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A. Pathophysiologie

**Objective** To investigate thymic T cell output, senescence of circulating T cell subsets, and changes of T cell subsets in patients with axial spondyloarthritis (aSpA). Results are compared with data from rheumatoid arthritis (RA) patients and healthy controls (HC).

**Methods** Patients with aSpA (n = 26; 26.9 % female, mean age 54.3 years) and RA (n = 20; 60.0 %, mean age 61.9 (± SD 11.2), 75 % female, median time since diagnosis 162.4 (range 0–552) months, SDAI 12.7 (± SD 9.3), 81 % and 50 % received synthetic and/or biologic DMARDs, respectively; 24 % used corticosteroids, 16 % were treated with bisphosphonates). Bone mineral density (BMD) was determined by lumbar spine (LS) and total hip DEXA and laboratory markers of bone metabolism included bone-specific alkaline phosphatase, osteocalcin, osteoprotegerin, β-crosslaps, and soluble RANKL. PBMCs were retrieved at the sample day of BMD measurement and were stained with anti-RANKL, CD3, CD4, CD8, CD28, CD45RA, CD45RO, and/or CD28 mAbs to measure surface expression of RANKL on T cells and to determine the prevalence of T cell subsets by flow cytometry.

**Results** A reduced BMD as determined by DEXA was found in 63 % of RA patients (13 % with osteoporosis, 50 % with osteopenia). The prevalence of aged CD4+CD28− and CD8+CD28− T cells inversely correlated with T scores of LS (corrcoeff = −0.235, p = 0.028, and corrcoeff = −0.266, p = 0.012, respectively) and hip (corrcoeff = −0.235, p = 0.025; corrcoeff = −0.253, p = 0.016, respectively). Patients with a T score below −1.0 tended to have higher prevalence of circulating CD4+CD28− [2.2 % (0.1–41.2) vs 0.5 % (0–17.6), p = 0.065] and CD8+CD28− T cells (44.8 ± 20.7 vs 37.4 ± 20.1, p = 0.134) than patients with normal bone mass. No association was found between frequencies of aged T cells and blood parameters of bone metabolism. RANKL expression was higher in CD4+CD28− and CD8+CD28− T cells compared to naïve CD4+CD28+CD45RA+ T cells (7.8-fold and 7.5-fold, respectively, p < 0.05) compared to naïve CD4+CD28+CD45RA+ T cells (4.4 (0.5–44.5) compared to naïve [3.3 (0.5–41.3), p < 0.001] and aged T cells [2.2 (0–20.1), p < 0.001]. In cell culture experiments IL-15 and anti-CD3 stimulation increased RANKL expression on all T cell subsets. IL-20.1), p < 0.001]. In cell culture experiments IL-15 and anti-CD3 stimulation increased RANKL expression on all T cell subsets. IL-15 stimulation showed largest effects on memory CD4+ and CD8+ T cells (4.5-fold and 6-fold higher expression, respectively compared to unstimulated cells, p < 0.05) compared to aged (3.9-fold and 5-fold, respectively, p < 0.05) and naïve T cells (1.5-fold and 3.8-fold, respectively, p < 0.05). Also, activation by anti-CD3 had the largest effect on RANKL expression on memory CD4+ and CD8+ T cells (7.8-fold and 7.5-fold, respectively, p < 0.05) compared to naïve (5.2-fold and 4.7-fold, respectively, p < 0.05) and aged cell subsets (2.9-fold and 3.2-fold, respectively, p < 0.05). IL-6 and TNF-α had no effect on RANKL.

**Summary/Conclusion** Thymic T cell renewal is impaired in aSpA patients. Consequently, increased peripheral T cell turnover compensates for failing thymus to maintain T cell homeostasis leading to accelerated telomere erosion and the accumulation of early aged T cells.

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Conclusion. Aged CD28− T cells are linked with the occurrence of systemic bone loss in RA. Increased expression of RANKL on CD4+CD28− T cells compared to other T cell subsets is compatible with direct stimulation of osteoclastogenesis by aged T cells in RA.

Sulphur Inhibits the Stimulation of Fibroblast-Like Synoviocytes from Osteoarthritis Patients in a 3-D Model

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Objective. Osteoarthritis (OA) is the most common degenerative joint disease showing characteristic features like loss of cartilage, formation of osteophytes, and alteration of subchondral bone leading to joint impairment and pain. The pathogenesis of OA is still not fully understood. Fibroblast-like synoviocytes (FLS), located in the intimal lining layer of the synovial membrane, were shown to promote secondary synovitis by the release of proinflammatory cytokines and matrix-metalloproteinases (MMPs). Patients suffering from OA are frequently treated using sulphur baths but the reported effects of these treatments are limited. Since wounded skin and bone have histologically been controversial. The objective of this study was to analyze the anti-inflammatory potential of hydrogen sulphide (NaHS), an exogenous H2S donor, on activated FLS cultured in a 3-dimensional micromass culture system.

Methods. Primary cell lines derived from FLS of patients with OA were cultured in spherical extracellular matrix micromasses for 3 weeks, stimulated with Interleukin-1β (IL-1β), and treated with NaHS. The micromass culture architecture was assessed by histological methods.

Results. We observed the spontaneous formation of a compacted, lining layer-like architecture by OA-FLS as described previously [Kienzer et al. 2010] for FLS of rheumatoid arthritis patients. Furthermore, clusters of elongated cells underneath the condensed cell layer were observed. Following stimulation with the proinflammatory cytokine IL-1β, a cellular response, which included increased formation of a synovial lining layer, a lack of clustering, as well as increased globular shape of cells located in the stromal sublining, could be observed. Treatment with 1 mM NaHS partially inhibited structural changes caused by cell activation induced by IL-1β.

Summary/Conclusion. These preliminary data show that NaHS has the potential to inhibit the IL-1β response of FLS suggesting cartilage protective effects of sulphur treatment that need to be elucidated in more detail.

mTOR Inhibition in Rheumatoid Arthritis – Another “Janus Paradox”? 04

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The mechanistic target of rapamycin (mTOR) is an evolutionarily conserved serine/threonine kinase that senses various environmental cues to control essential cellular processes, such as cytokeskeletal reorganization, protein translation, autophagy, cell growth, and cell survival. Importantly, recent evidence indicates a critical role for mTOR in the regulation of the immune response. Inhibitors of mTOR (e.g., rapamycin) are used for the prevention of allograft rejection and have been evaluated as a therapeutic in inflammatory diseases. So far, only one clinical trial examined the efficacy of mTOR inhibition in patients with rheumatoid arthritis (RA). Inhibition of mTOR ameliorates arthritis severity but resulted in an increase of parameters of inflammation such as the erythrocyte sedimentation rate (ESR). These results suggest a complex role for mTOR in chronic inflammatory diseases, especially in RA. In order to assess mTOR activity in RA synovitis, synovial tissue samples of RA patients were stained with phopsphospecific antibodies to mTOR and 2 well-known mTOR catalytic substrates, S6 and 4E-BP. In rheumatoid synovial tissues, mTOR, 4E-BP, as well as S6 were found to be phosphorylated. Strikingly, all 3 phosphoproteins were preferentially expressed in fibroblast-like synoviocytes (FLS), most prominently in FLS of the hyperplastic synovial lining layer. To explore the functional significance of mTOR activation in RA synovitis we used a simplified, 3-dimensional (3D) in vitro model of the synovial tissue. RA-FLS were resuspended in a preformed extracellular matrix (ECM). Subsequently, the FLS/ECM mixture was cultured as a floating sphere. In this model system, FLS spontaneously establish a cellular architecture that strikingly resembles the in vivo situation of the synovial tissue. As described, stimulation of the 3D cultures with the proinflammatory cytokine TNF resulted in the hyperplasia of the lining layer at the surface of the spheres. Strikingly, treatment of the 3D cultures with Torin-1, a well-known inhibitor of mTOR, prevented TNF-induced lining layer hyperplasia, suggesting a role for mTOR in the inflammatory remodelling of the synovial tissue. Analyses of supernatants revealed that the combined treatment of cultures with TNF and Torin-1 resulted in increased production of TNF compared to cultures that were solely exposed to TNF. These studies provide insight into the regulatory circuits that determine the synovial mesenchymal tissue response to inflammation and suggest a multifaceted role for mTOR in arthritis. Further, these studies may reveal a target for the therapeutic intervention in patients with RA.

Mice Deficient for Regulatory T Cells Develop Systemic Lupus-Like Disease 05

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Objective. CD4+FoxP3+ regulatory T cells play an important role in maintaining tolerance to self-antigens. In human SLE, both the absolute numbers and the functionality of these cells are reduced and correlate inversely with disease activity. Scurfy mice do not express FoxP3 and thus do not have CD4+FoxP3+ Treg function. We here show that Treg-deficient Scurfy mice develop systemic lupus-like disease.

Methods. 9 Scurfy and 9 matched controls (C57Bl/6) were analyzed at 4–5 weeks of age. We measured ANA and serum anti-dsDNA-abs by immunofluorescence and ELISA, respectively. Specimen of inner organs (lung, kidney, intestines, heart, liver, spleen) were stained with H/E or PAS (for kidneys), respectively, and analyzed for signs of inflammation by a blinded pathologist (W. U.). In addition, we also analyzed joints for occurrence of arthritis by staining with H/E (overview), toluidin blue (cartilage), and TRAP (osteoclasts). Immunohistochemistry allowed for further analysis of the cellular composition of the inflammatory infiltrate. Finally, joint pathology was quantified by image analysis systems (Osteomeasure and HistoQuest, respectively).

Results. All mice were positive for ANA and anti-dsDNA-abs. In line with the literature, all Scurfy but no control developed pneumonitis with periand peribronchial infiltrates (6 out of 6 vs 0 out of 6, p = 0.0022). Interestingly, all but one Scurfy mouse (but no control) developed mesangial-proliferative glomerulonephritis comparable to lupus nephritis WHO2 [8 out of 9 Scuffy (88.9 %) vs 0/6 (0 %) of controls, respectively, p = 0.0014]. In line with the hypothesis of an increased, generalized immune reaction, we found germinal center hyperplasia as well as lymphocyte-depleted mantle zones and parafollicular areas in Scurfy spleens, but not in controls. There were no signs of inflammation in the liver, large intestines, or the heart (not shown). Compared to matched controls, Scurfy mice showed increased cartilage degradation indicated by the increased ratio of destained/normal cartilage (0.050 ± 0.009 vs 0.018 ± 0.003, p = 0.004, t-test). Despite their low age at time of analysis, all (9 out of 9) Scurfy mice had developed pannus-like inflammatory infiltrates.
within the tarsal and metatarsal joints (mean area 0.38 ± 0.25 mm²), while wild-type controls did not (p < 0.0001). There were no osteoclasts within the joint space and, consecutively, no erosions detectable. Besides fibroblasts, the inflammatory infiltrate consisted mainly of CD3+ T lymphocytes (13 %) and < 3 % neutrophils and macrophages.

**Conclusion** Treg-deficient Scurfy mice develop systemic lupus-like disease characterized by typical auto-abs, organ involvement, and non-erosive arthritis. Our observations foster the hypothesis that CD4+FoxP3+ T reg are crucial for maintaining peripheral tolerance and that a lack of their function can lead to SLE.

**Changing ANCA Spectrum Associated with Cocaine Abuse Challenges the Differential Diagnosis of Vasculitis**

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**Background** Testing for anti-neutrophil cytoplasmic antibodies (ANCA) is well established in the diagnostic evaluation of patients suspected of having vasculitis because ANCA reactivity with proteinase 3 (PR3) and myeloperoxidase (MPO) have a high positive predictive value for the ANCA-associated vasculitides, granulomatosis with polyangiitis (GPA, former Wegener’s), and microscopic polyangiitis (MPA). However, prescription drugs as well as illegal street drugs can induce ANCA and clinical pathology that mimic GPA and MPA. The presence of ANCA reacting with human neutrophil elastase (HNE) is found in most patients with cocaine-induced midline destructive lesions (CIMDL) and drug-induced vasculitides syndromes, whereas patients with GPA and MPA do not have HNE-ANCA. Patients with CIMDL were also usually MPO-ANCA negative. In recent years, studies have increasingly shown that the anti-helminthic drug levamisole, and a broader autoantibody spectrum as well as more systemic clinical pathologies have been reported in cocaine abusers. Our study was conducted to determine whether there has been an identifiable shift in ANCA reactivity in serum samples from cocaine abusers over the course of the last decade.

**Methods** Multi-modality ANCA-testing by capture enzyme-linked immunosorbent assays (ELISAs), direct ELISAs, and indirect immunofluorescence was performed for HNE-ANCA, PR3-ANCA, and MPO-ANCA. 135 samples from 122 patients had been submitted to our laboratory for HNE-ANCA testing in order to differentiate cocaine-induced pathology from classic ANCA-associated vasculitides. 74 patients with at least one positive HNE-ANCA test result between 1999 and 2011 were included in this study. Additionally, the analytical sensitivity for different ANCA detection methods was analyzed. Among HNE-ANCA positive samples the reactivity with MPO changed dramatically in the last decade. All samples collected from 1999 to 2008 were negative for MPO-ANCA. However, in 2009, 2 of 5 (40 %) samples were MPO-ANCA positive, 15 of 100 (15 %) in 2010, and 10 of 13 (77 %) in 2011. A gradual increase in PR3-ANCA positivity was also noted. Between 1999 and 2006, 66 % of samples were PR3-ANCA positive, with a slight increase to 80 % in 2007 and 2008 and another rise to 85 % in 2010 and 2011 (**Figure 1**). Evaluation of immunofluorescence pattern on slides with ethanol-fixed neutrophils showed that a perinuclear staining pattern predominates in HNE-ANCA positive samples (71 %). In 2010 and 2011, all samples displayed a pANCA pattern. Comparison of the different methods showed that none of the methods identified all samples with detectable ANCA.

**Conclusion** Coinciding with the emergence of leva-misole as adulterant of street cocaine, serum samples from cocaine abusers with clinical pathology have become increasingly pANCA and MPO-ANCA positive, whereas MPO-ANCA negativity was the norm previously. This complicates the differential diagnosis of systemic vasculitis, particularly since the clinical spectrum associated with cocaine abuse has also changed from previously predominant CIMDL to a more systemic vasculitis mimic. HNE-ANCA remain a differentiating marker. To obtain optimal sensitivity, different ANCA testing modalities should be applied for every target antigen in parallel.

**PI3-Kinase Controls Inflammatory Bone Destruction by Regulating the Osteoclastogenic Potential of Myeloid Cells**

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**Objective** Local bone destruction in rheumatoid arthritis, psoriasis arthritis, or ankylosing spondylitis is a serious health burden and the major cause of disability and severely reduced quality of life in these diseases. This damage to the bony structures is exclusively mediated by a special cell type, the osteoclast (OC). Therefore, it is important to understand factors and pathways regulating the generation of OCs under inflammatory conditions. As PTEN is a lipid phosphatase and one of the main antagonists of the PI3-kinase, we analyzed the impact of the PI3-kinase/PTEN axis on OC generation and bone biology in an animal model of inflammatory bone loss.

**Methods** We induced osteoclastogenesis in wt and PTEN-deficient bone marrow cells and measured the generation of OCs, their resorptive capacity, and induction of OC differentiation markers in vitro. Moreover, we analyzed mice with a monococyte/macrophage-specific deletion of PTEN (myeloid-specific PTEN−/−) by bone histomorphometry and crossed these into hTNFtg mice. Results Among myeloid-specific PTEN−/− mice we increased osteoclastogenesis in vitro and in vivo when compared to wild-type animals. However, under non-inflammatory conditions, enhanced osteoclastogenesis did not result in systemic bone loss in vivo. However, when we crossed myeloid-specific PTEN−/− into hTNFtg mice, we found significantly decreased grip strength scores in myeloid-specific PTEN−/−/hTNFtg mice compared to wt hTNFtg mice. Joint swelling scores, however, were not different between both groups. In line, myeloid-specific PTEN−/−/hTNFtg mice displayed enhanced local bone destruction as well as OC formation in the inflamed joints, whereas the extent of synovial inflammation was not different between the groups. Analysis of the synovial membranes of wt and myeloid-specific PTEN−/− animals revealed similar relative compositions of the cellular infiltrate including macrophages, which serve as OC precursors. This suggests that increased capacity for osteoclastogenic differentiation rather than enhanced recruitment of precursor cells is responsible for the enhanced local generation of OCs.

**Summary/Conclusion** Taken together, these data demonstrate that sustained PI3-kinase activity in myeloid cells specifically elevated the osteoclastogenic potential of these cells, leading to enhanced inflammatory local bone destruction. Therefore, targeting the PI3-kinase pathway therapeutically may be especially useful for the prevention of structural joint damage.
Analysis of Biological Functions of TNFR2

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Objective The role of TNF in the induction and maintenance of human rheumatoid arthritis is well established. In contrast, the roles of its 2 receptors, especially of TNFR2, are not sufficiently understood. We have previously observed that lack of TNFR2 on hemopoietic cells leads to increased osteoclastogenesis in vitro and also in vivo in a TNF-dependent model of arthritis. It is therefore important to define specific functions of TNFR2, with respect to target genes and signalling cascades initiated by TNFR2. Here we investigated the role of TNFR2 on osteoclast precursor cells.

Methods/Results To study the function of TNFR2, we used osteoclast precursor cells (pOC) lacking TNFR1, leaving TNFR2 as the only TNF receptor expressed on these cells. We show that stimulation of TNFR2 with soluble TNF is not sufficient to induce activation of MAP-kinases p38, ERK1/2, or AKT/PKB. However, cross-linking TNF, thereby mimicking membrane-bound TNF, which has been reported to be a ligand for TNFR2, did lead to activation of ERK1/2 as well as AKT/PKB. In addition crosslinked TNF but not soluble TNF induces TNF mRNA in pOC lacking TNFR1. To obtain information on the global transcriptional response initiated by TNFR2, osteoclast precursors lacking TNFR1 were stimulated with soluble as well as crosslinked TNF. RNA was isolated and analysed by microarray. Thereby, we obtained a list of approximately 50 genes specifically induced via TNFR2, including chemokines, surface receptors, and many others.

Summary/Conclusion We show here that TNFR2 is capable of transmitting a TNF-dependent signal independent of TNFR1. We furthermore characterize a TNFR2-specific gene signature, which sheds light on the biological functions of TNFR2.

CD11c+ Dendritic Cells Play an Important Proinflammatory Role in Inflammatory Arthritis

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Background/Purpose Dendritic cells (DCs) play an important role in bridging the innate and the adaptive immune response by serving as antigen-presenting cells and are therefore implicated in the initiation of chronic autoimmune diseases, including rheumatoid arthritis. Using the K/BxN serum transfer arthritis, a model of human rheumatoid arthritis which depends on the innate immune system, allowed us to investigate the innate role of dendritic cells in inflammatory arthritis.

Methods K/BxN serum transfer arthritis was induced in CD11c- diphertheria toxin receptor (DTR) transgenic mice, which express the human diphertheria-toxin receptor under the CD11c promoter. This allows for specific depletion of CD11c+ cells by administration of diphertheria toxin (DT). DT or PBS were given on day –1, 3, 6, and 9, and the severity of arthritis was determined clinically and histologically. In addition, serum transfer arthritis was induced in wild-type animals who also received DT.

Results Efficient depletion of DCs from the spleen after injection of DT was confirmed by flow cytometry and histological analysis. Clinical scores of arthritis showed that CD11c- DTR transgenic mice had significantly reduced paw swelling and loss of grip strength compared to PBS-treated animals. In contrast, wild-type animals receiving DT showed identical clinical signs of arthritis as PBS-treated animals, excluding unspecific effects of DT in mice. Histological analysis found that CD11c- DTR transgenic mice that had received DT displayed decreased synovial inflammation and a trend towards reduced local bone destruction.

Conclusion These data show that dendritic cells are involved in innate reactions leading to inflammatory arthritis and suggest that dendritic cells could be an important target for rheumatoid arthritis therapy.

The Integrin-Linked Kinase Is Upregulated in the Rheumatoid Synovium in a TNF-Dependent Manner

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Objectives The integrin-linked kinase (ILK) is known to play a pivotal role in various processes involving connection of integrins to the actin cytoskeleton. The activity of this kinase is mainly perpetuated by phosphatidylinositol 3-kinase (PI3K). Due to its function and the pathways involved, we studied the ILK in both human RA and an animal model of inflammatory arthritis.

Methods The expression of ILK was quantified by immunohistochemistry in human synovial tissue specimen of RA and OA patients as well as in specimen of the hind limb paws of TNF transgenic (tg) mice and wild-type (WT) mice using a 5-point scale. Moreover, both the mRNA and protein expression of ILK in response to TNF was studied in human RA fibroblast-like synoviocytes (FLS) using real-time PCR and Western blot technique.

Results The expression of ILK was increased in both the human RA (3.5 ± 0.2) and murine arthritis (3.7 ± 0.2) synovial lining when compared to OA (0.3 ± 0.3, p < 0.002) and WT (2.0 ± 0.4, p < 0.02), respectively. Similar findings were observed for the endothelial cells within the synovial membrane (3.3 ± 0.2 in RA vs 1.8 ± 0.3 in OA, p < 0.01; 3.8 ± 0.2 in TNF tg mice). Both the amount of ILK mRNA (1.27 ± 0.07-fold, p < 0.02) as well as the protein expression of RA-FLS (2.03 ± 0.33-fold, p < 0.02) increased significantly when stimulated for 24 hours with TNF.

Conclusions ILK is highly upregulated in the rheumatoid synovial membrane and in the lining and the endothelium in particularly. In RA-FLS, this upregulation was also observed to be TNF-driven. Our findings make ILK a potential interesting candidate to intervene the disease course in future.

Characteristics of Arthritis in a Model for Systemic Lupus: Involvement of Joints, Inner Organs and Course of Autoantibodies in Pristane-Induced Lupus

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Objective Arthritis is frequently seen in human lupus, but rarely in lupus models. Pristane-induced lupus (PIL) can be induced in various strains such as BALB/c and C57Bl/6. We herein characterize clinical and histological features of arthritis in the context of systemic lupus and provide a prudent comparison with models of rheumatoid arthritis (RA).

Methods 57 BALB/c received pristane and were analyzed for serum autoantibodies (anti-chromatin, -histone, -Sm), as well as for clinical features and histopathology of joints, lungs, and kidneys. Joint pathology was quantified by image analysis and tissue cytometry. 10 C57Bl/6 mice and historical groups of 2 different RA models were analyzed accordingly.

Results In BALB/c, clinical arthritis started at 3 months, occurred finally in 79 % of PIL (but not in controls, p < 0.001), and correlated with areas of inflammation, erosion, cartilage damage, osteoclast numbers, and total severity score (for all: r > 0.7, p < 0.001). After 8 months, 58 % of PIL (but no controls, p < 0.001) had mild-erosive arthritis. In contrast to RA, the most frequent inflammatory cell type of the pannus was granulocytes (17.7 %). PIL had lower numbers of osteoclasts, erosions rarely affected both layers of the cortical bone, and there was no progression to complete joint destruction (even after 1 year of observation). Serum auto-abs preceded arthritis and became significantly elevated in all PIL. Affected joints showed increased deposits of IgG (and IgM) within the inflammatory tissue, indicative for an antibody-mediated process. All PIL mice with arthritis also had pulmonary (100 %) and renal (46 %) lupus. In contrast to BALB/c, B1/6 mice did not develop any signs of arthritis.
Antinukleäre Antikörper (ANA) bei Patienten unter Therapie mit TNF-α-Hemmern

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Ziel TNF-α-Blocker werden seit Beginn des vergangenen Jahrzehnts vermehrt in der Therapie chronisch entzündlich rheumatischer Erkrankungen (rheumatoide Arthritis [RA]; Spondylarthritis [SpA], Psoriasisarthritis [PsA]) eingesetzt. In den vergangenen Jahren wurden die Indikation für eine entsprechende Therapie auch auf andere rheumatische Erkrankungen wie Psoriasisarthritis (PsA) und Spondylarthropathie (SpA) erweitert. Während der Therapie mit TNF-Hemmern werden auch immunologische Begleitphänomene in Form von vermehrter Bildung von antinukleären Antikörpern (ANA) beobachtet. Das Ziel dieser Studie war es, durch retrospektive Überprüfung von Patienten unter Anti-TNF-Therapie das Auftreten von ANA bei Patienten mit unterschiedlichen rheumatischen Erkrankungen zu untersuchen.

Methoden Hierbei handelt es sich um eine retrospektive Fallkontrollstudie. Es wurden 117 Patienten, die über einen Zeitraum von mindestens 6 Monaten unter Anti-TNF-Therapie standen, mit indirekter Immufluoreszenz auf HEp-2-Zellen auf das Vorhandensein von ANA überprüft. Eingeschlossen wurden Patienten mit den Diagnosen chronische Polyarthritis (n = 83), Spondylarthritis (n = 26) und Psoriasisarthritis (n = 8).

Resultate Bei 24 Patienten ließen sich bereits vor Therapiebeginn als positiv zu bewertende ANA-Titer bestimmen, zum überwiegenden Teil bei Patienten mit PsA (n = 22) versus bei jeweils einem mit PsA bzw. SpA. Von den übrigen 93 Patienten entwickelten unter Anti-TNF-Therapie 11 einen Anstieg der ANA-Titer (entweder von negativen Werten auf über 1:100 oder zumindest ein Anstieg um 2 Titerstufen), davon 19 mit der Diagnose RA (22,9 %), 3 mit PsA (37,5 %) und 9 mit SpA (34,6 %). Die Immuffluoreszenzmarker präsentierten sich homogen (n = 20, 64,5 %), gemischt homogen und feingesprenkelt (n = 8, 25,8 %), feingesprenkelt (n = 2, 6,4 %) und nukleolär (n = 1, 3,2 %). Der mediane Zeitabstand zum Behandlungsbeginn betrug 33 Wochen, mit einem Minimum von 4 Wochen und einem Maximum von 308 Wochen. Alle in Österreich verfügbaren TNF-α-Blocker kamen zum Einsatz (Adalimumab, n = 39; Etanercept, n = 29; Infliximab, n = 27; Golimumab, n = 9; Certolizumab, n = 1). ANA wurden bei 15 mit Infliximab behandelten Patienten induziert (55,5 %), bei 11 mit Adalimumab behandelten Patienten (28,2 %), bei jeweils einem mit Etanercept (3,4 %) und Golimumab (11,1 %) behandelten Patienten und bei dem einzelnen Patienten unter Certolizumab-Therapie. Ein Patient wurde beobachtet, der unter Anakina (einem IL1-Rezeptorantagonisten) ANA entwickelte und unter Anti-TNF-Therapie messbare Titer beihielt. Es wurden 13 Therapiewechsel bei ANA-positiven Patienten beobachtet, bei 10 blieb sich keine Änderung der ANA-Titer feststellen. Bei 2 Patienten sanken die Werte, stiegen dann jedoch wieder an. Nur bei einem Patienten ging nach Therapiewechsel der Titer dauerhaft zurück. Kein Patient mit neu gebildeten ANA entwickelte eine zusätzliche Autoimmunerkrankung wie zum Beispiel einen medikamenten induzierten Lupus.

Schlussfolgerung Inzidenz und Anstieg von ANA-Titern unter Anti-TNF-Therapie sind bei Patienten mit verschiedenen Diagnosen vergleichbar, scheinen jedoch unterschiedlich bei mit verschiedenen Präparaten behandelten Patienten.

Involvement of the Nucleic Acid Recognizing Toll-Like Receptors TLR7 and TLR9 in the Pathogenesis of Erosive Arthritis

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Background The pathogenesis of rheumatoid arthritis (RA) is a complex process driven by autoimmune processes that are triggered by still poorly understood mechanisms. Inappropriate release and insufficient removal of intracellular molecules by the phagocytic system have been suggested to trigger arthritogenic autoimmune reactions. Potential involvement of Toll-like receptor (TLR) 4 has been shown in several studies while the role of the nucleic acid recognizing TLR7 and TLR9 is less clear. Remarkably, in rats with pristane-induced arthritis (PIA) disease can be transferred by T cells in the presence of antigen-presenting cells that are pre-activated with TLR7 or TLR9 agonists [1].

Objective To study the role of TLR7 and TLR9 in the pathogenesis of inflammatory erosive arthritis by antagonizing these TLRs in 2 different disease models, pristane-induced arthritis (PIA) and the KRN serum transfer model.

Methods Arthritis was induced in DA rats by subcutaneous injection of the mineral oil pristane, and in C57Bl/6 mice by injection of arthritogenic KRN serum. Immunoregulatory oligodeoxynucleotide (ODN) sequences (IRS) selectively antagonizing TLR7 or TLR9 were applied twice a week either subcutaneously (PIA) or intra-peritoneally (KRN). A non-inhibitory ODN was used as control, PBS served as placebo. Weight changes were monitored during the experiment and arthritis was scored using established scoring systems. The amount of inflammation and bone erosion was quantitated by histology and TRAP staining. Cytokines were measured in serum and cell culture supernatants by ELISA.

Results While the TLR7 inhibitor IRS681 and the control ODN showed no effect on arthritis development and severity, the TLR9 antagonist IRS869 reduced arthritis severity significantly (p < 0.05) by approximately 40 %. Remarkably, bone erosion was almost completely abolished (p < 0.01), whereas it appeared even moderately aggravated (p < 0.05) in animals treated with IRS681, in which also the acute disease phase was prolonged. Furthermore, serum levels of IL-6 were significantly reduced in IRS869-treated animals. However, these effects were only seen when the inhibitor was applied before disease onset. Moreover, and in line with this observation, neither inhibitor affected arthritis onset and severity in the serum transfer model which is independent of the adaptive immune system.

Summary/Conclusion The TLR9 inhibitor significantly reduced inflammation and bone erosion in PIA which is driven by autoimmun processes, but not in the KRN serum transfer model that reflects the late effector phase of erosive arthritis. Therefore, these results suggest important involvement of the DNA (CpG) recognizing TLR9 in the initiation of autoimmune arthritis whereas nucleic acid-binding TLRs do not seem to play a major role in the later phases of the disease. Antagonizing TLR9 in human RA may therefore show beneficial effects only in the very earliest phase of the disease.

References:
B. Kinderheumatologie

Biomarker of Inflammation in Juvenile Idiopathic Arthritis (JIA) 14
J. Brunner1, T. Giner1, G. Weiss2, D. Fuchs2
1Department Kinder- und Jugendheilkunde, 2Department Innere Medizin und Biologische Chemie, Biozentrum, MUG

Background Juvenile idiopathic arthritis (JIA) is a relevant autoimmune disease in children. T cells, B cells, and damage-associated molecular patterns (DAMPs) are involved in the pathogenesis of the disease. Biomarkers for JIA and its subtypes are not established. Proinflammatory pathways activate enzyme indoleamine 2,3-dioxygenase (IDO) which enhances tryptophan (Trp) conversion to kynurenine (Kyn). Thus, in conditions of chronic immune activation reduced Trp availability and production of Kyn and its downstream metabolites may inhibit cell proliferation. In rheumatoid arthritis (RA) Trp concentrations are lower in patients than in controls and the Kyn/Trp ratios are higher and correlate with neopterin concentrations [1–3].

Methods In this study, Trp and Kyn metabolism was investigated in children with JIA and compared to serum neopterin concentrations. 54 sera of 25 JIA patients and 10 samples of synovial fluid were examined with HPLC (Trp and Kyn) and ELISA (Neopterin, BRAHMS, Henningsdorf, Germany). 18 sera from 18 children with non-inflammatory diseases were used as controls.

Results Trp in the sera of patients was mean 57.2 ± SD 19.0 µmol/l and Kyn was mean 2.40 ± SD 0.81 µmol/l. Serum neopterin was 5.69 ± SD 1.72 nmol/l. In the synovial fluid, neopterin was mean 10.5 ± SD 7.41 nmol/l, Trp was 36.7 ± SD 17.4 µmol/l, and Kyn was 2.13 ± SD 0.75 µmol/l. In control patients, neopterin was 6.93 ± SD 3.10, Trp was 57.6 ± SD 14.8, and Kyn was 2.60 ± SD 1.60 µmol/l.

Conclusion Serum Trp concentrations showed no relevant difference in JIA patients vs controls. IDO activity reduces Trp primarily in the synovial fluid in JIA patients.

References

Adalimumab zur Behandlung juveniler Uveitis 15
A. Skrabl-Baumgartner1, B. Langen-Wegscheider2
1Univ.-Klinik für Kinder- und Jugendheilkunde und 2Universitäts-Augenklinik, MUG


Methoden 13 Patienten (4–22 J) mit visusbedrohender anterierer Uveitis wurden mit Adalimumab behandelt und über einen Zeitraum von 12 Monaten beobachtet. 10 Patienten hatten eine juvenile idiopathische Arthritis, 3 hatten keine assoziierte Erkrankung. 5 Patienten hatten einen bilateralen Befall, 8 einen unilateralen. Alle erhielten Adalimumab in der Standarddosisierung (24 mg/m² KO 2× wöchentlich und zumindest ein Immunsuppressivum. 2 Patienten waren zuvor mit Etanercept behandelt worden.

Ergebnisse 15/19 (79 %) betroffene Augen zeigten eine Verbesserung, 4/19 (21 %) blieben unverändert. Keines zeigte eine Verschlech-
Adalimumab bei juveniler idiopathischer Arthritis und Uveitis: Korreliert ein Therapieversagen mit dem Auftreten von Anti-Adalimumab-Antikörpern? 18

J. Jahnle1, W. Erwa2, A. Skrabl-Baumgartner1
1Univ.-Klinik für Kinder- und Jugendheilkunde und 2Inst. für Pathologie, MUW


Methoden Bei 16 Patienten im Alter zwischen 4 und 18 Jahren unter Adalimumab-Therapie wurde mithilfe eines ELISA-Kits die Serumkonzentration von Anti-Adalimumab-Antikörpern einmalig oder wiederholt bestimmt und in Korrelation mit klinischer Endzün-
dungssaktivität gesetzt.

limumab-Antikörper-Nachweis. Bei einem 14-jährigen Patienten mit visusbedrohender Autoimmunuveitis kam es nach promptem Thera-
pie-Ansprechen nach 12 Monaten zu einer massiven Verschlech-
terung ebenfalls ohne Anti-Adalimumab-Antikörper-Nachweis.

Zusammenfassung/Schlussfolgerung In unserem Pilotprojekt mit Adalimumab-behandelten JIA- bzw. Uveitis-Patienten konnte bislang keine Korrelation zwischen dem Auftreten von Anti-Adali-
mub-Antikörpern und einer klinischen Verschlechterung beobachtet werden.}

Myokardiale Beteiligung bei systemischer juveniler idiopathischer Arthritis – eine Fallpräsentation 19
S. Fodor, V. Zaller, S. Albinni, A. Ulbrich, W. Emminger
Univ.-Klinik für Kinder- und Jugendheilkunde, Medizinische Universität Wien

Wir berichten von einem 19-jährigen Patienten, bei dem nach Au-
fahren von Fieber, Arthralgien, Myalgien, lachsfarbenem Exanthem sowie hohen labormäßigen Entzündungswerten im Alter von 15 Jahren eine systemische juvenile idiopathische Arthritis (sJIA) diagnostiziert wurde. Nach Langzeit-Kortisongabe in Kombination mit Azathioprin konnte letztendlich durch Therapieumstellung auf Ana-
kinra eine Komplettremission erreicht werden. Im weiteren Verlauf wurde die immunsuppressive Therapie bei völliger Beschwerdefrei-
heit langsam ausgeschlichen und nach insgesamt 2 Jahren gänzlich abgesetzt. Nach weiteren 18 Monaten Restitutio praedicta präsentierte sich der Patient erneut in einem akuten Schub mit Fieber, Tachykardie, Myalgien sowie deutlich gesteigerten Entzündungsparametern bei gleichzeitig positivem Troponin T und mehrfach erhöhten proBNP-
Werten. Im EKG zeigte sich eine unspezifische Repolarisationsstö-
rung überall abettern. Echokardiographisch fand sich stets eine gute Ventrikelfunktion ohne Hinweis auf regionale Wandbewe-
gungsstörungen. Diese Veränderungen konnten insgesamt als myo-
kardiale Mitbeteiligung bei koronarer Vaskulitis im Rahmen der Grunderkrankung interpretiert werden. Unter sofortiger immunsup-
pressiver und antiinflammatorischer Therapie mit hochdosierten Kortikosteroiden, Immunglobulinen, nicht-steroidalen Antirheuma-
tika sowie Anakinra kam es innerhalb von 2 Wochen zu einer deutlichen klinischen Besserung sowie Normalisierung der labormäßigen Entzündungsparameter und Herzzyklen. Das EKG zeigte sich bis auf residuelle Repolarisationsstörungen im Sinne von negativen T-
Wellen in V5 und V6 normalisiert. Dieser Fallbericht stellt den Ver-
lauf einer myokardialen Beteiligung bei systemischer JIA dar, eine, die in der Literatur selten beschriebene Komplikation. Durch immunsup-
pressive Therapie inklusive Interleukin-1-Rezeptor-Antagonisten konnte bei diesem Patienten eine rasche Remission erreicht werden.

Fallbericht: JIA, systemische Arthritis mit begleitender schwerer Non-Specific Interstitial Pneumonitis 20
G. Artacker
Abteilung für Kinder- und Jugendheilkunde, SMZ Ost – Donauspital, Wien

Ein 3,5-jähriger Knabe österreichischer Herkunft leidet seit einem Jahr an Fieberschüben, Polyarthritis, häufigen Apathien im Mund und Genitalbereich und einer schweren interstitiellen Lungenkrank-

ÖGJR-Jahrestagung 2012 – Abstracts
Das Kawasaki-Syndrom – Klinische Daten aus Tirol

E. Binder, M. Sailer-Höck, E. Griesmaier, T. Giner, J. Brunner
Department für Kinder- und Jugendheilkunde, Medizinische Universität Innsbruck


Methoden Es handelt sich um eine retrospektive Analyse. Die Angaben zu den betroffenen Patienten wurden aus elektronischen Datenbanken generiert und eine deskriptive Analyse mittels SPSS Version 2.0 durchgeführt.

Ergebnisse Insgesamt wurden im Zeitraum von 2003 bis 2012 32 Patienten mit Kawasaki-Syndrom an der Universitätsklinik Innsbruck behandelt. Das Patientenkollektiv wurde in 3 Altersgruppen (≤ 6 Monate, 6 Monate bis 4 Jahre, > 4 Jahre) unterteilt, wobei 59,4 % der Patienten älter als 6 Monate und jünger als 4 Jahre waren und damit der altersabhängigen Häufigkeitsverteilung der Literaturangaben entsprach. Das mittlere Alter entsprach 32,96 Monaten (2–192 Monate). 46,9 % der Patienten waren männlich, 53,1 % weiblich. Die klinische Untersuchung zeigte die nicht-eitrige Konjunktivitis und das Exanthem mit in jeweils 84,4 % vorkommend als die häufigsten Symptome. 75 % wiesen oropharyngeale Veränderungen auf, darunter 43 % ein Exanthem, 46,9 % Lacklippchen und 18,8 % eine Erdbadrehung. Nur ein Patient zeigte während des stationären Aufenthaltes eine Exfoliation an den Fingern und Zehen. In 21,9 % konnte eine positive Anamnese bezüglich gastrointestinaler Symptome wie Diarrhö, Bauchschmerzen oder Erbrechen erhoben werden. Ein Drittel der Patienten wurde mit einer anderen vorläufigen Diagnose an unsere Abteilung transferiert, 78,1 % dieser Patienten wurden bereits mit einer biologischen Therapie vorbehandelt. Die mittlere Fieberdauer vor Erstvorstellung betrug 4,96 Tage (1–14), bei Diagnosestellung und somit Einleitung der entsprechenden Therapie 6,76 Tage (3–15). Bei 75 % der Patienten wurde ein komplettes, bei 25 % ein inkomplettes Kawasaki-Syndrom diagnostiziert. Es zeigte sich kein signifikanter Unterschied in der Fieberdauer bis zur Diagnosestellung zwischen inkomplett und komplettem Kawasaki-Syndrom oder in den verschiedenen Altersgruppen. Typische laborchemische Veränderungen waren ein erhöhtes C-reactives Protein (80,6 %), erhöhte Blutsenkungsgeschwindigkeit (96 %), Leukozytose (48,4 %) und Thrombozytose (40,6 %), jedoch ohne quantitativ signifikante Unterschiede zwischen komplettem und inkomplettem Kawasaki-Syndrom. Im Vergleich zwischen den Altersgruppen war der CRP-Wert in der Gruppe > 4 Jahre signifikant höher als in den anderen Altersgruppen (p < 0,05). 6 Patienten (18 %) erlitten kardiale Komplikationen, davon ein Koronar-Aneurysma diagnostiziert und 5 weitere Patienten (15 %) wiesen tubuläre Dilatationen der Koronararterien auf. Die mittlere Fieberdauer jener Patienten mit Komplikationen war 8,2 Tage im Vergleich zur Gruppe ohne Komplikationen mit 6,46 Tagen, bei sehr kleiner Fallzahl (6/32), jedoch nicht signifikant höher. Jener Patient mit der Komplikation eines Aneurysmas fieberte insgesamt über 2 Wochen, bis eine adaquate Therapie einsetzte. Dieser zeigte zudem eine massive erhöhte Blutsenkungsgeschwindigkeit im Vergleich zum Gesamtkollektiv, während die Patienten mit Komplikationen ansonsten keine signifikant höhere Entzündungsparameter aufwiesen.


C. Klinische Studien und Präsentationen

Sonoelestography Detects Salivary Gland Dysfunction in Patients with Primary Sjögren’s Syndrome

C. Deiaclo, T. DeZordo, D. Heberl, R. Lipp, A. Lutfi, M. Magyar, D. Zanoni, W. B. Graninger, J. Hermann
1Medizinische Universität Graz; 2Medizinische Universität Innsbruck

Objective Sialoscintigraphy (Szin) is used to investigate salivary gland function in patients with primary Sjögren’s Syndrome (pSS). Real-time sonoelestography (SEEIst) indicates tissue rigidity of salivary glands and correlates with an impaired saliva production. The objective of this study was to investigate the value of SEEIst and B-mode sonography to identify pSS patients with dysfunctional salivary glands.

Methods Prospective study on 37 pSS patients fulfilling the American-European consensus group criteria (mean age 59 years; 92 %...
female; median disease duration 3.1 years). Szinti was conducted according to a routine protocol and semi-quantitative scoring was performed: each gland was graded into 0 = no, 1 = up to 25 %, 2 = up to 50 %, 3 = up to 75 %, and 4 = more than 75 % hardened areas within the salivary gland (total score 0–16). Interobserver variability of sonography and Szinti were tested in 30 % of pSS patients.

**Results**
The mean Szinti score of pSS patients was 6.0 (± 4.3). Loss function of 1, 2, or 4 salivary glands was present in 5.3 %, 17.5 %, and 19.3 % of patients, respectively. B-mode (correlation 0.65, p < 0.001) as well as SELastO scores (correlation 0.39, p = 0.02) correlated with the Szinti score. Patients with at least one dysfunctional salivary gland had higher B-mode median 27.5 (range 10.0–44.0) vs 12.0 (2.0–6.9), p < 0.001) and SELastO scores (median 7.0 (range 3.0–12.0) vs 6.0 (2.0–7.0), p = 0.032) than patients with normal salivary gland function. In ROC curve analysis we found an area under the curve (AUC) of 0.91 (95 % CI: 0.8–1.0, p < 0.001) and 0.73 (0.56–0.89, p = 0.03) for B-mode sonography and SELastO, respectively, to detect patients with salivary gland dysfunction. A good reproducibility of B-mode and SELastO results was found as indicated by an ICC of 0.926 (95 % CI: 0.914–0.938) and 0.934 (0.927–0.941), respectively. Reproducibility of Szinti results was also good (kappa 0.871).

**Summary/Conclusion**
Structural changes and increased rigidity of major salivary glands as demonstrated by B-mode sonography and SELastO, respectively, correlates closely with salivary gland dysfunction in patients with pSS.

#### Ultrasound and Clinical Remission in Psoriasis Arthritis: DAPSA and Boolean Definitions Are Nearer to Ultrasound Remission than CPDAI

**C. Dejaco, R. Husic, J. Gretler, W. Graninger, J. Hermann Medizinische Universität Graz**

**Objective**
To compare ultrasound and clinical definitions of remission in psoriasis arthritis (PsA) patients.

**Methods**
Prospective study of 70 consecutive PsA patients [mean age 51.1 (± SD 11.6) years, 30 % female, median disease duration 7.0 (range 0–44.7) years]. Clinical and ultrasound examination was performed at 68 joints and 14 entheses (lateral epicondyle, triceps insertion, quadrizes insertion, proximal and distal insertion of patellar ligament, Achilles tendon, plantar fascia), and DAPSA, CPDAI, TJ, CRP, PGA, EGA, and HAQ were similar in both groups. Patients without PD signals at tendons [n = 46 (65.7 %)] had lower DAPSA [9.9 (0.1–70.2) vs 17.4 (0.2–60.8), p = 0.012], lower PGA [30 (0–80) vs 40 (0–80), p = 0.024], lower CRP [2.0 (0.2–20.3) vs 4.8 (0.6–94.5), p = 0.013], and lower ESR [6.0 (1.0–47.0) vs 18.0 (5.0–74.0), p < 0.001] compared to patients with active tenosynovitis. Patients without PD signals at entheses [n = 27 (38.6 %)] did not differ from patients with active disease regarding clinical scores and laboratory measures.

**Summary/Conclusion**
Our data demonstrate a disparity between ultrasound and clinical definitions of remission in PsA. DAPSA- and Boolean-based definitions of remission are closer to ultrasound defined remission than a CPDAI-based definition.

### Ultrasound for Diagnosis of Carpal Tunnel Syndrome – Comparison of Different Methods to Determine Median Nerve Volume and Value of Power Doppler Sonography


**Objective**
To compare ultrasound measurement of median nerve cross-sectional area (CSA) at different anatomical landmarks and to assess the value of Power Doppler (PD) signals within the median nerve for diagnosis of carpal tunnel syndrome (CTS).

**Methods**
Prospective study on 135 consecutive patients with suspected CTS undergoing 2 visits within 3 months. Final diagnosis of CTS was established by clinical and electrophysiological findings. CSA was sonographically measured at 5 different levels at forearm and wrist, and CSA wrist-to-forearm ratios or differences were calculated. Intra-neural PD signals were graded semi-quantitatively. Diagnostic values of different ultrasound methods were compared by receiving operating characteristic (ROC) curves using SPSS.

**Results**
CTS was diagnosed in 111 (45.5 %) wrists; 84 (34.4 %) had no CTS and 49 (20.1 %) were possible CTS cases. Diagnostic values were comparable for all sonographic methods to determine median nerve swelling with AUCs ranging from 0.75 to 0.84. Thresholds of 9.8 and 13.8 mm² for the largest CSA of the median nerve yielded a sensitivity of 91 % and a specificity of 92 %, respectively. A PD score ≥ 2 had a specificity of 90 % for the diagnosis of CTS. Sonographic median nerve volumetry revealed a good reliability with an intra-class correlation coefficient of 0.90 (95 % CI: 0.79–0.95).

**Summary/Conclusion**
Sonographic assessment of median nerve swelling and vascularity allows for a reliable diagnosis of CTS. Determination of CSA at its maximal shape offers an easily reproducible tool for CTS classification in daily clinical practice.

### Rheumatoide Arthritis ist ein Risikofaktor für einen erhöhten Augmentation Index unabhängig von der Koezistenz traditioneller kardiovaskulärer Risikofaktoren


**Ziel**
Die rheumatoide Arthritis (RA) ist mit einer erhöhten kardiovaskulären (CV) Morbidität und Mortalität assoziiert. Wir konnten...
Dysfunktion in diesem RA-Kollektiv vorliegt. Der Einfluss der RA
ren vorliegen oder nicht. Die Ergebnisse zeigen, dass eine vaskuläre
linearen Regressionsmodell eingesetzt. Ein p-Wert < 0,05 wurde als
(smoothing”) zeigte ein nicht-lineares Verhältnis zwischen Alter und
Die Basisdaten der Probanden sind in Tabelle 1 darge-
Die mittlere, unkorrigierte AIx lag bei 30,5 ± 9,0 % in der
Körpergröße –20,3149 5,882 –3,4 5   0,0006
BMI (kg/m²) 25,9 ± 4,8) 26,3 ± 6,0) 0,58
Körpergröße (m) 1,65 ± 0,08) 1,67 ± 0,07) 0,01
Alter (a) 56,3 ± 12,32 49,6 ± 12,7 < 0,001
Weiblich (n, %) 170 (83,7 %) 170 (81,7 %) 0,59
Gewicht (kg) 70,6 ± 14,3 72,9 ± 17,3 0,20
Körperfettanteil (mi) 1,65 ± 0,08) 1,67 ± 0,07) 0,01
BMI (kg/m²) 25,8 ± 4,8) 26,3 ± 6,0) 0,58
Diabetes (n, %) 7 (3,4 %) 61 (29,0 %) < 0,001
Antihypertensive Med. (n, %) 52 (25,6 %) 67 (32,2%) 0,14
Statine (n, %) 21 (10,5 %) 16 (7,7 %) 0,35
Ex-Raucher (n, %) 49 (24,1 %) 34 (16,3 %) 0,05
Raucher (n, %) 37 (18,2 %) 56 (26,9 %) 0,04
Triglyzeride (mg/dl) 119,9 (57,9) 135,7 (110,7) 0,13
Herzfrequenz (Schläge/min) 72,2 ± 11,2 72,7 ± 11,9 0,67
Brachialer syst. RR (mmHg) 138,2 ± 23,0 134,8 ± 23,9 0,04
Statine (n, %) 21 (10,5 %) 16 (7,7 %) 0,35
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Triglyzeride (mg/dl) 119,9 (57,9) 135,7 (110,7) 0,13
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Brachialer syst. RR (mmHg) 138,2 ± 23,0 134,8 ± 23,9 0,04

Zusammenfassung/Schlussfolgerung Der AIx ist bei RA-Pa-
Einfluss der RA auf vaskuläre Dysfunktion, bei RA-Patienten ohne tra-
frühzeitig und aggressive therapeutischen Interventionsmaßnahmen
dem AIx verzeichnet. In dieser Studie hat sich gezeigt, dass eine erhöhte

Wichtigkeit der frühzeitigen und aggressiven Behandlung von vaskulärer
der AIx vernachlässigbar wird, wenn bei RA-Patienten und auch Kon-

Is Fatigue in Rheumatoid Arthritis Represented by the RADAI-5? 26
J. Sautner, B. Rintelten, A. Maktari, I. Andel, T. Nothnagl, B. F. Leeb
LKH Stockerau

Objective To assess how fatigue correlates with a patient-centred outcome measure, the RADAI-5, in comparison with calculated tools like DAS28, CDAI, and SDAI.

Methods 189 outclinic RA patients were asked to indicate the amount of fatigue during the last 7 days on an 11-point NRS and also to complete the RADAI-5. DAS28, CDAI, and SDAI were calculated.

Results Correlations between fatigue and DAS28, CDAI, and SDAI were weak. Correlation between fatigue and RADAI-5 was moderate with rho = 0.584 (p < 0.01). Every single of the 5 RADAI-5 questions moderately correlated with fatigue showing the best correlation for question 4 (“How do you describe your general health today?”): rho = 0.604, p < 0.01.

Summary/Conclusion As shown by others, only a weak correlation of fatigue with the DAS28 was present. Far better correlations with the general RADAI-5 as well as with the single questions could be shown, the best correlation for question 4 addressing general health.


<table>
<thead>
<tr>
<th>Variable</th>
<th>Koeffizient</th>
<th>SE des Koeffizienten</th>
<th>T-Ratio</th>
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Summary/Conclusion As shown by others, only a weak correlation of fatigue with the DAS28 was present. Far better correlations with the general RADAI-5 as well as with the single questions could be shown, the best correlation for question 4 addressing general health.
Does the Change of Questions Assessing Patient’s Global Assessment Influence Composite Scores in Rheumatoid Arthritis? Is there also an Influence on Agreement of the Composite Scores to a Patient Outcome Measure like the RADAI-5? 28

B. Rinteler1, J. Sautner2, K. Stingl1, N. Kalmann3, F. F. Leeb1

Background In 2011 the ACR and EULAR proposed new remission criteria for rheumatoid arthritis (RA) [1]. According to this publication from now on wording of the question about patient’s global assessment should be as follows: “Considering all of the ways your arthritis has affected you, how do you feel your arthritis is today?” In the past general health was not explicitly connected to arthritis in the question wording of the RADAI-5. B. Polste, station – Worauf muss geachtet werden? 29

79: 57–62.


Objective It was of interest if the use of the different wording influences the agreement of composite scores to patient-centred disease activity assessment tools like for example the Rheumatoid Arthritis Disease Activity Index comprising 5 questions (RADAI-5) which has shown significant correlation to the commonly used composite indices [2, 3].

Methods 177 consecutive outclinic RA patients (74 % female, mean age 63.6 years, 55.9 % RF pos, mean disease duration 110 months) were asked to answer both questions (“How is your general health today?” and “Considering all of the ways your arthritis has affected you, how do you feel your arthritis is today?”) on a 100-mm visual analogue scale (VASGH and VASDA). Moreover DAS28, SDAI, and CDAI were calculated twice using both questions. Furthermore patients were asked to complete the RADAI-5 to correlate this questionnaire to the other composite scores. Cohen’s kappa was calculated to show the agreement of both results.

Results The mean RADAI-5 was 3.17 (95 % CI 2.85–3.49). Agreement of VASGH and VASDA was moderate (kappa = 0.41). The RADAI-5 agrees better to SDAI and CDAI using VASDA than VASGH (kappa = 0.68 vs 0.27 and 0.76 vs 0.27, respectively). No substantial difference was found for the agreement between RADAI-5 and DAS28 using both wordings (kappa = 0.20 vs 0.26).

Conclusion VASGH and VASDA showed a moderate agreement. No difference in agreement of the DAS28 and the RADAI-5 was seen using both wordings. Using the correct wording for VASDA, the SDAI and the CDAI become much more congruent with the RADAI-5.


Rheumapatienten im OP und auf der Intensivstation – Worauf muss geachtet werden? 29

B. Poßler1, M. Mustak1, B. Horvath-Mechtler1, L. Erlacher1
1Zentrum für Innere Medizin III, Medizinische Universität Wien

Zusammenfassung/Schlussfolgerung Rheumatologische Patienten erfordern pra-, peri- und postoperativ ein intensives interdisziplinäres Krankheitsmanagement, um ein optimales Outcome zu erreichen.

Frequencies of Boolean- and Index-Based ACR-EULAR Remissions Differ Slightly Depending on the Method of Patient Global Assessment 30

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Objective Two definitions of remission have been put forward by the ACR and EULAR: a Boolean-based definition, requiring swollen and tender joint counts (SJC, TJC), C-reactive protein (CRP in mg/dl), and patient global assessment (PGA on a 0–10-cm scale, VAS) to be ≤ 1; and an index-based definition, requiring the simplified disease activity index (SDAI) to be ≤ 3. The patient global has been shown to be crucial in fulfilling the criteria [1]. In many settings a numerical rating scale (NRS) is preferred instead of a VAS. Here, we investigated whether the use of an NRS-like assessment would lead to different remission frequencies compared to a VAS.

Methods We obtained data of a random cross-sectional visit of RA outpatients from a longitudinal observational database. We used simulated (s-) NRS values, in which VAS values were rounded to the closest integer, for calculation of the SDAI. We compared proportions of patients in Boolean and/or SDAI remission between PGA by VAS and sNRS, evaluating their difference or agreement descriptively by kappa and receiver operating curve analyses (ROC).

Results We identified 922 RA patients [80 % female, 56 % rheumatoid factor (RF) positive, mean disease duration 8 years]. In the main analysis, 12.8 % of patients were in Boolean remission using sNRS versus 11.3 % using VAS (Table 3). All patients in Boolean remission using VAS also were in remission by sNRS. Boolean remission using VAS and sNRS had a high agreement (κ = 0.93). SDAI remission frequencies were higher than Boolean remission frequencies with a good agreement (Table 3) and showed a x of 0.94 for the comparison of VAS and sNRS. In sensitivity analyses, in which we rounded all VAS values either up to the next higher integer or down to the next lower integer to obtain the sNRS, confirmed the
Fallbericht: Rheuma toide Arthritis und seltene Tumormanifestation – auf Umwegen zur Remission

Table 3: Studenic P et al. (# 30). Frequencies of remission using different types of PGA.

<table>
<thead>
<tr>
<th>VAS</th>
<th>sNRS – rounded arithmetically</th>
<th>sNRS – rounded up</th>
<th>sNRS – rounded down</th>
</tr>
</thead>
<tbody>
<tr>
<td>% SDAI remission</td>
<td>17.5 (16.6)</td>
<td>13.5 (21.0)</td>
<td></td>
</tr>
<tr>
<td>% Boolean remission</td>
<td>11.3 (12.8)</td>
<td>11.3 (15.2)</td>
<td></td>
</tr>
<tr>
<td>% Boolean remitters within SDAI remitters</td>
<td>64.7 (72.3)</td>
<td>71.7 (71.7)</td>
<td></td>
</tr>
<tr>
<td>% SDAI remitters within Boolean remitters</td>
<td>97.1 (90.7)</td>
<td>82.7 (95.7)</td>
<td></td>
</tr>
<tr>
<td>Agreement SDAI/Boolean remission (%)</td>
<td>0.74 (0.77)</td>
<td>0.74 (0.78)</td>
<td></td>
</tr>
</tbody>
</table>

Summary/Conclusion. When using SDAI to test for Boolean remission in a ROC analysis, SDAI evaluated by VAS and by sNRS showed similar characteristics (AUC = 0.99 for both). Sensitivity and specificity for the SDAI remission cut-off of 3.3 were 0.96 and 0.94 for VAS and 0.90 (rounded up: 0.81, rounded down: 0.96) and 0.95 (rounded up: 0.96, rounded down: 0.93) for sNRS.

Reference:

Does Joint Sonography Really Add Clinically Important Information Beyond Clinical Joint Examination?

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Objective. Sonographic assessment of joint activity in patients with rheumatoid arthritis (RA) is considered to be more sensitive than the respective clinical assessment. However, this difference may be less dependent on the physical technique used (ie, palpation vs sonography), but rather related to differences in arbitrary definitions of the presence or absence of “joint activity”. It was the aim of this study to evaluate the differences in numbers of clinically and sonographically active joints in RA, with special regard to the impact of sonographic definitions of activity.

Methods. We performed sonographic imaging of 22 joints of the hands of RA patients in clinical remission (n = 60; defined as CDAI ≤ 2.8). Each joint was assessed for grey scale synovitis (GSS) and Power Doppler (PD) signal on a 4-point scale (0 = no, 3 = marked). Sensitivity and specificity of the clinical swollen joint count (SJC) were calculated using different sonographic cut-points and combinations. We further assessed changes of CDAI if the clinical SJC was replaced by sonographically active joints (sCDAI).

Results. Among the 1320 joints of patients in remission, a total of 887 (67.2 %) was GSS positive and 269 (20.4 %) was PD positive. Clinical assessment of joint swelling was 100 % specific for sonographic activity, independent from the applied sonographic criteria. Sensitivity was low with a maximum of 25 % using the most stringent sonographic criteria (GSS ≥ 5 and PD ≥ 3). Calculation of sCDAI resulted in higher values using GSS ≥ 1 or PD ≥ 1 (mean sCDAI = 15.7) compared to the clinical CDAI of 1.0. However, accepting only grade-3 PD signals, sCDAI values approached the clinical CDAI with a mean of 1.1 (Figure 2).

Summary/Conclusion. Sonography revealed residual signals of joint activity in patients in CDAI remission, but low-grade PD and GSS signals may not reflect active synovitis. Changing the stringency of the sonographic criteria toward higher signals for determination of joint activity led to similar results when considered in the context of overall disease activity, such as in the CDAI.
Sonography-Verified Joint Inflammation but Not Ultrasound Scores for Enthesitis and Dactylitis Correlate with Corresponding Clinical Findings in Psoriatic Arthritis

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Objective To compare ultrasound-verified inflammation of joints, entheses, and tendons with corresponding clinical findings in psoriatic arthritis (PsA) patients.

Methods Prospective study of 70 consecutive PsA patients [mean age 51.1 (± SD 11.6) years, 30 % female, median disease duration 7.0 (range 0–44.7) years]. Clinical and ultrasound examination was performed at 68 joints and 14 entheses (lateral epicondyle, triceps insertion, quadriceps insertion, proximal and distal insertion of patellar ligament, Achilles tendon, plantar fascia), and clinical scores including the DAPSA, CPDAI, dactylitis score, Leeds enthesitis index (LEI), HAQ, and PASI were calculated. Sonography was performed by 2 rheumatologists blinded to clinical data using an ESAOTE Twice ultrasound device. Synovial hypertrophy and/or joint effusion (SH/E) as well as Power Doppler (PD) were subjectively graded at each joint from 0 to 3 in accordance with prior publications. At hands and feet we also recorded the presence of perisynovitis and tenosynovitis. For grading of enthesitis by ultrasound the MASEI and GUESS scores were used. Ultrasound signs of dactylitis were defined by the presence of synovitis plus tenosynovitis at MCP/PIP, PIP, and DIP joints.

Results The median DAPSA was 12.1 (0.1–70.2), median CPDAI 4.8 (± 2.5), median clinical Dactylitis score 0 (0–10), median LEI 0 (0–4), median HAQ 0.73 (± 0.81), and median PASI 1.0 (0–23.2). Using sonography, we found SH/E and/or PD at 12 [range 3–35] patients [median SH/E score 16.0 (range 3.0–56.0)] and/or 2 (0–19) PD scores. 18 patients (25.7 %) had evidence of perisynovitis in at least one MCP joint and 20 (28.6 %) patients demonstrated flexor tenosynovitis affecting at least one whole finger or toe. Median MASEI and GUESS scores were 32.5 (7.0–73.0) and 13.0 (4.0–27.0), respectively. Ultrasound signs of dactylitis were found in 5 (7.1 %) patients. DAPSA showed a moderate correlation with total SH/E (correcoeff 0.35, p = 0.003) and PD scores (correcoeff 0.36, p = 0.002), as well as with the number of joints affected by SH/E (correcoeff 0.24, p = 0.045) and/or PD (correcoeff 0.32, p = 0.006). Total CPDAI did not correlate with SH/E, PD, enthesitis, or dactylitis scores; however, within the CPDAI joint domain we found differences concerning SH/E and PD scores between patients with no [n = 17, median SH/E 12.0 (3.0–32.0); PD score 1.0 (0–11.0)] and moderate [n = 17, SH/E 25.0 (6.0–43.0), p = 0.009; PD 5.0 (0–31.0), p = 0.005] or high clinical activity [n = 26, SH/E 18.5 (6.0–56.0), p = 0.025; PD 5.5 (0–30.0), p = 0.005]. In the CPDAI enthesis and dactylitis domains no differences were found, comparing the MASEI/GUESS and ultrasound-defined dactylitis, respectively, between the groups. No correlation was found between clinical and sonographic dactylitis scores or LEI (clinical) and MASEI/GUESS (sonography).

Summary/Conclusion Ultrasound-verified joint inflammation moderately correlates with DAPSA and CPDAI joint components in PsA patients. No association was found between sonographic and clinical assessment of enthesis and dactylitis.

Seronegative Arthropathies: Value of Dual-Energy CT for Differential Diagnosis

M. Mustak1, J. Boltuch-Sherif1, M. Kasper1, G. Minimair1, J. Burmester1, G. Strauß1, L. Erlacher1

Objective Application of Dual-Energy CT for differential diagnosis in seronegative arthropathies.

Methods Retrospective analysis of 49 patients with seronegative arthropathies.

Results A retrospective analysis of 49 patients was used to investigate the value of Dual-Energy CT for differential diagnosis in patients with seronegative arthropathies. Puncture and analysis of the joint fluid was possible in 15 patients, whereas only CT without puncture could be performed in the remaining 34 patients. In the first group of patients (n = 15), where a crystal analysis was available, urate crystals could be identified in 14 patients and Dual-Energy CT investigation confirmed monosodium urate depositions in 11 of these patients. In 3 cases with positive urate crystal detection in joint fluid gout CT was negative and in one case pyrophosphate crystals were identified. In the second group (n = 34) joint puncture could not be performed as the affected joints were small finger and toe joints. 21 of these patients revealed urate depositions in Dual-Energy CT. In these cases the diagnosis of gout was confirmed and appropriate therapy could be started. 17 out of these patients had elevated uric acid levels.

Summary/Conclusion Dual-Energy CT can be applied as a tool for diagnosing gout in patients with seronegative inflammatory arthropathy especially in the case of polyarticular joint involvement and no possibility of joint puncture.

Lymphoid Chemokines in Granulomatosis with Polyangiitis (Wegener’s): Involvement of CXCL13

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Objectives The aim of the study was to assess the role of lymphoid homing chemokines CXCL19, CCL21, and CXCL13 in patients with granulomatosis with polyangiitis (GPA, Wegener’s).

Methods Sera from consecutive GPA patients before treatment and during remission were obtained. As controls, patients with other small vessel vasculitides, large vessel vasculitis, sarcoidosis and healthy controls were recruited. Serum levels of CCL19, CCL21, and CXCL13 were measured by ELISA and correlated to clinical parameters. Respiratory tract biopsies from active GPA patients were stained for CXCL13 expression by immunohistochemistry.

Results In active GPA, serum levels of CXCL13 and CCL21, but not CCL19 were elevated as compared to healthy controls. CXCL13 levels were much higher in systemic GPA as compared to localized/early systemic GPA patients. CXCL13, but not CCL21 levels correlated well with disease activity markers in GPA patients such as BVAS (r = 0.59, p = 0.0035), proteinuria (r = 0.52, p = 0.012), and C-reactive protein levels (r = 0.73, p = 0.0001). At a cut-off level of 78 pg/ml active GPA patients could be detected with 90 % sensitivity and 95 % specificity as compared to healthy controls. In addition, CXCL13 was highly expressed in respiratory tract tissue biopsies of active GPA patients.

Conclusions CXCL13 serum levels are an indicator of active vasculitis in GPA patients. CXCL13 may serve as a biomarker and is possibly involved in lymphoid tissue infiltration in GPA.

IgG4 Immune Response in Churg-Strauss Syndrome

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Objective T-helper type-2 responses are crucial in Churg-Strauss Syndrome (CSS) and may enhance the production of IgG4 antibodies. The authors assessed the IgG4 immune response in CSS patients.

Methods The authors included 46 consecutive patients with CSS (24 with active and 22 with quiescent disease), 26 with granuloma-
Figure 3: Radner H, et al. (# 38). Differences of sensitivity and specificity of 2010 ACR/EULAR criteria versus 1987 ACR criteria in different cohorts using different reference standards.

tosis with polyangiitis (GPA, Wegener’s), 25 with atopic asthma, and 20 healthy controls, and determined serum IgG, IgM, IgA, IgE, and IgG subclass levels. Tissue infiltration by IgG4 plasma cells was assessed in 9 patients with CSS, 10 with GPA, and 22 with chronic sinusitis (11 with and 11 without eosinophilia).

**Results** IgG4 levels were markedly higher in active CSS patients than in controls (p < 0.001 vs all control groups). Serum IgG4 correlated with the number of disease manifestations (r = 0.52, p = 0.01) and the Birmingham vasculitis activity score (r = 0.64, p = 0.001). Longitudinal analysis in 12 CSS cases showed that both the IgG4 level and IgG4/IgG ratio dropped during disease remission (p < 0.001 and p < 0.0001, respectively). Tissue analysis did not show an increased IgG4 plasma cell infiltration in CSS biopsies compared with control groups.

**Conclusions** Serum IgG4 levels are markedly elevated in active CSS and correlate with the number of organ manifestations and disease activity.

VCAM-1 Serum Levels Are Associated with Arthropathy in Hereditary Hemochromatosis

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1LBI für Osteologie, Hanusch-Krankenhaus, Wien; 22nd Dept. of Paediatrics, Comenius University Bratislava, Slowakische Republik; 3Abt. für Innere Medizin 3, Universität Erlangen-Nürnberg, Deutschland; 4KH Oberndorf

**Objectives** The aim of the study was to assess the role of VCAM-1 serum levels in patients with hereditary hemochromatosis (HH) with or without arthropathy.

**Methods** Sera from a large cross-sectional cohort of unselected HH patients (n = 147) were obtained and compared to healthy individuals. Serum levels of VCAM-1 were measured by ELISA and correlated to clinical measures.

**Results** VCAM-1 serum levels were elevated in HH patients as compared to healthy controls (mean 913 ± 456 vs 672 ± 216 ng/ml, p < 0.0001). Within the HH patient group, VCAM-1 levels were much higher in patients with arthropathy and joint replacement surgery. VCAM-1 levels correlated well with radiographic measures of HH arthropathy (r = 0.36, p < 0.0001). Multivariate regression analysis confirmed a highly significant association of VCAM-1 serum levels and the presence of HH arthropathy, independent from diabetes, BMI, and age.

**Conclusion** VCAM-1 serum levels emerge as a biomarker for hemochromatosis arthropathy.

Performance of the 2010 ACR/EULAR Classification Criteria for Rheumatoid Arthritis – A Systematic Literature Review

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**Objective** To summarize the diagnostic performance of the 2010 ACR/EULAR criteria from published literature performing a systematic literature search (SLR).

**Methods** Using a comprehensive search strategy a SLR was performed using the main databases (Medline, Embase, Cochrane central) as well as ACR and EULAR conference proceedings. Raw data of included studies were extracted in order to calculate sensitivity (SENS), specificity (SPEC), and positive and negative predictive values (PPV, NPV). Taking into account heterogeneity, meta-analyses were performed if possible.
BioReg – ein österreichisches Biologikaregister

BioReg – ein österreichisches Biologikaregister 39
M. Herold

Univ.-Klinik für Innere Medizin I, Medizinische Universität Innsbruck


Ziel Das österreichische nationale Biologikaregister ist eine prospektive Beobachtungsstudie mit Aufzeichnung von Krankheitsaktivität und unerwünschten Ereignissen.


Schlussfolgerung In der relativen kurzen Laufzeit von BioReg wurde das Register erfreulich rasch angenommen, was durch die mehr als 500 dokumentierten Patientendateien belegt wird. Die hohe Akzeptanz spricht auch für die Praktikabilität der angebotenen, einheitlichen Dokumentation.

Prämature Arthrose als Symptom einer Typ-II-Kollagenopathie: Fallbericht und Literaturrecherche

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1LBf für Osteologie, Hanusch-Krankenhaus, Wien; 2Inst. für Humangenetik, 1Inst. für Biochemie und 4Abt. für Innere Medizin 3, Universität Erlangen-Nürnberg, Deutschland


D. Rehabilitation

Dynamic Spinal Traction in Inpatient Rehabilitation of Low Back Pain: Sustained Improvement of Pain Experience

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1Boltzmann-Cluster für Rheumatologie, Balneologie und Rehabilitation, LBI für Rehabilitation interner Erkrankungen, Saalfelden; 2Rehabilitationszentrum/SKA der PVA, Saalfelden; 3MUI und Inst. für orthopädische Physiotherapie, UMIT, Hall in Tirol

Background/Aim Intensive multidisciplinary rehabilitation programmes can improve pain and function in chronic low back pain. Dynamic traction therapy with the device GammaSwing, which transfers rhythmic swings on the spinal column under traction, can be employed. Aim of the study was to observe if a series of dynamic extension treatments in inpatient rehabilitation would have a sustainable effect in patients with chronic low back pain.

Methods 57 patients (45 male, 12 female) with chronic low back pain were divided into 2 randomized groups at the beginning of a 3-week inpatient rehabilitation. Group A was treated with a standardised rehabilitation programme + 6 therapy units with the extension system GammaSwing (GS), while group B was treated with a standardised rehabilitation programme + 6 therapy units of back massage (MA). Pain at rest and pain on motion [measured with the visual
analogue scale (VAS), finger-floor distance, and Schober’s test were measured after each of the 6 treatments during the inpatient stay in the rehabilitation centre. PSQI (Pittsburgh Sleep Quality Index), RM (Roland & Morris Disability Questionnaire), and SES (Subjective Experience of Pain Scale) were assessed and statistically analyzed at baseline (admission), after 3 weeks (discharge), after 3 and 6 months.

Results In the course of the inpatient rehabilitation stay a significant improvement of the pain parameters in both groups was observed after application of GS respectively MA. The pain on motion decreased successively during the 6 treatments. This effect was more distinctive in the GS group and showed a statistic significance from the second treatment on, but in the MA group significant changes occurred first after the fifth treatment. In contrast to this, regarding the pain at rest the massage group showed better results at the beginning of the rehabilitation. The affective SES of both groups showed comparably good results after 3 weeks of rehabilitation. This effect could be kept up for 6 months only in the GS group. Also the sensory pain experience showed a significant improvement in the MA group, which only lasted a short time. People in employment showed a significantly reduced sensory SES after 3 months. In comparison to non-employed patients the affective SES in professionals was statistically sustainable (3 and 6 months; Figure 4).

Conclusion The integration of dynamic extension therapy with the GammaSwing to a rehabilitation concept achieves a sustainable, longer lasting improvement on the experience of pain in chronic low back pain than as a series of massages. A positive effect on the sustainability of the inpatient rehabilitation can be obtained.

Figure 4: Kullich W, et al. (# 41). The use of GammaSwing vs massage in inpatient rehabilitation of low back pain. B: baseline; E: discharge; 3M: 3 months; 6M: 6 months; SES: Subjective Experience of Pain Scale; * p < 0.05; ** p < 0.01; *** p < 0.001.

Table 4: Dür M, et al. (# 42). Characteristics of the identified patient-reported outcomes.

<table>
<thead>
<tr>
<th>Abbr.</th>
<th>Patient-reported outcomes</th>
<th>Content</th>
<th>Items</th>
<th>Response options</th>
<th>Time frame</th>
</tr>
</thead>
<tbody>
<tr>
<td>ADAPT</td>
<td>Assessment of the Demand for Additional Psychological Treatment</td>
<td>Need for psychological treatment</td>
<td>12</td>
<td>Visual analogue scales</td>
<td>Present</td>
</tr>
<tr>
<td>BDI-II</td>
<td>Beck Depression Inventory-II</td>
<td>Depression</td>
<td>21</td>
<td>4 statements: increasing severity</td>
<td>Past, present, future</td>
</tr>
<tr>
<td>CPWDQ</td>
<td>Crohn’s disease perceived work disability Questionnaire</td>
<td>Work capacity</td>
<td>14</td>
<td>4 statements: increasing frequency</td>
<td>Last year</td>
</tr>
<tr>
<td>DS-14</td>
<td>Type-D Scale 14</td>
<td>Negative affectivity &amp; social inhibition</td>
<td>14</td>
<td>Verifying statements (0 = false, 4 = true)</td>
<td>Present</td>
</tr>
<tr>
<td>EQ-SD</td>
<td>EuroQoL Health Questionnaire</td>
<td>Health status</td>
<td>5</td>
<td>Statement (no, some, extreme problems) &amp; visual analogue scale</td>
<td>Present</td>
</tr>
<tr>
<td>ESSI</td>
<td>ENRICHD Social Support Scale</td>
<td>Extent of social support</td>
<td>7</td>
<td>Question 1–6 (none, a little, some, most or all of the time), Question 7 (yes/no)</td>
<td>Present</td>
</tr>
<tr>
<td>FIOQ</td>
<td>Fecal Inconsistency Quality of Life Scale</td>
<td>Health-related quality of life</td>
<td>29</td>
<td>Different Likert scales</td>
<td>Present</td>
</tr>
<tr>
<td>HADS</td>
<td>Hospital Anxiety and Depression Scale</td>
<td>Anxiety, depression</td>
<td>14</td>
<td>Frequency: 4-point Likert scale (0 = not at all, 4 = definitely)</td>
<td>Present</td>
</tr>
<tr>
<td>IBDQ-32</td>
<td>Inflammatory Bowel Disease Questionnaire</td>
<td>Health-related quality of life</td>
<td>32</td>
<td>7-point Likert scale (1 = significant impairment, 7 = no impairment)</td>
<td>2 weeks</td>
</tr>
<tr>
<td>IBD-SES</td>
<td>Inflammatory Bowel Disease Self-Efficacy Scale</td>
<td>Self-efficacy</td>
<td>29</td>
<td>10-point Likert scale (1 = not sure at all, 10 = totally sure)</td>
<td>Present</td>
</tr>
<tr>
<td>LOT-R</td>
<td>Life Orientation Test-Revised</td>
<td>Optimism</td>
<td>8</td>
<td>5-point Likert scale (0 = strongly disagree, 4 = strongly agree)</td>
<td>Present</td>
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<tr>
<td>PAM-13</td>
<td>Patient-Activation Measure Short Form</td>
<td>Health management skills, knowledge, confidence, motivation</td>
<td>13</td>
<td>5-point Likert scale (0 = strongly disagree, 4 = strongly agree)</td>
<td>Present</td>
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<tr>
<td>PSQ (PSQ-V)</td>
<td>Perceived Stress Questionnaire recent form (PSQ-V)/ general form (PSQ-G)</td>
<td>Perceived stress</td>
<td>30</td>
<td>4-point scale on frequency (1 = almost never, 4 = usually)</td>
<td>Past month/ past 2 years</td>
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<td>PSQ-R</td>
<td>Perceived Stress Questionnaire Reconsidered</td>
<td>Perceived stress</td>
<td>20</td>
<td>4-point scale on frequency (1 = almost never, 4 = usually)</td>
<td>Present</td>
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<tr>
<td>RIFIP</td>
<td>Rating Form of Inflammatory Bowel Disease Patient Concerns</td>
<td>Worries, concerns regarding IBD</td>
<td>25</td>
<td>Visual analogue scale (0 = not at all, 100 = a great deal)</td>
<td>Present</td>
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<tr>
<td>SF-36</td>
<td>Short Form 36 health survey</td>
<td>Health-related quality of life</td>
<td>36</td>
<td>Different response scales</td>
<td>4 weeks</td>
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<td>SIBDQ</td>
<td>Short Inflammatory Bowel Disease Questionnaire</td>
<td>Quality of life</td>
<td>10</td>
<td>7-point Likert scale on frequency (1 = all the time, 7 = none of the time)</td>
<td>Present</td>
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<tr>
<td>STAI</td>
<td>State-Trait Anxiety Inventory</td>
<td>Anxiety about an event &amp; trait anxiety</td>
<td>40</td>
<td>Intensity 4-point Likert scale (1 = not at all, 4 = very)</td>
<td>Present</td>
</tr>
</tbody>
</table>
Table 5: Dür M, et al. (# 42). Coverage of the health determinants which determine health in a positive way by patient-reported outcome instruments.

| Health determinants | ICF Codes | Titles | ADAPT | BDI-II | CPQDV | EQ-14 | EQ-5D | ESSI | HADS | IBD-32 | IBID-SES | LOTR | PAM-13 | PSQ | PSQ-R | RFPC | SF-16 | SIBDO | STAI |
|---------------------|-----------|--------|--------|--------|--------|--------|--------|--------|--------|--------|--------|--------|--------|--------|--------|--------|--------|--------|
| Appreciation        | e4        | Attitudes | +      |        |        |        |        |        |        |        |        |        |        |        |        |        |        |        |
| Coping              | d240      | Handling stress and other psychological demands | +      |        |        |        |        |        |        |        |        |        |        |        |        |        |        |        |
| Gratification (vocational) | no     | Not covered by the ICF |        |        |        |        |        |        |        |        |        |        |        |        |        |        |        |        |
| Gain from illness (secondary) | pf  | Personal factor |        |        |        |        |        |        |        |        |        |        |        |        |        |        |        |        |
| Job satisfaction    | no        | Not covered by the ICF |        |        |        |        |        |        |        |        |        |        |        |        |        |        |        |        |
| Occupational balance| no        | Not covered by the ICF |        |        |        |        |        |        |        |        |        |        |        |        |        |        |        |        |
| Participation (social) | d9   | Community, social and civic life | +      | +      | +      | +      | +      | +      | +      | +      | +      | +      | +      | +      | +      | +      | +      | +      |
| Reflecting about one's life in an optimistic way | b126 | Temperament and personality functions | +      | +      | +      | +      | +      | +      | +      | +      | +      | +      | +      | +      | +      | +      | +      | +      |
| Resilience          | b1263     | Psychic stability | +      | +      | +      | +      | +      | +      | +      | +      | +      | +      | +      | +      | +      | +      | +      | +      |
| Sense of coherence  | no        | Not covered by the ICF |        |        |        |        |        |        |        |        |        |        |        |        |        |        |        |        |        |
| Social support      | + e3      | Support and relationships | +      | +      | +      | +      | +      | +      | +      | +      | +      | +      | +      | +      | +      | +      | +      | +      |
| Work-life balance   | no        | Not covered by the ICF |        |        |        |        |        |        |        |        |        |        |        |        |        |        |        |        |        |

ICF: International Classification of Functioning, Disability and Health; ADAPT: Assessment of the Demand for Additional Psychological Treatment; BDI: Beck Depression Inventory; CPQDV: Crohn's disease perceived work disability Questionnaire; EQ-14: Type-D Scale 14; EQ-5D: EQ-5D Health Questionnaire; ESSI: ENRICH-ID Social Support Scale; HADS: Hospital Anxiety and Depression Scale; IBD-32: Inflammatory Bowel Disease Questionnaire 32; IBID-SES: Inflammatory Bowel Disease – Self-Efficacy Scale; LOTR: Life Orientation Test Revised; PAM-13: Patient Activation Measure Short Form; PSQ: Perceived Stress Questionnaire; PSQ-R: Perceived Stress Questionnaire Reconsidered; RFPC: Rating Form of Inflammatory Bowel Disease Patient Concerns; SF-36: Short Form 36; SIBDO: Short Inflammatory Bowel Disease Questionnaire; STAI: State-Trait Anxiety Inventory.

Methods A qualitative study was conducted. Told life stories were analysed by the biographical narrative interpretative method, findings were linked to concepts determining health in a positive way. Furthermore the qualitative data were analysed regarding gender differences. Two systematic literature searches were done to identify relevant concepts and clinically relevant PROs. Concepts and the items of the PROs were linked to WHO International Classification of Functioning, Disability and Health (ICF) codes and compared to evaluate instruments’ coverage.

Results 15 people with CD with a median age of 46 years (IQR 34–60) and median disease duration of 15 month (IQR 8–30) participated. 14 participants mentioned self-efficacy and social support (93 %), and 13 described job satisfaction (87 %) as being important, which were the 3 commonest concepts. Most of them experienced relations between their health behaviour and disease course and tried to “gain control over their disease” by being self-efficient. While participation had more meaning for men, appreciation and resilience were more important for women. Work-life balance and secondary gain were hardly meaningful. The 18 patient-reported outcome tools (Table 4) covered 9 different ICF codes (Table 5).

Conclusion This is the first study elaborating the coverage of patient’s perspective by commonly used patient-reported outcome instruments. The use of the Perceived Stress Questionnaire – recent form is recommended because it covered most concepts, as well as the use of the Inflammatory Bowel Disease Self-Efficacy Scale due to the importance of self-efficacy for people with CD. Social support, self-efficacy, and gender differences at several concepts should get more attention in clinical daily routine and in the research of people living with CD.

Gender Differences of Concepts Important to People Living with Rheumatoid Arthritis and their Coverage by Standard Measures of Function, Health, and Well-Being

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Background/Purpose Rheumatoid arthritis is a chronic autoimmune disease that has a major impact on functioning, health, and well-being. Concepts which determine health in a positive way are often not addressed in a busy clinical setting. The aim of this study is to explore which concepts determine health in a positive way and are meaningful to patients with RA. Furthermore we wanted to analyse whether they are covered by patient-reported outcome (PRO) instruments and which of them could be recommended for clinical use and/or research.

Methods We conducted a qualitative narrative biographic study consisting of 3 steps (Figure 5). People with RA were asked to tell their life stories which were analysed with the biographical narrative interpretative method afterwards. Hereinafter, we linked concepts which determine health in positive way derived from a systematic literature search to the perspective of patients. Finally, we explored whether these concepts were covered by PROs identified in another systematic literature search. The evaluation of the PROs’ coverage was based on the model of the WHO International Classification of Functioning, Disability and Health (ICF).

Results 15 people with RA with a median age of 52.5 years (IQR 35.75–62.5) and median disease duration of 24.5 years (IQR 10–59.25) participated in the qualitative study. Occupational balance, social support, participation, and coping were the most frequently mentioned meaningful concepts (Table 6). While coping was men-
tioned by a higher number of men (83 % of all men), optimism and vocational gratification were only important for women (78 resp 67 %). The concept of work-life balance did not appear in the qualitative data. Secondary gain from illness was found only in 2 participants (13 %). 31 PROs were derived from the systematic literature search. The concepts coping, self-efficacy, participation, optimism, and social support were covered particularly.

Conclusion Several concepts which determine health in a positive way show a gender difference. Social support and coping should get more attention in clinical routine and research of people with RA. The use of the Life Orientation Test – Revised (LOT-R) [Scheier et al. 2005] and Functional Assessment Chronic Illness Therapy – Fatigue (FACIT-F) [Nicklin et al. 2010] is recommended, because they cover most determinants of health.

Educational Needs of Austrian Patients with Rheumatoid Arthritis, Psoriatic Arthritis, and Hand Osteoarthritis

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Background RA, PsA, and HOA are chronic disabling diseases which impact on body functions, but also on daily activities and participation in society as well as productivity and employment. As the active participation of patients is essential to successfully manage a rheumatic disease and to overcome potential limitation in daily activities and participation restrictions, it is essential to explore the educational needs of patients.

Method We conducted a quantitative study using the Educational Needs Assessment Tool (ENAT) questionnaire in a convenience sample of patients with either RA, PsA, or HOA in a rheumatology centre in Austria. 130 patients with RA, 125 patients with PsA, and 48 patients with HOA diagnosed according to the ACR criteria participated in this study. Descriptive statistics were calculated for demographic data, disease activity measures, and each item of the ENAT questionnaire. In addition, we ranked the items with the highest and lowest importance to the patients and compared between all 3 diseases.

Results 130 RA Patients (75 % female), 125 PsA patients (45 % female), and 48 HOA patients (83 % female) participated in the study. Age was comparable between the 3 groups (mean ± SD in RA: 56 ± 13.5 years; PsA: 51 ± 10.5 years; HOA: 64 ± 7 years), however, patients with HOA were slightly older. Mean disease duration ranged from 11 (both RA and PsA) to 14 years (HOA). A high percentage of patients (above 70 %) in each group expressed interest to receive education about their disease. RA and PsA patients described almost similar educational interests (items marked “extremely important” and “very important” were collapsed into one category), while HOA patients had also similar, but somewhat different interests. This refers to “Taking the best medicine for me” (RA group: 56.9 %, PsA group: 55.2 %, HOA group: 44.4 %), “What are the side effects of my medicines are” (RA group: 57.6 %, PsA group: 57.6 %, HOA group: 62.5 %), “Ways my arthritis can be treated” (RA group: 58.5 %, PsA group: 55.2 %, HOA group: 58.3 %), and “What might happen in the future” (RA group: 60 %, PsA group: 60 %, HOA group: 58.3 %). In addition, patients in the HOA group were most interested in “Things that should be avoided to do” (58.3 %) and “Foods and vitamins that might help” (54.2 %), deal with their disease. The following items were considered less important to know by patients of all 3 groups: “Where I can find groups who will help me to cope with arthritis” (RA group: 22.3 %, PsA group: 25.6 %, HOA group: 27.1 %) and “Who I can ask about financial help” (RA group: 22.3 %, PsA group: 26.4 %, HOA group: 18.8 %). Questions describing depression were also rated low by the RA group (“Why I am feeling down or depressed” (20 %), “Ways to deal with moods or depression” (18.5 %)).

Conclusions Educational interests of patients with RA and PsA were most similar, while the interests of HOA patients differed slightly from those 2 groups. As a large percentage of patients expressed interest in education in general, the ENAT might be an interesting tool to assess individual needs. While there are hardly structured education sessions for patients with arthritis in Austria, education may be taught informally by health professionals. Our findings of the ENAT questionnaire may also be useful in guiding physicians and health professionals in elaborating individualized and target-centred treatment programmes for patients with arthritis.

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E. Sozioökonomie/Berufspolitik

Der niedergelassene Rheumatologe in Österreich – erste Leistungsposition für Rheumatologie ab 1. Juli 2012

R. Puchner
Rheumatologische Praxis, Wels


Rheumatologische Versorgung in Österreich – eine Statuserhebung

R. Pechmann1, M. Gaugg2, W. Granninger3
1Rheumatologische Praxis, Wels; 2Abt. für Rheumatologie, MUG Ziel Erhebung der Umsetzung der internationalen Empfehlungen zum Behandlungsmanagement der rheumatoiden Arthritis in Öster- reich („treat-to-target“).


Ergebnisse Die durchschnittliche Fallzahl von chronischer Poly- arthritis bei den teilnehmenden Rheumatologen beträgt 15 Patienten pro Woche. Die Dokumentation der Patientenbehandlung erfolgt in 80 % durch den Arzt, in 20 % unterstützen medizinische Fachkräfte die Dokumentation. Rheumatologisch ausgebildetes, nicht-ärztliches Fachpersonal wird in 29 % der Praxen und Ambulanzen eingesetzt. In 88 % bzw. 81 % werden schriftliche Informationsmaterialien bzw. die Aufklärungs- und Einverständnissformulare der ÖGR zur Basis- therapie der rheumatoiden Arthritis verwendet. 82 % der Mediziner nehmen regelmäßig an Qualitätszirkeln und Arbeitskreisen teil. Zur regelmäßigen Erfassung der Krankheitsaktivität verwenden 71 % der Antwortenden immer einen validierten Summenwert, bei allen An- geboten ist allerdings die geringe Rücklaufquote der Befragung zu berücksichtigen (15 %). Als stärkstes Hindernis für eine optimalezielorientierte Therapie werden die fehlenden Abrechnungsmöglich- keiten der ärztlichen Leistungen mit den Krankenkassen gesehen.


ACQM als Beispiel für eine webbasierte Registerlösung

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Methoden Aufbauend auf die Erfahrungen von Swiss Clinical Qual- ity Management (SCQM) wurde eine webbasierte IT-Lösung ent- wickelt, die voll in die tägliche Routine integrierbar ist (Open Clini- cal Quality Management (OCQM) wurde eine webbasierte IT- Lösung für die Anwendung als Rheuma- register in der klinischen Praxis anzubieten.
Die Diagnosesicherung brachte der histologische Befund. Interessant an diesem Fall ist, dass sich die WG hier in einer ganz speziellen Form erstmals manifestiert hat. Manchmal ist es schwierig, allein durch die Klinik, vor allem bei Bestehen von Fieber, eine infektiöse Erkrankung von einer Autoimmunerkrankung zu unterscheiden.

**AVß Integrin Inhibition with Cilengitide both Prevents and Treats Collagen-Induced Arthritis**

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**Background/Purpose** Rheumatoid arthritis (RA) is a chronic inflammatory disease characterized by synovial inflammation and osteoclast- (OC) mediated bone erosions. Alphavbeta3 (avß3) integrin is highly expressed in osteoclasts and its inhibition disturbs their function. Avß3-blocking antibodies can reduce bone resorption and mice lacking ß3 are osteopetrotic. However, the role of avß3 in the development of collagen-induced arthritis (CIA), a well established model for human RA, has not been examined extensively. We aimed to study the role of the avß3 inhibitor cilengitide, a synthetic Arginine-Glycine-Asparagine amino acid peptide (RGD peptide), on osteoclastogenesis and its efficacy in preventing and treating CIA.

**Methods** In vitro analysis, mouse bone marrow-derived cells (BMCs) were differentiated into tartrate-resistant acid phosphatase (TRAP+) multinucleated mature OCs in the presence of macrophage colony stimulating factor (M-CSF) and receptor activator of nuclear factor kappa-B ligand (RANKL). Cilengitide was added in increasing concentrations (2 nM to 20 μM) to the culture. Moreover, we performed these osteoclastogenesis assays on plates coated with RGD containing matrix molecules such as osteopontin, fibronectin, and fibrinogen, but also on Poly-D-lysine coatings to assess for avß3 independent adhesion. For in vivo analysis, CIA was induced in 6–8 week-old male DBA/1 mice by immunisation with bovine type-II collagen at day 1, followed by boosting at day 21. For the CIA prevention study mice were injected 1.5 mg/kg cilengitide (n = 15) or placebo (n = 15) subcutaneously (s.c.), 5 days per week, starting one day prior to CIA induction until day 53. In the CIA treatment study mice with established arthritis were randomized and treated s.c. with 1.5 mg/kg (low-dose, n = 19) or 75 mg/kg (high-dose, n = 7) cilengitide or placebo (n = 15) subcutaneously (s.c.), 5 days per week until day 59. The preventive and treatment effects were evaluated by investigating the clinical course of arthritis assessed by paw thickness and grip strength.

**Results** In vitro increasing concentrations of cilengitide (KC50: 250 nM) dose-dependently reduced pre-OC numbers on all plate coatings, indicating an inhibiting effect at the early stage of pre-OC proliferation. OCs were significantly reduced between 20 nM and 200 nM, followed by complete blockade of OC formation above 2 μM. At 200 nM an intriguing morphological difference was observed with reduction in OC size, suggesting that cilengitide may disrupt spreading and the fusion capacity at the early pre-OC stage. In the in vivo preventive experiment, cilengitide significantly reduced incidence (92.8 % vs 40 %) and severity of CIA as evidenced by the reduction of the clinical disease activity scores of paw swelling and grip strength. In the in vivo treatment experiment, both low-dose and high-dose cilengitide effectively inhibited the progression of established arthritis.

**Conclusions** Osteoclastogenesis requires intact avß3 integrin function. Systemic avß3 integrin inhibition with cilengitide potently prevents and treats experimental CIA arthritis. Therefore, cilengitide may be a novel therapeutic target in RA.
Similar Problem in the Activities of Daily Living, But Different Experience – A Qualitative Analysis in Six Rheumatic Conditions and Eight European Countries


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Objective To compare the concepts of functioning in daily life important to patients with 6 rheumatic conditions for similarities and differences regarding their qualitative content.

Method A qualitative analysis of 44 focus groups of 8 European countries in 229 patients with fibromyalgia, hand osteoarthritis, psoriatic arthritis, rheumatoid arthritis, systemic lupus erythematosus, and systemic sclerosis using the WHO International Classification of Functioning, Disability and Health (ICF) as a framework. Concepts and, where necessary, also sub-concepts and transcripts were combined and compared independently by 2 researchers who – in case of disagreement – achieved consensus through discussion.

Results 20 concepts out of 109 were described similarly in all 6 diseases, eg, body image, fatigue, emotional issues, mobility, and hand function. However, even if the same concept was mentioned, patients’ experiences were different, such as mental and physical aspects limiting the ability to drive in patients with fibromyalgia compared to only physical problems in all other diseases. Within body functions and structures, several concepts were relevant for certain conditions only.

Conclusion A large number of similar problems is mentioned as “typical” by patients with different rheumatic conditions. These could probably be targeted, with a disease-specific approach, in interventions by non-physician health professionals.

The Polyphenols Curcumin and Resveratrol Effectively Block IL-1β and PMA-Induced IL-6 and VEGF-A Expression in Human Synovial Fibroblasts

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Objective To investigate the anti-inflammatory effects of polyphenols such as curcumin (diferuloylmethane) and resveratrol (trans-3,49,5-trihydroxystilbene) have a wide range of pharmacological and biological activities. The anti-oxidant, anti-inflammatory, and apoptotic effects of these compounds have been assessed in various in vitro and in vivo systems. This study investigated possible anti-inflammatory effects of curcumin and resveratrol on the human synovial fibroblast cell line (MHTA) and FLS obtained from RA patients. Particular attention was paid to the modulation of IL-6 and VEGF-A expression by these substances.

Methods The human synovial fibroblast cell line MHTA and FLS derived from RA patients were stimulated with 1L-1β (10 ng/ml) or PMA (100 ng/ml) in the absence or presence of increasing concentrations of curcumin or resveratrol (12.5–100 µM). After 6 h, the cell culture supernatants were harvested and IL-6 and VEGF-A release was quantified by enzyme-linked immunosorbent assays (ELISAs). Furthermore, modulation of mitogen-activated protein kinase (MAPKs) such as p38 and ERK1/2 as well as transcription factor NF-kB were analysed by immuno-blotting.

Results Both curcumin and resveratrol effectively blocked IL-6 and VEGF-A expression in MHTA cells and RA-FLS in a concentration-dependent manner. Notably, VEGF-A expression was only induced by PMA, but not by IL-1β, and could be detected only after mitogen stimulation. In MHTA cells however, VEGF-A expression could not be detected. Furthermore, both substances induced deactivation of ERK1/2 and blocked activation of NF-kB.

Summary/Conclusion Curcumin and resveratrol are natural compounds representing strong anti-inflammatory effects and could be natural remedies in the treatment of chronic inflammatory diseases like RA.

Alimentärer Marasmus bei Schizophrenie als Ursache einer Gichtarthritis

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Methoden Fallpräsentation.


The H$_2$S-Donor Sodium Hydrogen Sulphide Effectively Attenuates TNF-α and IL-6 Expression in the Human Monocyte Cell Line U937

**Objective**
Approximately 1% of the European population suffer from rheumatoid arthritis (RA), a chronic systemic inflammatory disease. Enhanced severe changes in the synovium and articular structures are characteristic features. To relieve arthritis pain and reduce or slow the pathogenic processes, treatments include drugs (e.g., “biologics”), surgery, and balneotherapy (i.e., Obersalz sulfur baths). Mononuclear cells, namely lymphocytes and monocytes, are considered to enfor the severity of RA dramatically. Their role as initiators of RA is unlikely but secretion of mediators by activated cells have broad proinflammatory, destructive, and remodelling functions. The object of this work was to analyze the efficacy of sodium hydrogen sulfide (NaHS) treatment on LPS-stimulated monocytes (U937 cell line).

**Methods**
After phorbol 12-myristate 13-acetate (PMA) treatment (10 ng/ml) for 24 hours, U937 cells were incubated with increasing concentrations of NaHS (0.125–1.0 mM) for 30 minutes before being stimulated for 6 hours with lipopolysaccharide (LPS; 100 ng/ml). In parallel, LPS-stimulated U937 cells have been treated with NaHS after 3 hours again. To quantify IL-6, TNF-α, and IL-1β secretion, enzyme-linked immunosorbent assays (ELISA) were performed. The effect of H$_2$S on ERK1/2 and p38 mitogen-activated protein kinases (MAPKs) modulation was examined by western blot analysis.

**Results**
Our data strongly suggest that H$_2$S suppressed IL-6 and TNF-α expression intrinsically. The highest H$_2$S concentration (1.0 mM) reduced TNF-α and IL-6 production up to 40–50%. Moreover, re-treatment of LPS-stimulated cells with NaHS resulted in almost complete IL-6 repression. Unlike suppressive effects of H$_2$S on IL-6 and TNF-α expression, high concentrations of H$_2$S stimulated IL-1β expression dramatically. We also observed that high H$_2$S concentrations (0.5–1.0 mM) induced phosphorylation of ERK1/2. U0126, a specific inhibitor of MEK1/2, suppressed TNF-α, IL-6, and IL-1β expression completely, while SB203580, a specific inhibitor of p38-MAPK pathway, blocked only IL-6 expression.

**Summary/Conclusion**
H$_2$S is a gaseous molecule with controversial effects. Its anti-inflammatory properties resulted in downregulation of IL-6 and TNF-α expression whereas its proinflammatory effects led to ERK1/2 phosphorylation and enhanced IL-1β expression.

Foxp3+ Regulatory T Cells that Lack CD25 Expression Might Serve as a Marker to Diagnose and Monitor Systemic Lupus Erythematosus (SLE) Patients with Kidney Involvement

**Objective**
CD4+CD25–Foxp3+ T cells have been shown to be a population of regulatory T cells which are increased in SLE patients. So far their detailed role in SLE patients has not been elucidated. We therefore investigated the role of disease activity, treatment, and organ involvement on proportions of CD4+CD25–Foxp3+ T cells in SLE patients.

**Methods**
Percentages of CD4+CD25–Foxp3+ regulatory T cells were determined in peripheral blood mononuclear cells (PBMC) in HC (n = 21) and SLE patients (n = 61) by 6-colour flow cytometry (FACS). In selected SLE patients suffering from active glomerulonephritis, proportions of CD4+CD25–Foxp3+ T cells were analyzed in urine samples. Percentages of CD4+CD25–Foxp3+ T cells were correlated with clinical data, the immunosuppressive therapy, and disease activity indices. Additionally time course analyses of proportions of CD4+CD25–Foxp3+ T cells were performed in patients suffering from active glomerulonephritis before and after treatment with cyclophosphamide and in patients with active skin involvement before and after cortisone treatment.

**Results**
Proportions of CD4+CD25–Foxp3+ T cells were significantly increased in SLE patients as compared to HC and proportions of CD4+CD25–Foxp3+ T cells were significantly higher in active SLE patients as compared to inactive patients. Moreover we observed a significant correlation of % CD4+CD25–Foxp3+ T cells with the disease activity scores SLEDAI, ECLAM, and SIS and with the daily cortisone dose. Time course analysis revealed no influence of cortisone treatment on the percentage of CD4+CD25–Foxp3+ T cells in patients with active skin involvement, whereas cyclophosphamide treatment of patients with active glomerulonephritis led to a decrease in CD4+CD25–Foxp3+ T cells, reflecting the role of the disease activity on proportions of CD4+CD25–Foxp3+ T cells. Further analyses of the different organ involvements revealed that only patients with renal involvement had significantly higher proportions of CD4+CD25–Foxp3+ T cells among SLE patients. Proportions were even increased in active nephritis patients as compared to patients with chronic kidney disease. Furthermore we observed a significant correlation between proportions of CD4+CD25–Foxp3+ T cells and the extent of proteinuria and could detect CD4+CD25–Foxp3+ T cells in urinary samples of patients suffering from active nephritis.

**Summary/Conclusion**
Proportions of CD4+CD25–Foxp3+ T cells are significantly increased in SLE patients with renal involvement. Since CD4+CD25–Foxp3+ T cells also correlate with the extent of proteinuria and were found to be decreased after cyclophosphamide treatment in long time course analyses, CD4+CD25–Foxp3+ T cells might represent a new biomarker to recognize and monitor patients with renal involvement.

The Role of miR-146 in Inflammatory Arthritis

**Objective**
During activation of innate immunity, miR-146a is an important regulator of the acute inflammatory response. Elevated miR-146a expression is observed in human diseases, such as the synovial tissue of arthritic patients. However, the consequence of this increase and its influence on the course of the disease is not clear yet. Thus the role of miR-146a in inflammatory arthritis is not known.

**Methods**
We induced K/BxN serum transfer arthritis in wild-type and miR-146a−/− mice, disease severity was assessed clinically and histologically. Serum cytokine levels were measured by ELISA. FACS analysis of the spleens was performed to determine its cellular composition.

**Results**
Absence of miR-146a leads to increased clinical signs of the serum transfer arthritis. In line, higher serum levels of the proinflammatory cytokines IL-12 and TNF were measured in the serum of miR-146a−/− mice compared to wt mice. When we analyzed the cellular composition of spleens after induction of serum transfer arthritis, we found elevated numbers of monocytes/macrophages in miR-146a-deficient mice compared to wt. Although in vitro-generated macrophages and dendritic cells did not show any difference in the cytokine production, we found increased activation of these cells in vivo.

**Summary/Conclusion**
These data demonstrate that miR-146a serves as a negative regulator of inflammatory arthritis, as miR-146a-deficient animals develop more severe clinical signs of serum transfer arthritis and produce significantly higher amounts of proinflammatory cytokines compared to wt mice. It needs to be clarified whether the cytokine levels in the serum of immunised miR-146a−/− mice derive from an enhanced myeloid cell number or emerge from a higher cytokine production of these cells. However, miR-146a seems to regulate the number of proinflammatory cells and moreover their vation status.
**Objective** To investigate the individual impact of synovial inflammation, subchondral bone erosion, or cartilage damage on functional impairment in an animal model of rheumatoid arthritis (RA).

**Methods** We analysed gait profiles in human tumour necrosis factor transgene (hTNFtg) animals, using the video-based Catwalk gait analysis system (from Noldus, Netherlands). In this system, mice run along an illuminated glass plate. A digital camera measures light emissions resulting from the contact of paws on the glass plate. We evaluated gait profiles at different time points of disease (6, 10, 15, and 20 weeks of age) in hTNFtg animals. Wild-type littermates served as controls. Bodyweight and clinical signs of arthritis including paw swelling and grip strength were also evaluated. To investigate whether gait changes are related to pain, we treated hTNFtg animals with diclofenac (50 mg/kg, i.p.) at week 10 and week 15 after birth and analysed gait profiles before as well as 1 h and 3 h after treatment. To analyse inflammatory joint destruction, we quantitatively assessed the extend of synovial inflammation, subchondral bone erosion, and cartilage damage on hematoxylin & eosine (H&E), tartrate-resistant acid phosphatase (TRAP), and toluidine-blue stained paw sections. We performed correlation studies between gait parameters and the histopathological components.

**Results** We identified several gait parameters, among them weight bearing, stride length, and contact area of the paw, to be significantly decreased in hTNFtg animals compared to sex- and age-matched wild-type animals. Moreover, we found a marked reduction in maximum intensity, an indicator for weight bearing, in week 10 and 15 compared to 6-week-old hTNFtg mice. Similar effects were seen in print width, print area, print length, max contact, max intensity, and max contact area at different stages of disease. Interestingly, analgesic treatment with diclofenac (50 mg/kg, i.p.) resulted in a better improvement of weight-bearing parameters in 10-week-old hTNFtg mice than in 15-week-old hTNFtg animals indicating a pain-independent, irreversible functional impairment in progressed disease. To further investigate to which extend synovial inflammation, subchondral bone erosion, or cartilage damage is responsible for the functional impairment of joints, we correlated these components with changes in different gait parameters. We observed strong correlations of various gait parameters with the amount of cartilage damage, whereas subchondral bone erosions correlated to a lesser extend and synovial inflammation did not correlate at all.

**Conclusion** Video-based Catwalk gait analysis is a useful tool for quantitative assessment of functional impairment in inflammatory, destructive arthritis. Joint destruction due to cartilage damage, but not synovial inflammation per se is the most important component leading to functional impairment of hTNFtg mice.

**Effects of Cholic Acid and its Derivatives in Experimental Arthritis**

**Introduction** Derivatives of cholic acid (CA) such as nor-ursodeoxycholic acid (norUDCA) are promising therapeutic agents in the treatment of cholangiopathies. Previous studies demonstrated anti-inflammatory and anti-fibrotic properties of norUDCA in experimen- t al sclerosing cholangitis.

**Objective** To investigate the anti-inflammatory potential of CA and its derivatives ursodeoxycholic acid (UDCA) and nor-UDCA in other inflammatory disorders, we investigated the effect of these substances in collagen-induced arthritis (CIA), an animal model for inflammatory erosive arthritis.

**Methods** To study the role of CA, UDCA, and nor-UDCA in inflammatory erosive arthritis, animals were prophylactically treated with CA-, UDCA-, or nor-UDCA-enriched diet pellets (5 mg/kg diet) or standard diet pellets (placebo) **ad libitum** starting 1 week before the first immunisation with collagen. Animals were weekly assessed for clinical signs of arthritis such as paw swelling and grip strength. Bodyweight and food consumption were also weekly assessed during the experimental period. After 10 weeks of treatment hind paws, liver, sera, and lymph nodes were isolated for further analysis. Sera were investigated for anti-collagen antibodies, cytokine responses, and liver parameters such as alkaline phosphatase (AP) and alanine transaminase (ALT). Paraffin-sections of hind paws were examined for histopathological changes in synovial inflammation, subchondral bone erosion, cartilage damage, and osteophyte formation. Joint pathology was quantified using Osteometer Software connected with a digital camera and a Zeiss microscope.

**Results** Prophylactic treatment of CIA mice with CA derivatives UDCA and norUDCA could not significantly prevent disease incidence. In contrast, treatment with CA showed a marked increase in disease incidence and severity compared to placebo-treated animals. Whereas UDCA and norUDCA showed a similar course of clinical signs of arthritis, CA significantly increased paw swelling and exacerbated the loss of grip strength compared to the placebo group. Histological analysis of hind paws revealed an increase in synovial inflammation, bone erosion, and cartilage damage in the CA-treated animals compared to the placebo group. No changes in joint pathology were observed in the UDCA- or norUDCA-treated group compared to the placebo group. Similar amounts of total anti-collagen IgG and its subtypes IgG2 and IgG2c were found in all treatment groups suggesting that CA, UDCA, and norUDCA have no effects on the adaptive immune system (T and B cells). Furthermore, FACS analysis revealed no differences in surface markers of lymph node cells including T cells, B cells, dendritic cells, and macrophages. Uptake of CA, UDCA, and norUDCA was confirmed by serum analysis. In addition, CA-, UDCA-, and norUDCA-treated animals showed reduced ALT levels and increased AP levels compared to the placebo-treated group, in addition, serum analyses revealed a trend toward increased IL-6 levels suggesting that CA exacerbates IL-6 levels driving disease onset and severity in the CIA model.

**Conclusion** Bile acid derivatives UDCA and norUDCA could not modulate collagen-induced arthritis. In contrast, cholic acid exacerbated the incidence and severity of inflammatory erosive arthritis in this model. Thus, promising anti-inflammatory and anti-fibrotic agents for cholangiopathies have no beneficial effects on an experimental arthritis model.

**Physical Function Continues to Improve in Sustained Clinical Remission of Rheumatoid Arthritis**

**Objective** Physical function is one of the major outcomes in RA as it predicts work disability, quality of life, health care resource utilisation, and mortality. It is currently still unclear what the minimum duration of remission is that would improve functional capacity to the best possible degree. To investigate the course of functional status assessed by health assessment questionnaire (HAQ) in RA patients with sustained clinical remission for at least 6 months.

**Methods** We provided a random 80–90 % data sample of RA patients enrolled in recent clinical trials (ASPIRE, ATTRACT, DEO19, ERA, Leflunomide, PREMIER, and TEMPO; n = 4863) by the respective sponsors. We identified patients who at some point during the trials achieved sustained remission in consecutive visits of at least 6 months by the DAS28-CRP < 2.6 or SDAI ≤ 3.3. We obtained HAQ scores during these 6-month remission periods, and were thus able to investigate the course of physical function over...
**Ergebnisse** Der Paarvergleich zeigt in keiner Gruppe einen signifikanten Unterschied der Anti-Sa-Titer zwischen den verschiedenen Zeitpunkten. Nur in der Gruppe mit sinkendem DAS28 nach 6 und 12 Monaten und in der gemessenen optischen Dichte der Substratreaktion konnten signifikante Unterschiede erkannt werden ($p = 0.020/ p = 0.005$).

**Schlussfolgerung** Auch wenn sich in einzelnen Fällen eine Korrelation zwischen dem Krankheitsverlauf und dem Anti-Sa-Antikörpertiterverlauf lässt, so gilt dieser Zusammenhang nicht für das Kollektiv. Die Ergebnisse weisen darauf hin, dass auch der Anti-Sa-Antikörpertiter sich nicht mit der Krankheitsaktivität der RA ändert.

**Monocytes Are Targets of Abatacept (CTLA-4Ig) Therapy in Patients with Rheumatoid Arthritis (RA)** 61


**Medizinische Universität Wien**

**Objective** Abatacept (CTLA-4Ig) inhibits the binding of CD28 to the B7 ligands CD80/CD86 and thereby effector T cell activation. In addition, binding of CTLA-4Ig and reverse signalling via CD80/CD86 potentially exerts effects on antigen-presenting cells (APC) and might therefore contribute to the therapeutic effect. In order to further elucidate the mechanism of CTLA-4Ig we performed phenotypic and functional analysis of APC in rheumatoid arthritis (RA) patients before and after the initiation of CTLA-4Ig therapy.

**Methods** Peripheral blood mononuclear cells (PBMC) from RA patients (n = 12) were analyzed before and 2 and 4 weeks after the initiation of CTLA-4Ig therapy. Proportions of CD14+ monocytes, CD19+ B cells, CD1c+ myeloid dendritic cells (DC), and CD303+ plasmacytoid DC were determined by flow cytometry. Monocytes were further analyzed for the expression of costimulatory and adhesion molecules and for their transendothelial migratory capacity in vitro. Further, CD14+ cells from healthy controls (HC) were isolated by fluorescence-activated cell sorting (FACS) and magnetic cell sorting (MACS), incubated with CTLA-4Ig, and analyzed for their migratory and spreading capacity.

**Results** Proportions of CD14+ monocytes were significantly increased in RA patients treated with CTLA-4Ig. Phenotypic analysis revealed no significant differences in the expression of costimulatory molecules whereas the expression of several adhesion molecules was found to be significantly diminished. In addition isolated monocytes displayed a significant reduction in their adhesion and transendothelial migratory capacity upon treatment with CTLA-4Ig. Likewise, isolated monocytes from HC displayed a significant reduction in their migratory capacity after pre-incubation with CTLA-4Ig in a dose-dependent manner. In line with these findings, spreading assays also revealed a profound impact of CTLA-4Ig on actin cytoskeletal and focal adhesion reorganization in CD14+ monocytes.

**Summary/Conclusion** Our data suggest that CTLA-4Ig directly affects phenotypic and functional characteristics of monocytes, which might decrease monocyte migration to the synovium. These findings represent an additional mechanism of CTLA-4Ig therapy in RA.

**Abatacept (CTLA-4Ig) Therapy Reduces the Susceptibility of T Cells to Regulatory T Cell Suppression in Patients with Rheumatoid Arthritis (RA)** 62

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**Medizinische Universität Wien**

**Objective** Abatacept (CTLA-4Ig) inhibits the binding of CD28 to the B7 ligands CD80/CD86 on antigen-presenting cells (APC) and thereby effector T cell activation. Besides APC, costimulatory molecules can also be expressed on T cells upon activation. Whether this allows CTLA-4Ig to directly affect distinct T cell subsets, exerting a positive or negative effect, remains unclear. Our aim was to perform phenotypic and functional analysis of T cells in RA patients before and after the initiation of CTLA-4Ig therapy.

**Methods** Peripheral blood mononuclear cells (PBMC) from RA patients (n = 15) were analyzed before and 2 and 4 weeks after the initiation of CTLA-4Ig therapy. Proportions of naïve and memory CD4+ T cells and CD4+CD25+Foxp3+ regulatory T cells (Treg) were determined by flow cytometry (FACS). T cells were analyzed for the expression of marker molecules characteristic for activated T cells and Treg. PBMCs from healthy controls (HC) were pre-incubated with different doses of CTLA-4Ig before T cell receptor (TCR) stimulation and analyzed by FACS. Apoptosis was induced in CTLA-4Ig incubated cells by anti-Fas antibody and DNA fragmentation was measured by TUNEL staining. CD4+CD25+ Treg were isolated from RA patients by cell sorting and analyzed for their functional capacity. Suppression assays were performed with Treg and responder T cells from HC after pre-incubation of individual cell populations with
CTLA-4Ig or with antibodies (Abs) against costimulatory B7 molecules.

**Results** Proportions of CD4+ T cells and T_{reg} substantially increased 2 and 4 weeks after the initiation of CTLA-4Ig treatment. No differences were observed for the percentage of memory and naive CD4+ T cells. Phenotypic analyses revealed a downregulation of activation-associated marker molecules and of CD95 on CD4+ T cells and T_{reg}. Likewise, pre-incubation of PBMCs from HC with CTLA-4Ig before stimulation led to a dose-dependent downregulation of activation markers on CD4+ cells and T_{reg}. Moreover in vitro analyses of CD4+ T cells and T_{reg} from HC showed a dose-dependent decrease in AICD after incubation with CTLA-4Ig. Functional analysis of isolated T_{reg} from RA patients revealed a diminished suppressive capacity of T_{reg} 4 weeks after treatment with CTLA-4Ig. However, only the pre-incubation of responder T cells, but not of T_{reg} from HC with CTLA-4Ig or with Abs against B7 molecules resulted in a decreased T cell suppression.

**Summary/Conclusion** Within our study we were able to demonstrate for the first time a direct effect of CTLA-4Ig on T cells in RA patients, which results in increased proportions of CD4+ and T_{reg}, the downregulation of CD95, and a decrease in AICD. Blockade of B7 costimulatory molecules on T cells by CTLA-4Ig leads to a diminished susceptibility of T cells for T_{reg} suppression which might be counterbalanced by increased T_{reg} numbers.
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