD was developed which has to be tested for feasibility in clinical settings and applicability to answer important research questions.

Erste Erfahrungen mit Inflectra

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Ergebnisse: Von 20 Patienten, die Inflectra bekommen haben, zeigte sich bei 15 (75 %) eine mit der Originalsubstanz vergleichbare Wirkung. Eine Patientin erlitt bei der ersten Infusion eine allergische Reaktion, die ein sofortiges Absetzen der Infusion erforderlich machte. Eine weitere Patientin klagte nach jeder Infusion über eine ausgeprägte anhaltende Übelkeit, die erst kurz vor der nächsten Infusion nachließ, um danach wieder voll aufzulassen. Weitere 3 Patienten (15 %) zeigten nach der Umstellung eine deutlich zunehmende Krankheitsaktivität, sodass ein Zurückwechseln auf die Originalsubstanz erfolgte.

Zusammenfassung/Schlussfolgerung: Im kurzen Beobachtungszeitraum mussten 25 % der Patienten wieder vom Biosimilar auf die Originalsubstanz umgestellt werden. Ob diese ungewöhnlich hohe Ausfallsquote Zufall und dem kurzen Beobachtungszeitraum und der niedrigen Fallzahl geschuldet ist, oder auf eine tatsächliche Unterverlegkeit des Biosimilars gegenüber der Originalsubstanz zurückzuführen ist, wird sich in den nächsten Monaten zeigen.

Sonographie versus Magnetresonanz-Tomographie in der Diagnostik des primären Sjögren-Syndroms

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Ziel: In der Diagnostik des primären Sjögren-Syndroms (pSS) nimmt neben der Speicheldrüsensintigraphie und -biopsie die Bildgebung mittels Ultraschall (B-Bild und Echzzeit-Sonoelastographie,engl. RTS) und Magnetresonanz-Tomographie (MRT) der Speicheldrüsen eine zunehmende Rolle ein. Bislang gibt es noch keinen direk-
ten Vergleich der beiden Bildgebungsverfahren zur Diagnose und Be- urteilung der Funktions einschränkung bei dieser Erkrankung.


**Ergebnisse** Patienten mit pSS wiesen signifikant höhere B-Mode- (Mittelwert = 25 [2–44] vs. 9 [1–20], p < 0,001) und RTS-Scores (6,5 [2–13] vs. 4 [1–9], p < 0,001) als Sicca-Patienten auf. Gleiches galt auch für die morphologische MRT-Bewertung (6,96 vs. 2,33, p = 0,001) In einer Spearman-Rang-Korrelation wurden klinische Parameter mit den Bildgebungsverfahren in Verbindung gesetzt. Dabei zeigten sich beim Ultraschall mittels B-Bild sign. Korrelationen mit dem Saxon- test (r = −0,505, p = 0,002), ANA (r = 0,751, p < 0,0001), pos. Ro/La-Ak (r = 0,765, p < 0,0001), γ-Globulin (r = 0,571, p < 0,0001) und der MRT (r = 0,792, p < 0,0001). Auch in der MRT zeigte sich eine negati- ve Korrelation mit dem Saxon-Rating (r = −0,523, p = 0,001). Beide Bild- gebungsverfahren wiesen keinen Zusammenhang mit dem CRP auf.

**Zusammenfassung/Schlussfolgerung** Sonographie und MRT sind hinsichtlich Diagnostik vergleichbar. Bei der Funktionsbeurteilung haben beide eine negative Korrelation mit Saxon, während Patientenfragebögen keine Assoziation aufweisen.

**Literatur:**

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**The Predictive Value of IgA Rheumatoid Factor and IgA Antibodies to Cyclic Citrullinated Peptide in Rheumatoid Arthritis**

**33**

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**Aim** Autoantibodies such as rheumatoid factor (RF) and anti-citrullinated protein antibodies (ACPA) are important diagnostic mark- ers in rheumatoid arthritis (RA). These antibodies are predominant- ly of the IgM (RF) or IgG (ACPA) isotype. In previous studies IgA-RF was almost exclusively found in RF/ACPA positive patients, therefore the additional diagnostic value was considered to be low. Neverthe- less, some studies suggested a correlation between IgA-RF isotypes, and poor response to anti-TNF (TNFi) treatment. However, the prog- nostic and predictive value of single markers seems not to be strong enough to predict response to therapy in single patients. Combined screening for routine markers and additional isotypes (IgA) might improve their predictive value. This study aimed to investigate the predictive value of RF and ACPA IgA antibodies regarding response to treatment in patients with RA.

**Methods** 255 patients who had undergone at least one TNFi treat- ment were tested for the presence of IgA-RF and IgA-ACPA by ELISA (Phadia Laboratory Systems). The incidence of IgA antibodies was correlated with routine measurements of RF (nephelometry) and IgG-ACPA measured by anti-CCP assay. To define response to therapy SDAI50, ACR20 responses and SDAI relative changes were calculated.

**Results** Among the 255 patients 114 (44.7 %) were found to be IgA- RF positive: 12 of them were negative for RF by routine diagnostics and only 6 patients were double negative for both RF and ACPA. IgA-ACPA were detected in 79 (31 %) patients and almost all of them (98.7 %) had also IgG-ACPA. Patients positive for both IgA-RF and IgA-ACPA showed a significantly reduced response (p = 0.0003) to anti-TNF treatment compared to the IgA-RF+ACPA+ cohort. Pa- tients without any antibodies (seronegative) were found to have the poorest response (p < 0.0001) to TNFi. A similar result was obtained when analyzing the therapeutic response to other biologicals including rituximab, abatacept and tocilizumab.

**Discussion/Conclusion** IgA antibodies were found in approxi- mately 50 % of the patients. The additional diagnostic value of IgA antibodies was marginal but the presence of IgA antibodies seemed to have a predictive value for treatment with TNF inhibitors, which is in line with previously published data. In conclusion, additional test- ing for IgA-RF and IgA-ACPA could help in stratification of RA pa- tients and might add a predictive value regarding response to therapy with TNF inhibitors and other biologicals.

**Anti-Acetylated Peptide Antibodies and their Predictive Value in RA Patients Starting MTX Treatment**

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**Aim** Anti-acetylated-peptide antibodies (AAPA) have recently been described in rheumatoid arthritis (RA) patients and may be used as a further diagnostic marker in patients with undifferentiat- ed arthritis.

In this study we aimed to determine the prevalence of AAPA in a cohort of RA patients starting their first conventional synthetic DMARD treatment (csDMARD) and additionally evaluated the use- fulness of AAPA as potential predictors of clinical response to metho- txate (MTX) therapy.

**Methods** We measured IgG and IgA AAPA by ELISA using two acetylated peptides derived from vimentin. We tested by regression, parametric and non-parametric analyses of disease activity measures if AAPA show potency for predicting response to MTX.

**Results** IgG and/or IgA AAPA were detected in 74.5 % of the 110 RA patients who stated MTX treatment: 49 % were positive for either IgG or IgG antibodies and 25.5 % were IgA/IgG double-positive. In the AAPA-positive patients, 73.6 % were positive for IgG AAPA while 26.4 % showed IgA antibodies. Importantly, of the 36.4 % of patients negative for both RF and ACPA (double negative), 55 % were positive for IgG and/or IgA AAPA, and the remaining patients (i.e. 16 % of the total cohort) were completely seronegative (triple-negative). When comparing triple-negative patients with the AAPA-positive double- negative ones, no significant difference in baseline characteristics was found but a trend that patients with more seroreactivities showed higher composite disease activity scores. Analyzing the clinical re- response to MTX, IgG-AAPA positive double-negative patients showed a significantly greater relative SDAI change after 6 months compared to triple-negative patients [p = 0.028, median (IQR): −44.6 % (−58.5 to −28.90) vs 5.26 % (−23.9 to 55.5 %)]. In addition, there was a sig- nificantly greater relative change in CRP (p = 0.035) and erythrocyte sedimentation rate (p = 0.003) in AAPA positive double-negative pa- tients.

**Summary/Conclusion** AAPA commonly occur in RA patients. Measuring AAPA in addition to RF and ACPA reduced the preva- lence of seronegative patients by more than 50 %. These AAPA posi- tive but RF and ACPA negative patients responded significantly bet- ter to MTX. Therefore, AAPA positivity in RF and ACPA negative patients identifies a subgroup of patients with a more favourable re- sponse to MTX.
**D. Rehabilitation**

Medizinische Rehabilitation der Zukunft in Österreich 35


**Ziel** Empfehlungen für die Rehabilitationszukunft durch den Arbeitskreis (AK) für Rehabilitation der ÖGR

Mit „10 Geboten der Rehabilitation“ soll die Bedeutung der Rehabilitation bei der Bevölkerung und bei den Zuweisern hervorgehoben werden, welche Themen für einen „guten Rehabilitationserfolg 2030 in Österreich“ ein Rehabilitationsexpertenkreis als besonders erachtet. Der AK will damit erklären, was in der Zukunft für eine gute Rehabilitation erforderlich ist.

**Methoden** In einer mehrstufigen Expertenbefragung über das Internet wurden von den Mitgliedern des Arbeitskreises Rehabilitation 10 Punkte aus allen Antworten ausgearbeitet als Kriterien, wie in der Zukunft eine gute medizinische Rehabilitation in Österreich erreicht werden könnte. Die vielen Vorschläge umfassten allgemeine Empfehlungen bis zu sehr detaillierten Einzelpunkten.

**Ergebnisse** Folgende Punkte der Österreichischen Rehabilitation 2030 wurden erarbeitet:

- **Ziele**
  - Begriff und Ziele der Rehabilitation anerkannt
  - Alle Grundlagen für die medizinische Rehabilitation gegeben
  - Rehabilitation hat IC als Richtlinie
  - Anweisung, Durchführung und Nachsorge wird durch Rehabilitationstransmediziner entschieden
  - Rehabilitationsspezialist mit großer Variabilität und Flexibilität
  - Erweiterte Kooperation zwischen medizinischer, beruflicher und sozialer Rehabilitation
  - Rehabilitationsergebnisse als Grundlage der Weiterentwicklung
  - Optimalen Voraussetzungen zum Erhaltstilmanagement sind realisiert
  - „Barrierefreier“ Zugang für jeden Menschen mit Rehabilitationen
  - Die Rahmenbedingungen fördern die Patientenmotivation und -eigenverantwortlichkeit

Neben diesen 10 Punkten wurden noch weitere Zusatzüberlegungen angeführt, welche ebenfalls für die Rehabilitation der Zukunft von Bedeutung erscheinen:

- Patientensteuerungssystem
- Rehabilitationstransmanagement
- Rehabilitation für geriatrische Patienten
- Ausreichende Pflegekapazitäten
- Therapiefreiheit nach wissenschaftlicher Evidenz
- Multifachärztliche Abdeckung der Therapie
- Breite fachärztliche Begleitung
- Bestes Rehabilitationsausbildung

**Zusammenfassung/Schlussfolgerung** Der Arbeitskreis für Rehabilitation der ÖGR hat in 10 Statements Empfehlungen für die Rehabilitation der Zukunft ausgearbeitet.

**Osteoporose bei Beinamputation – eine Pilotstudie**

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**Ziel** Eine Amputation als letzter Ausweg bei akuten oder chronischen arteriellen Durchblutungsstörungen, Verletzungen oder In- fektionserkrankungen zählt zu einem der ältesten Eingriffe am Menschen. Unter Fragen stellt, dass für Patienten eine Amputation ein schwerwiegenderes Ereignis darstellt und zu grundlegenden Veränderungen in den täglichen Leben führt. In Österreich hat die Zahl an „Majoramputationen“, Amputationen oberhalb der Knöchelregion im Zeitraum 2002–2006 um 10,62 % zugenommen, was einer Steigerung von 29 auf 32 pro 100.000 Einwohner entspricht. 40–60 % aller nicht traumatischen Amputationen der unteren Extremität werden bei Diabetikern durchgeführt. Veränderungen des Ganges und der Belastung auf Bein und Prothese, eine verminderte Aktivität und weitere notwendige Adaptationsprozesse bedeuten erhöhte körperliche Belastung für die Betroffenen im Alltag.


E. Verschiedenes

Resveratrol and a Resveratrol-Salicylate Hybrid Molecule: A Comparative Study in CD4+ T-Cells 37

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Aim Aberrant T-cell responses are crucially involved in the pathogenesis of autoimmune diseases such as rheumatoid arthritis (RA) leading to chronic inflammation and organ damage. Consequently, substances modulating T-cell activation may have therapeutic benefits in inflammatory diseases. Resveratrol is a naturally occurring polyphenol mainly produced in plants. The beneficial effects of resveratrol are due to its anti-inflammatory, anti-angiogenic and anti-oxidant activities. The aim of this study was to compare the effects of resveratrol and a novel resveratrol-salicylate hybrid molecule (C10) on human CD4+ T-cells.

Methods CD4+ T-cells from healthy donors were pre-incubated with different concentrations of resveratrol or C-10 before being stimulated with anti-CD3/anti-CD28 antibodies. After 24 h and 72 h, respectively, cell culture supernatants were harvested and IL-2, IFN-γ and TNF-α levels were quantified by ELISA. Proliferation rate was measured by thymidine incorporation. In addition, the up-regulation of the early activation markers CD25, CD69, CD71 and CD98hc was analyzed and phosphorylation of ERK, AKT, S6RP and STAT5 was assessed by westernblot or flow cytometry.

Results Inhibition of IL-2, IFN-γ and TNF-α release was significantly more effective when the cells were treated with C-10. A decrease of cytokines was observed already at 6.25 µM C-10 whereas resveratrol inhibited cytokine production only at 25 µM or 50 µM significantly. Moreover, proliferation rate in CD4+ T-cells was significantly more decreased in the presence of C-10. The expression of CD25, CD69, CD71 and CD98hc was reduced to a similar degree by both compounds. Phosphorylation of ERK, Akt and S6RP was attenuated when the cells were incubated with resveratrol or C-10. For STAT5, a significantly higher inhibition by C10 in comparison to resveratrol was observed.

Summary/Conclusion Our data demonstrate that C-10 suppressed cytokine secretion and proliferation more effectively than resveratrol. Both compounds influence the phosphorylation of important signaling molecules. Thus, the resveratrol-salicylate hybrid molecule C-10 significantly amplified the effects of resveratrol in CD4+ T-cells and might be used in the future for treatment of RA and other T-cell-driven autoimmune diseases.

Detection of Finger Joint Osteophytes and Bone Erosions by Ultrasound; a Comparison to Computed Tomography 38

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Background Ultrasound (US) is an emerging technique for the examination of osteoarthritis of the hands (HOA). Bone erosions and osteophytes are hallmarks of advanced HOA. We studied the reliability of US findings in proximal interphalangeal (PIP) and distal interphalangeal (DIP) joints compared to micro computed tomography (µCT) and histology in fingers of dissecting room cadavers.

Methods We obtained 30 fingers with and without signs of nodal OA from 15 cadavers donated to the Institute of Anatomy. Written informed consent had prior been given in the lifetime of the individuals. We analyzed PIP and DIP joints using an Esaote MyLabTwice US machine with a 6–18 MHz probe and a Siemens INVEON µCT. The occurrence of erosions and osteophytes was scored for 16 defined regions of each joint (ulnar, radial, dorsal, palmar, dorso-ulnar, palmo-ulnar, dorso-radial, palmo-radial aspect of the joint region of the proximal and distal articulating bone). Thereafter, finger joints were fixed in 4% formalin and embedded in acrylic resin. Serial sections of the joints were stained with haematoxilin/eosin, safranin O, and Pappenheim’s solution. Erosions and osteophytes in the different joint regions were assessed. Differences between groups were analyzed using Wilcoxon signed-rank test. Correlations were analyzed with Spearman-Rho test.

Results In the PIP joints US detected more erosions than µCT (28 vs 19, p = 0.028). The findings of both methods correlated well (r = 0.51, p = 0.004). The number of erosions in histology correlated significantly with the findings of the µCT (r = 0.61, p = 0.047) but not with US. US and µCT detected a similar frequency of osteophytes (225 vs 248, p = 0.028) in the PIP joints. Bone erosions correlated well with each other (r = 0.47, p = 0.009). Only US correlated with histology (r = 0.76, p = 0.006). In the DIP joints US, µCT and histology did not yield correlating results. US and µCT detected a similar number of osteophytes in the DIP joints (333 vs 245, p = 0.13) and the findings of both methods correlated significantly (r = 0.46, p = 0.013). The number of osteophytes on histologic examination did not correlate with osteophytes in US or µCT (r = 0.14, p = 0.63 and r = 0.43, p = 0.13, respectively).

Conclusions US is comparable to µCT in the identification of osteophytes in PIP and DIP joints. Erosions identified by US should be interpreted with caution. Both US and µCT overestimate the frequency of erosions and osteophytes compared to histologic examination.

Systematic Literature Review of Ultrasound in Large Vessel Vasculitis for Establishing Omeract Definitions 39

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Objectives (1) To identify definitions of US lesions in LVV; (2) to evaluate the role of US in monitoring disease response; and (3) to assess the value of identified US lesions for diagnosis of LVV.

Methods A systematic literature search was conducted in PubMed, Embase and the Cochrane Library (till 23rd November 2014). Research articles enrolling at least 20 patients with suspected cranial giant cell arteritis (GCA) or large-vessel GCA (LV-GCA), Takayasu arteritis (TAK), published in English or German were selected. The study design, subjects, methods, imaging protocols and diagnostic values were evaluated, as well as the US definitions of vasculitis. The quality of the included studies was assessed by the QUADAS2 tool.

Results Of 2960 articles identified, 34 studies were included in the review for the extraction of definitions of vasculitis in US. Thirty-two reports addressed the role of US in diagnosis of cranial GCA, whereas only 6 studies evaluated US in the settings of LV-GCA. The role of US in disease monitoring was evaluated in 11 articles on cranial GCA and in 2 articles on LV-GCA. No studies assessing the role of US in TAK fulfilled the inclusion criteria. Most studies investigated the value of the “halo sign” (32 articles), whereas “compression sign”, “stenosis”, “occlusion” or “decreased vessel wall pulsation” as signs of vasculitis were addressed in 1, 22, 19, and 1 paper(s), respectively.

Conclusions US is a valuable diagnostic tool in patients with suspected GCA. In this systematic literature review we identified “halo sign”, “stenosis”, “occlusion”, “compression sign” and a “decreased vessel wall pulsation” as possible key US lesions for vasculitis. Based on these results future research on the role of US in LVV is now being performed by the OMERACT US group.
Results
The response rate was 24/25 (96%) in round 1 and 24/24 (100%) in round 2. A consensus was achieved for 9/9 Delphi statements [normal temporal and extracranial large arteries, arteriosclerosis, halo sign, stenosis, occlusion, compression sign, and vessel wall pulsation]. The experts were asked to express their level of agreement or disagreement with the proposed statements. A consensus was defined as agreement of ≥75% of participants.

Conclusions
This is the first international consensus on definitions for elementary US lesions in GCA. The next steps of the OMERACT project will be web- and patients-based exercises testing the reliability of the new definitions.

The Nuclear Factor of Activated T-Cells (NFAT) of Chondrosarcoma Cal-78 Cells Is Influenced by the Disease-Modifying Osteoarthritis Drug Diacerein through Changes in Calcium Homeostasis

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Background and Aims
Current therapies for osteoarthritis (OA) aim to preserve normal joint function, to reduce the intensity and symptoms and to restrain the progression rate of OA. It has been shown that the disease modifying osteoarthritis drug (DMOAD) diacerein reduces the severity of OA and modifies the course of the disease. The efficiency of diacerein is based on downregulating the interleukin-1β (IL-1β)-induced inflammatory pathways and by decreasing the production of metalloproteinases (MMPs), both known to be mainly responsible for cartilage destruction. Studies further revealed that diacerein antagonizes the IL-1β triggered mitogen-activated protein kinase (MAPK) signalling cascades of articular chondrocytes and stimulate cartilage repair by up-regulating the expression of the transforming growth factor (TGF-β). However, less is known of diacerein and its influence on the nuclear factor of activated T-cells (NFAT) transcription factors. It has been demonstrated that silencing NFAT1 in chondrocytes, decreased the levels of TNF-α and MMPs induced by IL-1β [1]. Due to the fact that the NFAT itself is regulated via an increase in intracellular calcium ([Ca2+]i), influencing calcium homeostasis in chondrocytes might change NFAT regulation.

The aim of our study is to investigate the modulation of intracellular calcium ([Ca2+]i) signalling in Cal-78 chondrosarcoma cells as a possible mechanism of the action of the DMOAD diacerein, and NFAT regulation.

Methods
Changes in [Ca2+]i were measured by the calcium imaging technique in Fura-2 loaded cells pretreated with diacerein. Hista- mine, a mediator of inflammation, was applied in different concentrations to provoke calcium signalling. As a consequence, ATP production (ATP Assay Kit, Abcam) as well as the calcineurin (Calcineu-
Background and Objective
In Vitro-Induced Regulatory T-Cells Can Reduce Se-
2. Poteser M, Schleifer H, Lichtenegger M, et al. PKC-dependent coupling of calcium permea-

Results
Cal-78 cells pretreated with diacerein showed a reduction in histamine-induced calcium release. Interestingly, the levels for resting calcium concentration and the time constant for calcium re-
movement were increased. A change in the production of ATP was not observed although diacerein modulated the activity of both calcineu-

Conclusion
Our results demonstrate that diacerein modulates intracellular calcium signalling in chondrosarcoma cells. The observed up regulation in resting Ca2+ points out a modulation of the rate be-
tween influx and efflux of Ca2+ with the Na+/Ca2+ exchanger as a possible target. The observed down regulation of histamine-induced [Ca2+]i peak, by diacerein obviously influences NFAT activity repre-
senting an important transcription factor involved in cell cycle regu-
lation. Taken further into account the significance of NFAT in the pathology of OA, diacerein by targeting NFAT could function as Calcineurin-NFAT modulator underlying once more its beneficial function in the treatment of OA.

References:
2. Poteser M, Schleifer H, Lichtenegger M, et al. PKC-dependent coupling of calcium permea-

In Vitro-Induced Regulatory T-Cells Can Reduce Se-
verity of Lupus Arthritis

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Background and Objective
Even though joint involvement is a major burden in patients suffering from systemic lupus erythematoso-
sus (SLE), it is not the focus of scientific research and treatment strat-
egies continue to be limited. Studying lupus arthritis and possible treatment options can be done with the murine model of pristane-in-
duced lupus (PIL). We herein investigate if in vitro-induced regulato-
y T-cells (iTreg) are capable of ameliorating PIL arthritis and help us evaluate possible new treatment options.

Methods
BALB/c mice were injected i.p. with either 0.5 ml of pris-
tane (PIL-group) or PBS (controls). Naive CD4+ thymocytes were sorted and cultured and cell suspensions with > 80% of CD4+FoxP3+
cells (iTreg) were injected intravenously (i) once when PIL was in-
duced (5 × 106 iTreg, iTreg-boost), or (ii) every 4 weeks (1 × 106 iTreg, iTreg-rep). Animals were monitored for paw swelling and grip strength. After 8 months histological analysis evaluated for cartilage
degradation, number of osteoclasts and the extent of inflammation and bone erosion. In addition, the cellular composition of the inflam-
matory tissue was determined by a cell-identification algorithm for
nuclear segmentation (HistoQuest). Serum levels of anti-dsDNA, anti-
myeloperoxidase (MPO), and anti-β2-glycoprotein I (β2-GPI) antibodies were measured by ELISA.

Results
Monthly injections of 1x106 iTreg reduced the clinical as well as the histological severity of PIL arthritis, seen by a higher mean grip strength (2.964 ± 0.024 vs 2.732 ± 0.063, p < 0.01), mean paw swelling (0.044 ± 0.020 vs 0.360 ± 0.069) and retardation of the symptom onset. 62 % of PIL mice and 33 % of iTreg-rep mice had erosive arthritis. There was a significant reduction of arthritis severity in all histological parameters (inflammatory area 0.188 ± 0.0574 vs 0.688 ± 0.113; erosive area 0.011 ± 0.009 vs 0.069 ± 0.017; number of osteoclasts 2.000 ± 1.125 vs 9.143 ± 1.999; cartilage degradation 0.059 ± 0.004 vs 0.187 ± 0.033). The single boost of 5 × 106 iTreg could not prevent joint manifestation. However, a slight retardation in ‘loss of grip strength’ and a significantly less erosive area was seen. In regards to the cellular composition of the inflammatory tissue, a significant-
ly increased relative amount of Foxp3 cells was seen in the iTreg-rep group compared to the PIL group (5.2 ± 2.3 vs 0.6 ± 0.2). Correspond-
ing to the reduced severity in joint involvement, the iTreg group had significantly lower serum levels of antibodies.

Conclusion
Repeated injections of iTreg ameliorate the clinical and histological severity of PIL arthritis. A single boost of iTreg at the time of disease induction does not prevent joint manifestation, but retards the onset of symptoms and progression of erosive bone deg-
radation. Thus, iTreg have significant positive effects on PIL arthritis, which may have consequences for future therapeutic considerations.

FOXO3 Differentially Regulates the Expression of TNF-Induced Genes in FLS

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Aim
FOXO3 is known to regulate diverse gene expression pro-
grams and to affect many cellular processes, such as cell cycle regu-
lation, cell survival and metabolism. Several lines of evidence allow for the assumption that FOXO3 also plays a significant role in the cellu-
lar response to inflammation. Thus, an association between a FOXO3 genotype (SNP) and the severity of rheumatoid arthritis (RA) was re-
cently described. Nevertheless, the role of FOXO3 in fibroblast-like synoviocytes (FLS), which are known to actively participate in rheu-
matoid synovial inflammation and joint destruction, has not yet been investigated.

Methods
With approval by the ethics committee synovial tissues from patients fulfilling the ACR/EULAR classification criteria for RA were obtained as discarded specimens following synovectomy. RA-
FLS were isolated according to standard procedures and cultured in DMEM. FOXO3 phosphorylation was determined by western blots. MK2206 was used to inhibit the kinase AKT. FLS were transfected ei-
ter with control or FOXO3 siRNA pools in order to investigate the role of FOXO3 in the TNF-induced inflammatory response. Expression of cytokines, chemokines and proteases, that are all known to be involved in RA pathogenesis, was assessed by ELISA, qPCR and western blots.

Results
TNF, which is well known to be at the apex of the inflam-
matory cytokine network in RA, promoted the phosphorylation ofFOXO3 in FLS. FOXO3 phosphorylation by TNF was inhibited by the AKT-inhibitor MK2206, demonstrating that TNF induces AKT phos-
phorylation to subsequently control FOXO3 activity in FLS. To fur-
ter investigate the role of FOXO3 in the TNF-induced inflammatory response we next silenced FOXO3 expression by using specific siRNA pools. Interestingly, while IL6 and IL8 expression was not affected by FOXO3 knockdown, a significant reduction in MMP3 expression was observed. Contrary, FOXO3 knockdown promoted the TNF-induced expression of BAFF, TNFSF10 and CXCL11, suggesting that FOXO3 is a negative regulator of these genes.

Summary/Conclusion
Our data reveal differential regulation of arthritis-associated gene expression by FOXO3 and support the idea that FOXO3 plays a crucial role in the FLS response to inflammation.

Rheumaschule Tirol

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Ziel
Verbesserung des Wissens über rheumatologische Erkrankun-
gen und deren Therapiepotentialen bei betroffenen Patienten.

Methoden
Die Rheumaschule Tirol wurde 2015 als Initiative Ti-
roler Rheumatologen gegründet. In Modulen informieren Rheuma-
tologen gezielt betroffenen Menschen in Kleingruppen über Krank-
heit und Behandlungsmöglichkeiten. Angeboten werden Module zu folgenden Erkrankungen: RA, axiale SpA, PsA, Arthrose der großen Gelenke, Fingergegenknothrose, Osteoporose, Fibromyalgie, Poly-
myalgia rheumatica, Gicht. Ergänzt werden diese Module durch In-

ÖGr-Jahrestagung 2016 – Abstracts
Ein ungewöhnlicher Fall eines SLE-like-Krankheitsbildes mit Hautefloreszenzen

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Eine Patientin mit primärem Sjögren-Syndrom, Angina pectoris und Belastungsdrangsyne

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Schlussfolgerung/Empfehlung Eine PAH stellt eine sehr seltene, schwerwiegende Form der Lungenbeteiligung bei SJÖGREN-SYNDROM dar. Bei unserer Patientin besteht eine PAH vom PVOD-Typ. Ret-

„Der wird sterben...“, Zitat eines nicht gänzlich wohlwollenden Thoraxchirurgen – Infektion mit Nocardia abscessus bei einem Patienten mit rheumatoider Arthritis unter Tocilizumab-Therapie

Im Folgenden präsentieren wir den Fall eines 64 Jahre alten Mannes, der aufgrund einer Keratitis beider Augen im Rahmen einer rheumatoiden Arthritis (RA) eine systemische Thera-

Schwere therapiereistente polyartikuläre Gicht bei Niereninsuffizienz und Herzensuffizienz

Fallbeschreibung

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Steroidinduzierte Myopathie i.e.l. bei Latrogenen Cushing-Syndrom

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Knochenschmerzen bei Osteoporose: Business as usual? – Ein Fallbericht

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Fallbeschreibung
Eine 64-jährige Patientin mit bekannter Osteoporose wurde aufgrund von Knochenschmerzen und multiplen nichtheilenden Frakturen an unserer Abteilung vorgestellt. Im Rahmen der Staging-Untersuchung eines Mammakarzinoms (DCIS) zeigte sich im CT, axiale Schichtführung: bizarr, axiale Schichtführung: dünnwandig, ein deutscher residuum nach 3 Monaten. klinisch beschwerdefrei.

Schlussfolgerung/Empfehlung für die Praxis


Kryptokokkose als fatale Komplikation eines M. Boec


Schlussfolgerung/Empfehlung für die Praxis: Bei immunsupprimierten Patienten, insbesondere unter Steroidtherapie, sollte differenzialdiagnostisch immer auch an eine Kryptokokken-Infektion gedacht werden.

Schlussfolgerung/Empfehlung für die Praxis Bei der chron. rezidivierenden Urtikaria mit Fieber und Arthralgien kommen verschiedene Differenzialdiagnosen in Frage. Gerade bei insuffizientem Aneign auf die eingeleitete Therapie sollte man nicht davor zurückschrecken, die Diagnostik mittels Hautbiopsie zu wiederholen und ev. die Diagnose zu überdenken.

Differenzialdiagnose Muskelschwäche und -schmerzen: eine interdisziplinäre Fragestellung!


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Nicht nur asiatische Urlaubsgründe …

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Erworbene Hämophilie A bei Patienten mit SLE

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Vorhydropses Vorhofflimmern als Hinweis auf eine Systemerkrankung

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Schlussfolgerung/Empfehlung für die Praxis

Wenn nach ansprechender Therapie CRP erhöht bleibt, zusammen mit dem klinischen Befund von Gelenkschmerzen, immer an Gicht/Pseudogicht denken! Auch wenn klinisch ein eindeutiger Hinweis für einen punktionswürdigen Gelenkertruss vorliegt, hilft die Sonographie, dies zu beurteilen. Ein Nativ-Röntgen ist nicht zielführend.

Paroxysmales Vorhofflimmern als Hinweis auf eine Systemerkrankung

J. Miner STOFFWECHS MUSKULOSEKET ERKRANK 2016; 23 (4) 23

**Diskussion**


**Fallbeschreibung**


**Frühe Rehabilitation bei Dermatomyositis: Ein Fallbericht**

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**Einleitung** Wir berichten über den Fall eines Patienten mit Dermatomyositis (DM). Die Kombination immunmodulierender Therapie und sehr früher Einzelheilgymnastik, gefolgt von einer stationären Rehabilitation unter internistisch-rheumatologischer Kontrolle führte zu einem Therapieerfolg.

**Methode** Klinischer Fallbericht: Der Pat., 52 a. m., präsentierte sich mit seit etwa 4 Monaten symptomatischer DM (Muskelschmerzen, V-sign, Gottron'sche Papeln, heliotropes Exanthem, nicht erosive Polyarthritis). Nach Diagnosesicherung (Klinik, Labor und MRT) wurde eine immunmodulierende Therapie mit Prednisolon und Azathioprin eingeleitet. Die Einzelheilgymnastik wurde früh etabliert, gefolgt von einem stationären Rehabilitationsaufenthalt, beginnend 17 Wochen nach Beginn der medikamentösen Therapie.

**Ergebnisse** Sämtliche therapeutische Maßnahmen wurden gut toleriert und führten zu einem mittelfristig sehr guten Therapieerfolg.

**Zusammenfassung/Schlussfolgerung** Die Kombination immunmodulierender Therapie, sehr früher Einzelheilgymnastik, gefolgt von einem stationären Rehabilitationsprogramm unter internistisch-rheumatologischer Kontrolle scheint sehr gut geeignet, das Ziel einer weitgehenden Remission der DM zu erreichen.