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Abstracts der Posterpräsentationen

A. Pathophysiologie

Abatacept (CTLA-4Ig) Therapy Reduces the Susceptibility of T Cells to Regulatory T Cell Suppression in Patients with Rheumatoid Arthritis (RA) 01

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Background 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. We therefore performed 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.

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

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 Treg, 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 Treg suppression which might be counterbalanced by increased Treg numbers.

Monocytes Are Targets of Abatacept (CTLA-4Ig) Therapy in Patients with Rheumatoid Arthritis (RA) 02

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Background 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.

Summary 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.

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.

A Combined Dynamic Real Time *In Vivo* and Static *Ex Vivo* Analysis of Granulomonocytic Cell Migration in the Collagen-Induced Arthritis Model 03

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Background Granulomonocytic cells (GMC) drive the inflammatory process at the earliest stages of rheumatoid arthritis (RA). The mi-

gratory behaviour and functional properties of GM cells within the synovial tissue are, however, only incompletely understood. This tempted us to study GMC in the murine collagen-induced arthritis (CIA) model of RA with the help of multi-photon real time *in vivo* microscopy together with the subsequent and sequential *ex vivo* analysis of GMC on tissue sections.

Methods CIA was induced in LysM-EGFP C57BL/6 transgenic animals that carry the EGFP fluorescence protein under the lysozyme promoter. Individual joints were prepared by surgical microscopy in healthy control and in CIA subjects and EGFP+ GMC were analyzed by 2-photon laser microscopy over 2 hours. One group of animals received one single dose (0.25 mg) of prednisolone i. v. before *in vivo* imaging. Afterwards the animals were sacrificed and cryo- and paraffin sections were prepared for immunofluorescence and histomorphological analysis, respectively.

Summary GMC were barely detectable in healthy animals but were abundant in the synovial tissue as soon as clinical arthritis was apparent. GMC were motile and migrated randomly through the synovial tissue with a reduced mean velocity (2.75 ± 1.17 µm/min) of as compared to healthy controls (3.11 ± 1.51 µm/min; $p < 0.001$). In CIA subjects the frequent formation of cell clusters was observed that consisted of both EGFPhigh neutrophilic granulocytes and EGFPlow monocytes. In addition EGFPlow F4/80+ TRAP+ osteoclast precursor cells were occasionally observed at the synovial-bone junction and areas of bone erosions. Prednisolone treatment reduced the mean velocity of cell migration (2.19 ± 1.06 µm/min; $p < 0.001$) and significantly diminished the immigration of GMC into the synovial tissue, but did not affect GMC allocation within cell clusters or throughout the entire tissue.

Conclusion The combined application of real time *in vivo* microscopy together with elaborate static *post mortem* analysis of GMC enabled the description of dynamic migratory characteristics of GMC together with their precise allocation in a complex anatomical environment. Moreover this approach was found sensitive enough to detect subtle therapeutic effects within a very short period of time.

Elevated Proportions of CD25-Treg are Indicative of Kidney Involvement in Patients with Systemic Lupus Erythematosus (SLE) 04

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Aim CD4+CD25-Foxp3+ T cells resemble regulatory T cells and are increased in SLE patients. Their precise role in SLE pathogenesis, however, has not been determined so far. Our aim was the analysis of CD4+CD25-Foxp3+ T cells in SLE patients with different organ manifestations as compared to healthy controls (HC) to gain further insight into SLE pathogenesis.

Methods Proportions of CD4+CD25-Foxp3+ T cells were determined by 6 colour flow cytometry (FACS) within peripheral blood mononuclear cells (PBMC) in HC (n = 21) and SLE patients (n = 61) with different organ manifestations. In selected SLE patients with active glomerulonephritis, proportions of CD4+CD25-Foxp3+ T cells were also analyzed in urine samples. CD4+CD25-Foxp3+ T cells proportions were correlated with clinical data, immunosuppressive therapy, and disease activity indices. Finally time course analyses of proportions of CD4+CD25-Foxp3+ T cells were performed in patients with 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. We observed a significant correlation of % CD4+CD25-Foxp3+ T cells with the SLEDAI, ECLAM, and SIS disease activity score and with the daily cortisone dose. The analysis of patients with different organ manifestations revealed increased proportions of CD4+CD25-Foxp3+ T cells in SLE patients with renal involvement. Moreover, CD4+CD25-Foxp3+ T cells were also detected in urine samples of patients with active glomerulonephritis and proportions of CD4+CD25-Foxp3+ T cells significantly correlated with the extent of proteinuria. 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. Ongoing experiments have been designed to further reveal the origin and precise role of CD4+CD25-Foxp3+ T cells in SLE patients.

Conclusion The increase in proportions of CD4+CD25-Foxp3+ T cells in patients with SLE who suffer from glomerulonephritis suggests their involvement in kidney pathology. In addition the analysis of CD4+CD25-Foxp3+ T cells might allow to recognize and monitor patients with renal involvement.

RNAi-Mediated Silencing of the Autoantigen hnRNP-A2 Decreases Inflammatory Arthritis by Inhibiting Activation of Cells of the Mononuclear Phagocytic System 05

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Background/Purpose HnRNP-A2 belongs to a heterogeneous family of nuclear proteins importantly involved in mRNA trafficking, transcriptional and translational processes. Recent evidence let suggest that hnRNPs posttranscriptionally modulate expression of inflammatory mediators such as COX-2, TNF-α, IL-1β, and iNOS by affecting mRNA stability and translation. Strong upregulation of hnRNP-A2 at sites of inflammation and the generation of antibodies and autoreactive T cells against hnRNP-A2 in patients with rheumatoid arthritis (RA) and various arthritis models points towards a potential involvement of this protein in the pathogenesis of inflammatory arthritis.

Method Expression of hnRNP-A2 in tissues and cells was analysed by flow cytometry and immunoblotting. *In vitro* silencing of hnRNP-A2 was studied in J77.4 cells. Collagen-induced arthritis (CIA) in DBA1 mice and K/BxN serum transfer arthritis in BL/6 mice were used as arthritis models. For silencing of hnRNP-A2 expression, siRNA-containing lipoplexes were used, which were injected intravenously once a week. Control animals were treated with unspecifc siRNA/lipoplexes or PBS. Silencing efficiency was analyzed by immunobloting and real time PCR. Arthritis was measured by an established clinical scoring system, inflammation and bone erosions were analyzed by histomorphometry.

Result HnRNP-A2 was highly expressed in lymphoid organs such as lymph-nodes, spleen, and thymus. Among cells of the immune system monocytes/macrophages showed the strongest expression of hnRNP-A2. Silencing of hnRNP-A2 in a monocytic cell line diminished the proliferative capacity of transfected cells. Silencing of hnRNP-A2 *in vivo* revealed a 60–70 % silencing efficiency in lymph nodes and spleen of injected mice. Remarkably, incidence of arthritis in those mice which were injected with hnRNP-A2 specific siRNA-lipoplexes was only 20 % as compared to 70 and 80 %, respectively, in the control groups. Moreover, arthritis scores and weight loss differed significantly from control animals. Histological analysis of paws confirmed that both inflammation and bone erosion were significantly reduced in animals treated with hnRNP-A2-specific siRNA. Serum levels of cytokines typically produced by cells of the mononuclear phagocytic system such as TNF-α, IL-23, and IL-1 were strongly reduced. The effects observed were similar in both arthritis models indicating that hnRNP-A2 is crucially involved in the effector arm of autoimmune arthritis.

Conclusion *In vivo* silencing of hnRNP-A2 largely prevents induction of arthritis development by inhibiting activation of the mononuclear phagocyte system thereby diminishing the inflammatory immune response.

A TLR9 Antagonist Diminishes Arthritis Severity and Inhibits Bone Erosion in a Rat Model of Rheumatoid Arthritis 06

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Background There is increasing evidence that release of endogenous nucleic acids may trigger autoimmune reactions crucially involved in the induction of systemic autoimmune diseases such as SLE or rheumatoid arthritis (RA). In recent years, endosomal Toll-like receptors (TLRs, ie, TLR3, TLR7, TLR8, and TLR9) have been implicated in autoimmune processes due to their ability to recognize these nucleic acids. To study the role of TLR7 and TLR9 in the pathogenesis of erosive arthritis by antagonizing these TLRs in rats with pristane-induced arthritis (PIA).

Methods First, the inhibitory capacity of immunoregulatory sequences (IRS) known to antagonize TLR7 and/or TLR9 activation was investigated in cultured rat splenocytes by measuring production of pro-inflammatory cytokines. Subsequently, using the PIA model, these IRS were also tested for their efficiency to inhibit arthritis development in rats with PIA. The IRS' were applied twice a week subcutaneously at the base of the tail, a non-inhibitory IRS and PBS served as control substances. Weight changes were measured during the experiment and arthritis was assessed using an established scoring system. Expression of TLRs was analyzed in paws, lymph nodes, and spleen by Western blotting, RT-PCR, and immunohistochemistry. Further, the impact of antagonizing TLR7/9 in osteoclastogenesis was analyzed by performing *in vitro* osteoclast assays.

Result IRS specific for TLR7, TLR9, or TLR7/9 inhibited in a dose-dependent manner production of pro-inflammatory cytokines in rat splenocytes pre-activated by TLR-specific stimulators. However, neither the TLR7-specific inhibitor nor the inhibitor targeting both TLR7 and TLR9 showed an effect on incidence and severity of PIA. Remarkably however, antagonizing TLR9 solely led to delayed disease onset and reduced arthritis severity, which was accompanied by diminished TLR9 protein expression levels in paws and lymph nodes compared to placebo-treated control animals. Moreover, bone erosion was largely reduced in animals treated with the TLR9 antagonist. Furthermore, inhibition of TLR9 but not of TLR7 in an *in vitro* osteoclast formation assay diminished osteoclastogenesis significantly in a dose-dependent manner.

Conclusion Our *in vitro* and *in vivo* results indicate a potential involvement of TLR9 not only in the initiation of inflammatory arthritis but also in the later phase of inflammatory bone loss pointing toward a hitherto unknown role for TLR9 in the regulation of osteoclast activity.

Pristane Induces Apoptosis/Secondary Necrosis in Pristane-Induced Arthritis (PIA) 07

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Background Increased apoptosis/necrosis and/or deficient clearance of apoptotic material may lead to the release of potential autoantigens provoking the break of self-tolerance mechanism causing autoimmune diseases such as rheumatoid arthritis (RA). Major autoantigens in RA include immunoglobulin G, the target of rheumatoid factor (RF), citrullinated proteins, and the heterogeneous nuclear ribonucleoprotein (hnRNP) A2. To gain more insight in the role of apoptotic processes in the generation of arthritogenic auto-antigens we are studying autoimmune responses in the pristane-induced arthritis (PIA) model which shows some striking similarities with human RA including symmetrical polyarthritis, massive bone erosion, and the presence of RF and auto-antibodies and auto-reactive T cells against hnRNP-A2.

Objective To gain more insight in the early pathogenesis of PIA with special regard to apoptosis/necrosis and consecutive generation of auto-antigens and their involvement in arthritis development.

Methods Pristane (2,6,10,14-tetramethylpentadecane) was injected subcutaneously at the base of the tail in DA.1F rats. Lymph nodes and blood were analyzed at various time points after pristane application in regard to apoptosis/necrosis rates by means of immunohistochemistry and flow cytometry. Further phagocytose efficiency of peripheral blood cells was analyzed by using Ig-coupled beads. *In vitro* apoptosis/necrosis assays using pristane-cyclodextrin complexes were established.

Results 3 days after pristane application draining inguinal lymph nodes of DA.1F rats showed a strongly increased rate of cleaved caspase 3-positive cells indicating apoptosis. Interestingly, apoptosis rate decreased to levels of naïve animals within 2 weeks but draining lymph-nodes became extremely hypercellular. In peripheral blood both apoptosis and necrosis rates doubled during the first week after pristane injection. In the acute disease phase we observed four times increased apoptosis and necrosis levels compared to naïve rats which was in contrast to the draining lymph nodes which normalized during the disease course. We could not observe any phagocytose deficiency in pristane injected animals, rather strongly increased phagocytose activity in the acute disease phase was observed.

Conclusion Our data points toward a strong apoptosis/necrosis inducing effect of pristane both *in vitro* and *in vivo*. This strongly increased cell death might be one crucial initial trigger for the development of the pristane-induced arthritis. Thus, PIA might be a good model for studying very early immune processes, including the occurrence of auto-antigens, in the pathogenesis of RA.

Behandlung von hTNFtg-Mäusen mit 18β-Glycyrrhetinsäure 08

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Einleitung Die Rheumatoide Arthritis ist eine chronische, entzündliche Autoimmunerkrankung, die aufgrund einer ätiologisch ungeklärten Entzündungsreaktion zu einer zunehmenden Zerstörung der Gelenke führt. Mit derzeitigen Therapien ist nur ungefähr die Hälfte der Patienten in eine klinische Remission zu bringen. Daher werden neue Therapien benötigt, um die Gelenkszerstörung vollständig zu verhindern. In den vergangenen Jahren konnte der Einfluss der 18β-Glycyrrhetinsäure, die aus Süßholz gewonnen wird, auf zahlreiche Entzündungsmediatoren gezeigt werden. Außerdem wurde berichtet, dass Süßholz die Entzündung und Gelenkszerstörung in der Collagen-induzierten Arthritis vermindert. Ziel dieser Studie war, den Effekt der 18β-Glycyrrhetinsäure in einem Mausmodel der Rheumatoiden Arthritis zu studieren.

Material & Methoden: Humane-Tumornekrosefaktor-transgene-(hTNFtg-) Mäuse wurden mit 18β-Glycyrrhetinsäure durch subkutane Injektion behandelt. Untersucht wurde, ob die Behandlung eine Besserung der Arthritis bringt. Als Negativkontrollen wurden hTNFtg-Mäuse in gleicher Weise mit der Trägerlösung (Olivenöl) behandelt. Als Positivkontrolle diente die Hemmung von Tumornekrosefaktor mit dem Anti-Tumornekrosefaktor-Antikörper Infliximab.

Resultate 18β-Glycyrrhetinsäure-behandelte hTNFtg-Mäuse zeigten während der Studie denselben Krankheitsverlauf wie die mit der Trägerlösung behandelten Mäuse. Im Gegensatz dazu bewirkte eine TNF-hemmende Therapie mit Infliximab eine signifikante Verbesserung der klinischen Arthritiszeichen (Pfotenschwellung und Griffstärkenabnahme) im Vergleich zur Kontrollgruppe. In Übereinstimmung mit den klinischen Daten führte die Therapie mit der 18β-Glycyrrhetinsäure auch zu keinem Rückgang der Inflammation, der Erosion und der Zahl der Osteoklasten im Gelenkschnitt, während die Gabe von Infliximab auch zu einer signifikanten Besserung der histologischen Arthritiszeichen führte.

PTEN in Antigen-Presenting Cells is a Master Regulator for Th17-Mediated Autoimmune Pathology 09

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Autoreactive T cells are a central element in many systemic autoimmune diseases. The generation of these pathogenic T cells is instructed by antigen-presenting cells. However, signalling pathways in APC that drive autoimmunity are not completely understood. Here we show that conditional deletion of PTEN in myeloid cells is almost completely protected from the development of 2 prototypic model autoimmune diseases, collagen-induced arthritis (CIA) and experimental autoimmune encephalomyelitis (EAE). Myeloid specific deletion of PTEN leads to a significant reduction of cytokines pivotal for the induction of systemic autoimmunity such as IL-23 and IL-6 *in vitro* and *in vivo*. In addition, PTEN-deficient dendritic cells showed reduced activation of p38 MAP-kinase and increased inhibitory phosphorylation of GSK3β *in vitro*. Dendritic cell and macrophage phenotypic maturation and migration to lymph nodes as well as collagen-specific T and B cell activation was comparable in wt and myeloid-specific PTEN–/–. However, analysing the impact of myeloid-specific PTEN deficiency on T cell polarization, we found a significant reduction of a Th17-type of immune response characterized by reduced production of IL-17 and IL-22. Moreover, there was an increase in IL-4 production and higher numbers of regulatory T cells myeloid-specific PTEN–/–. In contrast, myeloid-specific PTEN deficiency did not affect serum transfer arthritis, which is independent of the adaptive immune system and solely depends on innate effector functions. These data demonstrate that the presence of PTEN in myeloid cells is required for the development of systemic autoimmunity. Deletion of PTEN in myeloid cells inhibits the development of CIA and EAE by preventing the generation of a pathogenic Th17-type of immune response.

Analysis of TNFR2-Mediated Functions on Osteoclast Precursor Cells 10

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Background & Objectives The role of TNF in the induction and maintenance of human rheumatoid arthritis is well established. However, the role of its two receptors, especially of TNFR2, is not sufficiently understood. We have previously demonstrated that lack of TNFR2 on hematopoietic cells leads to increased osteoclastogenesis *in vitro* and *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. Therefore, we investigated the role of TNFR2 on osteoclast precursor cells (pOCs).

Methods & Results To study the function of TNFR2, we used pOCs 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 or ERK1/2 or AKT/PKB. However, crosslinking TNF and thereby mimicking membrane-bound TNF, which has been reported to be a ligand for TNFR2, led 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 and RNA was isolated and analysed by microarray. We obtained approximately 50 genes specifically induced via TNFR2, including chemokines, surface receptors, and many others.

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.

Class Effects of Tyrosine Kinase Inhibitors on Osteoclastogenesis *In Vitro* 11

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Introduction Rheumatoid arthritis (RA) is a systemic inflammatory autoimmune disease featuring a persistent synovitis of peripheral joints, which leads to severe bone destruction and functional impairment. The pathogenesis is still not fully understood, but when it comes to bone resorption, osteoclasts (OCs) are exclusively responsible, which renders them a unique therapeutic target. Several studies suggested that tyrosine kinase inhibitors (TKIs) – well established in the therapy of chronic myeloid leukaemia (CML) and other tumour entities – are powerful inhibitors of osteoclastogenesis.

Aims To investigate the effects of 4 tyrosine kinase inhibitors, namely imatinib, dasatinib, inno 406, and sunitinib, on the different phases of osteoclastogenesis, including the generation of osteoclast precursors (pOCs) and the fusion of pOCs into mature osteoclasts. We were further interested whether TKIs also affect mature OCs. Gained data should serve as a basis for the future investigation of TKIs in an appropriate *in vivo* mouse model.

Material & Methods *Ex vivo* osteoclastogenesis: Bone marrow cells from naïve C57/bl6 mice were treated with M-CSF and RANKL ± DMSO, imatinib, dasatinib, inno 406, or sunitinib. Thereafter osteoclast generation was evaluated under a light microscope. Apoptosis assay (AnnV-, 7-AAD-double staining): Bone marrow cells from naïve C57/bl6 mice were cultured for 6 days and treated with M-CSF and RANKL ± 1 µM DMSO, 1 µM imatinib, 10 nM dasatinib, 1 µM inno 406, or 50 nM sunitinib for 24 h. Annexin V-FITC was used as a marker for the identification of apoptotic cells; annexin V-FITC plus 7-AAD labelled the necrotic/late-apoptotic cells. RNA analysis: The amount of measured mRNA was normalized to the GAPDH expression for the specific treatment condition. The following OC markers were analysed: RANK, Nfatc1, CathK, MMP-9.

Conclusion All 4 TKIs significantly reduce the number of OCs, the number of pOCs, and the number of OC nuclei *in vitro*. Particularly imatinib and inno 406 profoundly diminish the expression of osteoclast effector molecules. We have planned an *in vivo* study, using the TNF-α transgene mouse model, to further investigate the effect of TKIs on bone resorption and osteoporosis as well as on arthritis.

Nicotinic Acetylcholine Receptors Are Key Regulators of Osteoclastogenesis 12

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Background In the last few years, the discovery of various neurotransmitter receptors on bone cells suggested that the nervous system may participate in the control of bone metabolism.

Objectives To investigate the role of nicotinic acetylcholine receptors (nAChRs) in osteoclastogenesis.

Methods The presence of nAChR subunits on osteoclasts (OCs), defined as tartrate-resistant acid phosphatase- (TRAP-) positive multinucleated cells, derived from mouse bone marrow, differentiated in the presence of receptor activator of nuclear factor κB ligand (RANKL) and macrophage colony stimulating factor (M-CSF), was investigated by PCR. Osteoclastogenesis was evaluated in knockout (KO) mice lacking individual nAChR subunits, while the effects of various nAChR agonists and antagonists was tested on *ex vivo* osteoclastogenesis in both wild type (WT) and KO mice. The effect of cholin-

ergic agonists on *in vivo* osteoclastogenesis was tested in the lipopolysaccharide-induced bone resorption model. Bone phenotype of KO and wildtype mice was evaluated by dual energy x-ray absorptiometry and histomorphometrical analysis.

Results PCR investigation confirmed the presence of nAChR subunits α1–9 and β1, 2, and 4 in mouse bone marrow-derived OCs differentiated as stated above. The nAChR agonist nicotine dose-dependently and markedly reduced the number of Ocs by 99 % (IC50: 25 µM). Nicotine also completely reduced the number of pre-OCs, defined as TRAP-positive mononuclear cells. The nicotinic agonist epibatidine showed similar effects as nicotine. Nicotinic agonists virtually abrogated osteoclastogenesis, however, the authors observed no difference in total cell number between treated and untreated cells; 80 % of cells stained positive for CD11b at the termination of the culture suggesting a highly specific effect on osteoclastogenesis. Nicotine was also capable of inhibiting osteoclastogenesis while having a markedly anti-inflammatory effect in the *in vivo* osteoclastogenesis model. Agonists had no effect on very early stages of osteoclastogenesis, when cells were stimulated only in the presence of M-CSF, but their effect was apparent in the presence of RANKL indicating interference downstream of RANK. The non-competitive nicotinic antagonist mecamylamine at high doses also inhibited osteoclastogenesis, suggesting that inhibition caused by the agonists might be associated with the desensitisation of the receptor. This is further supported by our finding that RANKL-mediated osteoclastogenesis was markedly inhibited in mice lacking the α7 nAChR or β2-containing nAChRs, suggesting an essential role for these receptors in physiological osteoclastogenesis. Bone histomorphometry confirmed this finding by revealing an increased bone volume coupled with a reduction in osteloclastogenesis in mice lacking the α7 nAChR.

Conclusions The authors have shown that osteoclastogenesis is inhibited in mice lacking the α7 nAChR or β2-containing nAChRs. Osteoclastogenesis could also be completely blocked by nicotinic agonists as well as high-dose antagonists. The function of nAChRs and the effect of nAChR agonists suggest that these receptors and the cholinergic nervous system may play an important regulatory role in osteoclastogenesis.

Clock Gene Expression in Rheumatoid Arthritis 13

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Background & Objectives Patients with rheumatoid arthritis (RA) show modulated circadian rhythms of inflammatory cytokines and cortisol. Furthermore, in mouse models of rheumatoid arthritis the expression of clock genes, which are an integral part of the circadian system, is modified. Therefore it is assumed that clock genes are involved in the pathology of RA. In our study we aimed to examine the expression and localization of clock genes in synovial tissues of patients with RA compared to the expression in samples of patients with osteoarthritis (OA), which is a degenerative disease showing little inflammation.

Methods Synovial fibroblasts (SFs) of patients with rheumatoid arthritis or osteoarthritis were isolated by sequential enzymatic digestion and centrifugation steps. Cells were synchronized by serum shock or treated with TNF-α and gene expression profiles of different clock genes were determined over 24 hours by real time PCR. Additionally, the *in situ* expression of clock genes in synovial tissues was examined by immunohistochemistry.

Results We found differences in the expression profiles of certain clock genes in the synovial tissues between RA and OA patients. Differences were most pronounced for the Brain and muscle aryl hydrocarbon receptor nuclear translocator-like 1 (Bmal1), a core clock gene which builds a complex with clock and binds to E-box response elements in promoter regions of many genes including those encoding the Period (Per1, Per2, Per3) and Cryptochrome (Cry1 and Cry2) proteins. Tendential differences were also observed for the expression of the clock-controlled transcription factor albumin D site-binding protein (DBP), which is especially important for the robustness of the Period gene rhythms. Furthermore, we used SFs isolated from the joints of RA and OA patients, juvenile fibroblasts, and the cell line MH7A to investigate differences in the induction and synchronization (up to 24 h) of clock gene expression by serum shock or TNF-α. First experiments showed that human SFs can be synchronized by a 2 hour serum shock (50 % serum) as well as by 50 ng/ml TNF-α.

Summary Taken together, these data indicate that the expression and possibly also the synchronization of certain clock genes appear to be altered in RA patients, suggesting an important role of clock genes in the pathogenesis of the disease.

Multi-Targeted Kinase Inhibitor PKC412 Is a Potent Inhibitor of Osteoclastogenesis 14

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Background Rheumatoid arthritis (RA) is a chronic inflammatory disease characterized by osteoclast-mediated bone erosions. Small molecule multi-kinase inhibitors are being explored as novel therapeutics. PKC412 is a small molecule multi-kinase inhibitor targeting class III tyrosine-protein-kinases such as FMS-like tyrosine kinase 3 (FLT-3) and multiple isoforms of serine/threonine protein kinase C. PKC412 has been shown to inhibit macrophage function *in vitro*. However, the role of PKC412 in modulating the commitment of the monocyte/macrophage lineage to osteoclast precursors and their differentiation into mature osteoclasts has not been fully explored.

Objectives To investigate the effect of PKC412 on osteoclast differentiation and function.

Methods Mouse bone marrow-derived cells were differentiated in the presence of macrophage-colony stimulating factor (M-CSF) and receptor activator of nuclear factor kappaB ligand (RANKL) into tartrate-resistant acid phosphatase positive (TRAP+) mononuclear osteoclasts (pre-osteoclasts) and TRAP+ multinucleated mature osteoclasts. PKC412 was added in increasing concentrations (10 nM to 10 µM) to the culture. The role of PKC412 in the bone resorbing capacity of osteoclasts was evaluated by culturing osteoclasts on dentine slices. In order to characterize the effect of PKC412 on cell proliferation, MTT assays were performed. Quantitative PCR was used to evaluate expression levels of mRNA encoding for osteoclast-specific markers such as nuclear factor of activated T cells cytoplasmic 1 (NFATc1), matrix metalloproteinase 9 (MMP-9), and cathepsin K. Flow cytometry analysis for annexin V and 7-AAD was employed to determine potential apoptotic effects of PKC412 on pre-osteoclasts and osteoclasts.

Results Increasing concentrations of PKC412 (IC50: 250 nM) dose-dependently reduced osteoclast numbers. Pre-osteoclasts were also significantly decreased after addition of PKC412, indicating an inhibiting effect of PKC412 on the early stages of osteoclastogenesis. In accordance with this finding, a dose-dependent reduction of pre-osteoclast proliferation was shown in the MTT assays. A significant time- and dose-dependent increase in the ratio of apoptotic cells in the PKC412-treated cells was detected by annexin V and 7-AAD staining. In the presence of PKC412 a significant reduction in osteoclast size and nuclei number, as well as in the size of resorption pits on dentin slices was obtained. This suggests that the bone resorbing capacity of osteoclasts is inhibited by PKC412. Consistently, expression levels of mRNA coding for osteoclast markers, such as NFATc1, MMP-9, and Cathepsin K were downregulated in the presence of PKC412.

Conclusions These results suggest a regulatory role of PKC412 in pre-osteoclast differentiation and osteoclastogenesis through apoptosis induction.

Combined Depletion of Interleukin-1 and Interleukin-6 Does Not Exceed Single Depletion of Interleukin-1 in TNF-Mediated Arthritis 15

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Background Previous studies demonstrated a regulatory role of interleukin 1 (IL-1) in inflammatory cartilage damage and bone destruction in human tumour necrosis factor transgenic (hTNFtg) mice, an animal model for rheumatoid arthritis (RA). Moreover, blocking of IL-6 has been shown to reduce local bone erosions in this model. Therefore we wanted to investigate the effect of a combined depletion of IL-1 and IL-6 on the development and severity of inflammatory, erosive arthritis.

Methods We first crossed IL1α- and β-deficient (IL1–/–) mice with IL6–/– mice to generate IL1–/–IL6–/– double knockout mice. We next intercrossed these animals with arthritogenic hTNFtg mice to receive IL1–/–IL6–/–hTNFtg mice. We weekly assessed clinical signs of arthritis in hTNFtg mice, IL1–/–hTNFtg mice, IL6–/–hTNFtg mice, and IL1–/–IL6–/–hTNFtg mice starting from week 4 after birth until week 16. We stained decalcified paw sections from all 4 genotypes with hematoxylin and eosin to determine the amount of inflammatory synovial pannus formation, with tartrate-resistant acid phosphatase (TRAP) to evaluate the number of synovial osteoclasts and the occurrence of subchondral bone erosions, and with toluidine-blue to assess articular cartilage damage. Quantitative analysis of histopathological changes were performed using the Osteomeasure Software System.

Results We found a significant reduction in the clinical signs of arthritis, indicated by an increase of paw swelling and a decrease in grip strength, in IL1–/–IL6–/–hTNFtg mice when compared to their hTNFtg littermates. In line with these findings we observed a significant decrease in synovial inflammation in IL1–/–IL6–/–hTNFtg mice when compared to hTNFtg animals. Moreover, the number of synovial TRAP+ osteoclasts was markedly diminished in IL1–/–IL6–/–hTNFtg mice, and reduced osteoclast formation was accompanied by significantly less subchondral bone erosions. Additionally, we found a conserved articular cartilage structure showing almost no cartilage degradation in IL1–/–IL6–/–hTNFtg mice compared to their hTNFtg littermates. In IL1–/–IL6–/–hTNFtg mice clinical as well as histological signs of disease, including joint inflammation, bone destruction, and cartilage damage were also significantly diminished when compared to IL6–/–hTNFtg mice. However, by comparing IL1–/–IL6–/–hTNFtg mice with IL1–/–hTNFtg mice we found a similar reduction on synovial inflammation, as well as subchondral bone erosions and articular cartilage destruction.

Conclusion The phenotype of IL1–/–IL6–/–hTNFtg mice does not differ from IL1–/–hTNFtg animals indicating no synergistic effects when IL-1 and IL-6 is simultaneously blocked in TNF-mediated arthritis.

Increased Th1 and Th17 Reaction in Pristane-Induced Lupus (PIL) Is Associated with Lupus Nephritis 16

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Introduction Pristane-induced lupus (PIL) is a widely accepted murine model for SLE. As in human SLE, all mice develop auto-Abs (ANA, anti-chromatin, anti-histone etc), but only some have severe SLE with typical involvement of inner organs. Lupus nephritis is a severe, life threatening condition, but it is not clear yet why some SLE patients are prone to develop nephritis, while others are not. Auto-reactive Th cells (T effector cells, Teff) are pivotal players in SLE pathogenesis: Activated Th1 and Th17, in particular, are attributed with pro-inflammatory properties, which can be opposed by regulatory T cells (Treg). We herein characterize the T cell response at 3 major immunological sites in PIL in order to discriminate differences between mildly affected PIL mice ("mild-PIL") vs severe PIL with nephritis (nephritis-PIL).

Methods Mice were injected i. p. with either 0.5 ml of pristane or with PBS as control and killed after 8 months. Kidneys were prepared and stained with HE and PAS. Lymphocytes were isolated from (i) intraperitoneal granulomas (ectopic lymphoid tissue which forms after pristane injection), from (ii) regional lymph nodes (LN), and from (iii) spleens and were analyzed separately for each mouse to allow correlation with renal histology. We assessed frequencies of CD4, CD8, CD19 lymphocytes and CD4+CD25+FoxP3+Treg. CD4+CD25+ activated T effector cells (Teff) were also analyzed for their Th1, Th2, and Th17 phenotype.

Results 28 % of PIL mice had severe SLE as indicated by proliferative lupus glomerulonephritis resembling human nephritis WHO III and IV. We compared the T cell response in nephritis-PIL with mild-PIL and with controls: In LN and spleens, there was no difference in the distribution of CD4, CD8, and CD19 cells. In PIL granuloma, the percentage of Teff (13.5 ± 12.9 %) was significantly higher than in PIL-LN (5.2 ± 4.6 %; $p < 0.0001$) or PIL-spleens (3.6 ± 2.5 %; $p < 0.0001$), where Teff were similarly frequent as in controls. In granuloma, both PIL groups had a similar frequency of Teff and Treg, an increased Teff/Treg ratio (compared to LN or spleens), and a similar Th1 response (28 and 26 %, respectively; p = n. s.). In contrast to mild-PIL, nephritis-PIL had an increased frequency of Th2 (42 ± 25 % vs 22 ± 12 %; $p = 0.004$) and, more prominent, of Th17 (35 ± 27 % vs 15 ± 9 %; $p = 0.002$). Both groups of PIL mice developed anti-chromatine- and anti-histone-Abs, but without difference in serum levels or temporal occurence.

Conclusion In PIL, intraperitoneal granulomas represent the major site of inflammation. They show an upregulated Th1 response in all PIL mice and an increased frequency of Th2 and, especially, Th17 cells in nephritis-PIL: The pronounced Th17 activation may drive lupus activity and, as a consequence, may thus contribute to the development of lupus nephritis.

Feasibility of Chondrocyte Cultures from Cadaver Finger Joints 17

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Introduction Chondrocyte cultures are instrumental for studying the pathogenesis of osteoarthritis of the hands. We investigated the feasibility of using human cartilage from fingers of dissecting room cadavers donated to the institute of anatomy.

Methods Proximal interphalangeal joints (PIP) were obtained from 14 untreated dissecting room cadavers (mean age 75) at *post mortem* times up to 101 hours. The joint surface appeared macroscopically osteoarthritic in 2 cases. Cartilage and connective tissue was harvested under sterile conditions. Tissues were digested in collagenase B and cultured in Ham's F-12/DMEM (1:1) and 10 % FBS over 2 passages. Gene expression of collagen II and aggrecan was evaluated using quantitative real time PCR and compared to cultures of skin fibroblasts. We also determined the expression of the chondrocyte biomarker genes matrix metalloprotease (MMP-) 13, inducible nitric oxide synthase (iNOS), Collagen X, Runx2 and Runx3, and alkaline phosphatase.

Results Isolated cells from PIP exhibited typical morphology. To test whether the isolated cells were chondrocytes, we compared mRNA expression levels of the 2 chondrocyte marker genes – Collagen II and Aggrecan – of finger chondrocytes with skin fibroblasts. Collagen II expression was exclusively found in finger chondrocytes but not in skin fibroblasts, the aggrecan expression levels were 293-fold higher in finger chondrocytes, suggesting that the isolated cells were chondrocytes. Chondrocytes from cadavers up to 101 hours *post mortem* were viable in all cases. The average cell yield per PIP was 2.4 × 106 cells and 500–1000 ng of RNA after 2 cell culture passages. mRNA transcripts for MMP-13, iNOS, Collagen X, Runx2

and Runx3, and alkaline phosphatase were also detectable in finger chondrocytes.

Conclusion Cadaver chondrocyte culture from finger joints is feasible. In this pilot study we demonstrate that a respectable number of chondrocytes from hand osteoarthritis with typical morphology and chondrocyte marker genes are obtainable. Thus, a new source for primary human chondrocyte isolation for *in vitro* experiments is made accessible.

Muscle Wasting in hTNFtg Mice, an Animal Model for Rheumatoid Arthritis, Due to Increased Cathepsin L Expression 18

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Objective To investigate skeletal myopathy in a chronic inflammatory, erosive animal model for rheumatoid arthritis, the human tumor necrosis factor transgenic (hTNFtg) mice.

Methods To evaluate whether hTNFtg mice are suffering from skeletal muscle atrophy, we isolated triceps surae muscles from hTNFtg animals from various points in time of age starting 4 weeks until 16 weeks after birth. Muscle weight and body weight were assessed from these animals. Muscle tissue, muscle weight, and body weight from age- and sex-matched wildtype (wt) animals served as controls. To investigate whether TNF blockade protects hTNFtg animals from muscle atrophy, 5 female hTNFtg animals were treated with anti-TNF Ab (Infliximab, 10 mg/kg, 3× per week, i. p.). Untreated hTNFtg animals served as controls. To identify proteolysis pathways and pro-inflammatory cytokine expression involved in muscle atrophy, we performed quantitative real time PCR for Cathepsin L, B, S, H, D, MMP-9, and Interleukin- (IL-) 1 and IL-6 from mRNA isolated from muscle tissues of hTNFtg and wt animals. To further investigate infiltration of inflammatory cells, muscle tissue sections are stained for macrophages, neutrophils, T cells and B cells, and convential hematoxylin/eosin.

Results We demonstrate that hTNFtg mice show significantly less triceps surae muscle weight compared to sex- and age-matched wt animals. Reductions in muscle weight became already manifest at the early age of 4 weeks and were continuously reduced until week 16. Due to decreased muscle weight, body weight was also significantly decreased in hTNFtg animals compared to their wt littermates. We found a significantly increased mRNA expression level of Cathepsin L, a lysosomal endopeptidase responsible for muscle protein degradation, in muscles from hTNFtg compared to their wt littermates. In contrast, other proteases such as Cathepsin B, S, H, D did not reach significantly increased expression levels between these 2 genotypes. Moreover, pro-inflammatory cytokines such as IL1 and IL6 are also significantly upregulated in muscles from hTNFtg mice.

Conclusion Despite spontaneous development of chronic inflamed, erosive arthritis, chronic overexpression of TNF leads to skeletal muscle atrophy due to increased tissue-degrading cathepsin L in hTNFtg animals.

Matrix-Metalloproteinase-3 (MMP-3) im Serum von Patienten mit entzündlichen und nicht-entzündlichen Gelenkserkrankungen 19

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Einleitung Matrixmetalloproteinasen sind proteolytische Enzyme für den enzymatischen Abbau von extrazellulärer Matrix und sind an der Progression des Knorpel- und Knochenabbaus bei entzündlichen Gelenkserkrankungen, insbesondere der Rheumatoiden Arthritis (RA) beteiligt. Deren Bedeutung bei nicht-entzündlichen Gelenkserkrankungen ist unklar.

Ziel Vergleich der Serumkonzentrationen von MMP-3 bei Patienten mit entzündlichen und nicht-entzündlichen Gelenkserkrankungen sowie serielle Bestimmung von MMP-3 mit Korrelation zu Aktivitätsparametern bei ausgewählten Patienten.

Methoden Im Serum von 76 Patienten der Rheumaambulanz mit unterschiedlichen Diagnosen wurde mit einem kommerziell erhältlichen ELISA der Fa. AESKU.DIAGNOSTICS, Wendelsheim, Deutschland, die Konzentration von MMP-3 gemessen. Zusätzlich wurden bei 14 Patienten (4 RA, 4 Spondylarthritis [SpA], 6 Arthrose [OA]), deren Sera im Rheumalabor eingefroren waren, MMP-3-Konzentrationen im zeitlichen Verlauf (1–9 Jahre) der Behandlung gemessen und mit Markern der Krankheitsaktivität (DAS-28, BASDAI, BSG, CRP) verglichen.

Ergebnisse Patienten der Rheumaambulanz mit Gelenkschmerzen, aber ohne genauere Diagnose einer Gelenkserkrankung zeigen ähnliche MMP-3-Werte wie Normalpersonen. Grob übereinstimmend mit den Angaben der Herstellerfirma finden wir einen deutlichen Konzentrationsunterschied zwischen den Geschlechtern (w 35–116 ng/ml, n = 9; m 78–164 ng/ml, n = 4; p = 0,006). Patienten mit Arthrose (OA) unterscheiden sich in den MMP-3-Konzentrationen nicht von Patienten ohne Gelenksbeschwerden (w 37–109 ng/ml, n = 9; m 55–92 ng/ml, n = 3; p = 0,769). Patienten mit aktiver RA (DAS-28 < 3,2) zeigen deutlich höhere Konzentrationen (w 65–800 ng/ml, n = 7; m 246 ng/ml, n = 1) als Patienten mit inaktiver RA (DAS-28 > 3,2) (w 40–265 ng/ml, n = 18; m 60–108 ng/ml, n = 4; p = 0,006) und höhere Konzentrationen als OA-Patienten und Patienten ohne Gelenkserkrankungen. MMP-3-Konzentrationen lassen bei Patienten mit OA oder SpA keine klaren Veränderungen oder Trends im zeitlichen Verlauf der Erkrankung erkennen. Die 4 Patienten mit RA zeigen dagegen einen weitgehend parallelen Verlauf der MMP-3-Konzentrationen mit dem DAS-28, den CRP- und den BSG-Werten.

Schlussfolgerung Die Serumkonzentrationen von MMP-3 korreliert mit der Krankheitsaktivität bei Patienten mit Rheumatoider Arthritis. Patienten mit Arthrose oder Spondylarthritis haben vergleichbare Werte wie Patienten ohne Gelenksbeschwerden und zeigen im Krankheitsverlauf keine wesentlichen Schwankungen.

H_2S- and Sulphur-Containing Molecules Inhibit LPS-Induced IL-6 Expression in Human Synovial Fibroblasts 20

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Objectives Pro-inflammatory cytokines such as interleukin (IL-) 6 are known to be involved in the progression of pathological inflammatory events such as rheumatoid arthritis (RA). IL-6 is highly expressed in the synovium of RA patients. In RA, most of the production of pro-inflammatory cytokines has been attributed to 2 main cell types; macrophages and synovial fibroblasts (FLS). Interestingly, there is mounting evidence for a role of Toll-like receptor (TLR-) 4 in inflammatory diseases such as RA. FLS can respond directly to TLR antigens by producing cytokines and growth factors that recruit and regulate the functions of immune cells during infection and tissue damage.

Methods The rheumatoid synovial fibroblast cell line MH7A was stimulated for 12 h with LPS (100 ng/ml) in the absence and presence of different concentrations of the H_2S-donor sodium hydrogen sulphide (NaHS), dimethyl sulphoxide (DMSO), or dimethyl sulphone (DMS). After 3, 6, and 12 h of incubation, IL-6 release was quantified by enzyme-linked immunosorbent assay (ELISA). IL-6 mRNA levels were measured by quantitative real time PCR (qRT-PCR). Furthermore, we investigated whether the tec kinase Bmx was responsible for the TLR4/LPS-induced expression of IL-6 in synovial fibroblasts.

Results H_2S blocked IL-6 expression up to 12 h upon LPS treatment. DMSO and DMS showed similar anti-inflammatory effects. We demonstrate here that Bmx kinase activity was increased in response to TLR4 stimulation and elevated the production of IL-6 in the MH7A fibroblast cell line.

Conclusion This study gives an important insight into the role of LPS/TLR4 in RA and the role of H_2S and other sulphur-containing molecules in inflammatory processes.

IFN-Gamma Promotes the Invasive Behavior of Fibroblast-Like Synoviocytes 21

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In rheumatoid arthritis (RA), a systemic autoimmune response translates into an inflammatory attack on the synovium that yields the formation of an aggressive cell mass, called pannus, which invades into and destroys the articular cartilage. Cartilage destruction is primarily mediated by fibroblast-like synoviocytes (FLS). Among the pro-inflammatory mediators produced by infiltrating T cells, IFN-gamma may contribute to FLS-driven joint destruction. Of note, IFN-gamma elicits its effects via the JAK1/JAK2-Stat1 signalling pathway. To establish a role for IFN-gamma in the invasive potential of FLS, we used an *in vitro* invasion assay (matrix-associated trans-epithelial resistance invasion- [MATRIN-] assay). Strikingly, FLS that were stimulated with IFN-gamma demonstrated a markedly increased invasive capacity when compared to un-stimulated FLS. Cell invasion involves several steps, including attachment to extracellular matrix (ECM), cell migration, and digestion of the ECM by proteases. As determined by qPCR, however, IFN-gamma did not up-regulate the expression of metalloproteinases (MMPs) by FLS. Therefore, we hypothesized that IFN-gamma directs FLS motility. Indeed, exposure of FLS to IFN-gamma resulted in their increased migratory activity as determined in Boyden chamber assays. Since cell motility is partly controlled by focal adhesion kinase (FAK), we next analyzed whether or not IFN-γ modulates FAK activity in FLS. Western blot analysis revealed that activation of the IFN-gamma-JAK1/2-Stat1 signaling cascade is associated with phosphorylation of FAK. As Stat1 deficient U3A cells similarly responded to IFN-gamma stimulation, activation of FAK was independent of Stat1. Instead, inhibition of JAK1/2 abrogated IFN-gamma-induced activation of FAK in FLS, indicating that IFN-gamma regulates FAK activity through JAK1/2, but not Stat1. Importantly, inhibition of JAKs abrogated IFN-gamma-induced invasive activity of FLS. These results confirm that JAK1/2 play a critical role in translating the signal induced by IFN-gamma to promote invasion in FLS. These studies suggest a role for IFN-gamma in the destructive mesenchymal tissue response to inflammation and may provide insight into FLS behaviour and function in RA.

Pristane-Induced Lupus Is Featured by Erosive Arthritis, Which Can be Influenced by Early Administration of Regulatory T Cells 22

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Introduction The mineral oil pristane is accused to induce autoimmune deregulations in humans and can induce a lupus-like disease in mice. Murine PIL resembles human SLE in many respects such as presence of anti-chromatin antibodies (abs) and the involvement of inner organs. In human SLE, arthralgia is common and often accompanied by arthritis (ranging from 35 % to 95 % of the patients). In most cases, lupus arthritis is non-erosive, but it can also present as more severe, erosive disease. Regulatory T cells (Treg) play an important role in maintaining the peripheral tolerance and help preventing autoimmune diseases; their therapeutic potential is in the focus of intense research.

Methods For disease induction BALB/c mice were injected i. p. with either 0.5 ml of pristane (PIL group n = 51) or PBS (controls n = 32) and sacrificed after 8 months; some additional mice were co-injected with pristane and freshly drawn Treg (Treg group n = 8). Blood samples were tested for anti-chromatin-abs, anti-histone-abs, and rheumatoid factor. Animals were monitored for (i) clinical signs of arthritis (paw swelling, loss of grip strength) and finally analyzed by (ii) histopathology techniques: staining with H/E (for allowing an overview), TRAP (osteoclasts), and toluidine blue (cartilage). In order to analyze and compare disease severity, histological features of arthritis were quantified by osteomeasure and also combined to define an arthritis severity score (ASS). Specimens were also stained for granulocytes (G1), T (anti-CD3) and B cells (anti-CD45) for immunohistochemistry.

Results All PIL finally became positive for auto-abs (anti-chromatin, anti-histone, RF), which were detectable 3 months after disease induction, as were first clinical signs of arthritis (paw swelling, loss of grip strength). Clinical symptoms constantly increased for 8 months; finally $^3/_4$ of mice experienced at least one episode of arthritis (73 % showed paw swelling, 75 % loss of grip strength), while HC were free of arthritis ($p < 0.001$). Histological analysis of paws showed arthritis in 61 % of PIL-group, but none in HC ($p < 0.001$). PIL showed an erosive form of arthritis with cartilage degradation; inflammatory infiltrates were rich in granulocytes and B cells (but low in T cells). In PIL, both clinical features of arthritis (paw swelling, loss of grip strength) correlated well with histological results gained by osteomeasure: cartilage destaining, inflammatory area, erosive area, number of osteoclasts and severity score ASS (for all: $r > 0.7$; $p < 0.0001$). In contrast, only 38 % of the Treg group showed clinical signs of arthritis as compared to 75 % in the PIL group ($p < 0.05$) and only 25 % of Treg mice had histologically proven arthritis. The co-injection of Tregs also significantly reduced the ASS from 4.5 ± 3.6 in PIL to 1.4 ± 2.8 in Treg groups ($p = 0.04$).

Conclusion In contrast to most murine models of SLE, PIL is featured by arthritis, which – as in humans – occurs in some, but not all animals. The erosive nature of the disease may reflect pathophysiological differences between mice and men, since the two other arthritis-prone SLE models also show erosive disease. We herein analyzed in-depth both clinical and histological features by standardized, established methods and found good correlations. The addition of Treg reduced the frequency of arthritis and the histological severity score, which further underlines the role and curative potential of these cells in autoimmune diseases.

Blockade of IL-6 Does Not Protect from TNF-Mediated Erosive Tenosynovitis 23

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Objective To investigate the effect of IL-6 or TNF blockade, respectively, on the development of tenosynovitis and adjacent bone erosion in human tumour necrosis factor transgenic (hTNFtg) mice, an established animal model for rheumatoid arthritis (RA).

Methods The development of tenosynovitis is one of the first pathological processes in hTNFtg mice. To investigate the role of the proinflammatory cytokines IL-6 and TNF in this process, we treated hTNFtg animals either with anti-TNF antibodies (Infliximab, 10 mg/kg, i. p., 3 times per week) or anti-IL-6R antibodies (rat anti-mouse IL-6R antibody MR16-I from Prof. Nishimoto, Japan; 200 mg/kg, 1× i. v., subsequently i. p. 3× per week) or with PBS as control for 5 weeks, starting 8 weeks after birth. After treatment, we quantitatively analysed histological sections from hind paws for presence and extend of tendosynovitis, infiltration of inflammatory cells into the effusion sites, and subchondral bone erosion of the adjacent bone using the Osteomeasure software system. Therefore, we stained sections for hematoxylin and eosin and for tartrate-resistant acid phosphatase (TRAP) to identify bone-resorbing osteoclasts. To discriminate different infiltrating cell populations, we immunostained sections for macrophages, granulocytes, and T and B cells.

Results We show that inflammation of the tendon sheath of the long peroneal muscle, a major preclinical hallmark in hTNFtg mice, is closely linked to subchondral bone erosion on the calcaneus bone, which is in direct contact of the tendon, in 66 % of hTNFtg mice. In addition, we also found tenosynovitis without concomitant eroded bone in 33 % of hTNFtg animals. Interestingly, TNF blockade prevented erosive tenosynovitis (11 % erosive tenosynovitis; 89 % non-erosive mild tenosynovitis), whereas inhibition of IL-6 did not protect from erosive tenosynovitis. We found no difference in the extend of inflamed tendon sheaths as well as in the area of subchondral bone erosion in anti-IL-6R antibody-treated animals in comparison to placebo-treated hTNFtg animals (anti-IL-6R: 62,5 % erosive tenosynovitis; 37.5 % non-erosive tenosynovitis; placebo: 66 % erosive tenosynovitis, 33 % non-erosive tenosynovitis). Moreover, no difference was found in the number of infiltrating cells mainly granulocytes and macrophages into the effusion site between these 2 groups.

Conclusion Blockade of IL-6 does not prevent TNF-mediated erosive tenosynovitis, suggesting that TNF is the major mediator and sufficient for the initiation and maintaining of erosive tenosynovitis.

B. Kinderrheumatologie

Prevention of Rheumatic Fever – die neuen Empfehlungen der American Heart Association 24

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„Prevention of Rheumatic Fever and Diagnosis and Treatment of Acute Streptococcal Pharyngitis. A Scientific Statement from the American Heart Association" [Gerber MA, et al. Circulation 2009; 119: 1541–51]: Die Diagnose des akuten rheumatischen Fiebers beruht trotz neuer Erkenntnisse (Polyarthritis-Monarthritis, echokardiografische Kriterien usw.) auf den Jones-Kriterien, deren letzte Revision 1992 erfolgte. Nach dem Scientific Statement der American Heart Association 1995 wurde 2009 ein Update zur Prävention des rheumatischen Fiebers und zur Diagnose und Therapie der Streptokokkenpharyngitis mit Bewertungen der Therapieempfehlungen nach den Kriterien der Evidence-Based Medicine publiziert. Diagnostisch wird die klinische Beurteilung und die Sicherung der Diagnose Streptokokkenpharyngitis entweder durch einen Streptokokkenschnelltest oder einen Rachenabstrich empfohlen. Träger von β-hämolysierenden Streptokokken der Gruppe A (GAS) ohne klinische Symptomatik und ohne Nachweis einer immunologischen Reaktion können allerdings hiermit nicht von Patienten mit GAS-Pharyngitis unterschieden werden. Zur primären Prävention des ARF wird weiterhin Penicillin *per os* empfohlen, als Alternative eignen sich Amoxicillin, Cephalosporine der 1. und 2. Generation, Clindamycin und Makrolide, Dauer der Therapie jeweils 10 Tage, bei Azithromycin 5 Tage. Nach einem rheumatischen Fieber besteht ein hohes Risiko von durch neuerliche pharyngeale Infektionen mit GAS ausgelöste Rezidive der Erkrankung, daher ist eine kontinuierliche sekundäre Prävention notwendig. Für die sekundäre Prophylaxe wird eine monatliche intramuskuläre Gabe von Benzathinpenicillin G empfohlen, in Hochrisikoländern 3× wöchentlich, in sozioökonomischen Gruppen mit niedrigem Risiko eine orale Prophylaxe mit PenicillinV 2× täglich. Bei der oralen Prophylaxe besteht aufgrund der häufig fraglichen Compliance ein entsprechend höheres statistisches Risiko eines Rezidivs. Die Dauer der Prophylaxe ist abhängig von der Anzahl der vorangegangenen Attacken, dem Abstand zur letzten Attacke, dem persönlichen Risiko von Streptokokkeninfektionen, dem Alter des Patienten und den kardialen Residuen nach vorangegangenen Schüben der Erkrankung. Sie variiert von mindestens 5 Jahren (ohne kardiale Residuen) bis zu lebenslänglich bei Hochrisikopatienten mit rezidivierenden Verläufen mit kardialen Residuen bis hin zum Klappenersatz. Akute rheumatische Fieber nach pharyngealer Infektion mit Streptokokken der Gruppen G und C wurden bisher nicht beschrieben. Eine Endokarditisprophylaxe wird nach akutem rheumatischem Fieber nicht mehr generell empfohlen, mit Ausnahme der Patienten nach Klappenersatz. Die Wertigkeit der Poststreptokokken-reaktiven Arthritis bleibt unverändert ungesichert. Die beschriebenen klinischen Unterscheidungsmerkmale gegenüber dem ARF wie kürzere Latenzzeit nach GAS-Infektion, schlechteres Ansprechen auf Therapie mit Acetylsalicylsäure, nicht-migratorischer Verlauf mit Mono- bis Polyarthrtis mit möglichem Befall der großen und kleinen Gelenke sowie der Wirbelsäule erlauben keine sichere Zuweisung zur Diagnose ARF oder PSRA. Da in der Literatur einzelne Patienten mit Herzklappenveränderungen nach PSRA beschrieben worden sind, wird eine Penicillinprophylaxe entsprechend dem rheumatischen Fieber für 1 Jahr empfohlen. Nach einem Jahr wird das Krankheitsbild retrospektiv noch einmal evaluiert, bei fehlender kardialer Mitbeteiligung kann die Penicillinprophylaxe beendet werden. Das Krankheitsbild „Pediatric Autoimmune Neuropsychiatric Disorders Associated with Streptococcal Infections" (PANDAS) wird als noch unbewiesene Hypothese beurteilt. Deshalb werden Untersuchungen auf vorangegangene Streptokokkeninfektionen, eine Langzeitpenicillinprophylaxe oder immunregulatorische Therapien wie IvIg oder Plasma Exchange derzeit nicht empfohlen.

Etanercept bei Kindern mit juveniler idiopathischer Arthritis – Daten der Kinderrheumaambulanz des AKH Wien und des Gottfried von Preyer´schen Kinderspitals der Stadt Wien 25

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In einer retrospektiven Datenanalyse wurden insgesamt 74 Kinder mit juveniler idiopathischer Arthritis (JIA), die seit dem Jahr 2000 im Verlauf ihrer Erkrankung eine Therapie mit Etanercept erhalten haben, analysiert. Davon wurden insgesamt 20 Kinder im Gottfried von Preyer´schen Kinderspital, 52 Patienten im AKH Wien und 2 Patienten in beiden Kinderrheumaambulanzen betreut. Das mittlere Alter bei JIA-Diagnosestellung lag bei 8,7 ± 4,9 Jahren (Alter von 7 Monaten bis 16 Jahren). Davon waren 20 Knaben (27,0 %) und 54 Mädchen (73,0 %) (Verhältnis 1:2,7) betroffen. Der Zeitraum bis zum Beginn der Methotrexat- (MTX-) Therapie nach Diagnosestellung lag im Mittel bei 1,4 Jahren (Staw ± 1,6; 1,9 Monate – 7,34 Jahre). MTX wurde insgesamt für 2,7 Jahre (Staw ± 2,7; 3 Monate – 2,8 Jahre) verabreicht, wobei derzeit 12 Patienten unter Therapie mit MTX und Etanercept stehen. Der Zeitraum bis zum Beginn der Etanercept-Therapie nach Diagnosestellung lag im Mittel bei 4,4 Jahren (Staw ± 3,6; 3,9 Monate – 15 Jahre). Etanercept wurde insgesamt für 1,8 Jahre (Staw ± 1; 2 Monate – 4,1 Jahre) verabreicht. Im September 2011 stehen derzeit 37 Patienten (50 %) unter laufender Therapie. Davon sind 16 (43,2 %) Patienten in Remission, 6 (16,2 %) Patienten haben einen aktiven Entzündungsstatus, 5 (13,5 %) Patienten zumindest ein Gelenk schmerzhaft (POM), 9 (24,3 %) Patienten zumindest ein Gelenk eingeschränkt (LOM) und 1 (2,7 %) Patient zumindest bei einem Gelenk sowohl POM als auch LOM. Zum Zeitpunkt der Diagnosestellung waren 1–38 Gelenke (Mittelwert 8), bei MTX-Beginn 1–38 Gelenke (Mittelwert 8) betroffen. Derzeit sind bei unseren Patienten 0–22 Gelenke (Mittelwert 2,1) betroffen. Unsere Daten zeigen, dass es bereits im Mittel nach 3,7 Monaten (Staw ± 5,2; 0 Monate – 1,9 Jahre) Etanercept-Therapie zu einer Remission gekommen ist, die bei 28 (37,8 %) Patienten (16 on Therapie, 12 off Therapie) bis dato angehalten hat und nach Absetzen der Therapie seit 2,2 ± 1,2 Jahre anhält.

Etanercept als Therapieoption bei therapierefraktärer CRMO 26

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Zielsetzung Bericht einer wenig bekannten Erkrankung und Einsatz eines neuen Medikamentes.

Hintergrund Die uneinheitlich als CRMO (chronisch rekurrierende multifokale Osteomyelitis), CNO (chronische nichtbakterielle Osteomyelitis) oder SAPHO-Syndrom (Synovitis, Akne, Pustulosis, Hyperostosis, Osteitis) bezeichnete entzündliche Knochenerkrankung stellt eine wichtige Differenzialdiagnose zur bakteriellen Osteomyelitis und Knochentumoren dar. Die initial osteolytischen, später hyperostotischen Läsionen können uni- oder multifokal auftreten und bevorzugen die Metaphysen der langen Röhrenknochen, Becken-, Schultergürtel und die Wirbelsäule. Die Ätiologie ist unbekannt. Man vermutet eine reaktive Inflammation bei genetischer Disposition (HLA-B27), womit pathogenetisch ein enger Zusammenhang zur Enthesitis-assoziierten Arthritis und Psoriasisarthritis besteht. Die unterschiedlichen klinischen Verläufe reichen von Ausheilung bis zu Übergängen in destruierende Spondylarthropathien. Therapeutisch werden NSARs, Sulfasalazin, Steroide und Bisphosphonate eingesetzt.

Kasuistik Ein 16-jähriger Leistungsfußballspieler wurde wegen seit einem respiratorischen Infekt aufgetretener Schmerzen am Rippenbogen vorgestellt. Klinische Untersuchung, Thorax-Röntgen und Laboruntersuchungen (BBD, CRP) waren unauffällig. 3 Wochen später traten LWS-Schmerzen auf, die manualtherapeutisch behandelt wurden. Bei fehlender Besserung erfolgt eine MRT der LWS mit Nachweis einer Bandscheiben-Protrusion L5/S1. Bei weiterer Verschlechterung unter NSAR-Therapie erfolgte die MRT des Beckens, die eine ausgeprägte Osteomyelitis des linken Os ileum bei laborchemisch geringen Entzündungszeichen zeigte. Eine i. v. Antibiose mit Dalacin über 4 Wochen führte zu keiner Besserung. Bei Diskrepanz von Klinik und Labor erfolgte die rheumatologische Vorstellung. Immunologische Befunde waren unauffällig. Die Tc99-Skelettszintigrafie zeigte eine Mehrspeicherung im Os ileum sowie an der 3., 4. und 7. Rippe. Bei ausgeprägter Akne papulopustulosa et nodulocystica wurde die Diagnose CRMO-/SAPHO-Syndrom gestellt und auf eine Biopsie verzichtet. Eine 3-monatige konsequente NSAR-Therapie zeigte keine Besserung. Unter systemischer Steroidtherapie mit initial gutem Ansprechen konnte keine Reduktion unter 1 mg/kg Prednisolon erreicht werden, weswegen eine Methotrexat-Therapie (10 mg/m^2 KO) eingeleitet wurde. Bei weiterer klinischer und radiologischer Progression mit Ausbreitung der Entzündung in die Massa lateralis des Os sacrums, Erguss im SIG-Gelenk und Mitbeteiligung der Glutealmuskulatur bei kaum mehr gehfähigem Patienten wurde eine Antizytokintherapie mit Etanercept (25 mg 2× wöchentlich s. c.) begonnen, worauf sich ein prompt es Ansprechen, vollständige radiologische Regression und anhaltende Beschwerdefreiheit seit nunmehr 6 Monaten zeigten.

Schlussfolgerung Der Fallbericht soll diese im Kindesalter nicht seltene, aber zu wenig bekannte Erkrankung in Erinnerung rufen und die TNF-α-Blockade als Therapieoption darstellen.

Fieberschübe und Exanthem beim Neugeborenen 27

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Zielsetzung Bericht einer seltenen Erkrankung und Beschreibung einer neuen Mutation.

Hintergrund Das CINCA-/NOMID-Syndrom ist eine seltene und mit schweren Komplikationen verbundene autoinflammatorische Krankheit, bei der eine frühe Diagnosestellung und die Einleitung einer spezifischen Therapie essenziell sind. Bei etwa der Hälfte der Patienten bleibt der Nachweis der bisher bekannten Mutationen negativ. Ein Frühgeborenes der 34. SSW fiel durch urtikarielle Exantheme, Fieberschübe und Hyperexzitabilität auf. Im Verein mit exzessiv erhöhten Akutphase-Proteinen und einer typischen Physiognomie sowie erhöhter Liquorzellzahl wurde trotz initial negativem Mutationsnachweises im Exon 3 des NLRP3-Gens die Diagnose eines NOMID-Syndroms gestellt und der Patient erfolgreich mit einem Interleukin-1-Rezeptorantagonisten behandelt. Nach Beschreibung einer neuen Mutation bei einem Patienten mit einem NOMID-ähnlichen Phänotyp wurde auch bei unserem Patienten an der gleichen Stelle eine Mutation detektiert, womit die klinische Verdachtsdiagnose auch genetisch untermauert werden konnte. Bislang ist es bei unserem Patienten durch die frühe Diagnose und raschen Einsatz der Antizytokintherapie zu keinen typischen Krankheitsfolgen gekommen.

Schlussfolgerung Bei sog. „Mutations-negativen" Patienten mit klinischem Verdacht auf Vorliegen eines CINCA-/NOMID-Syndroms sollte ein Therapieversuch mit einem IL-1-Blocker unternommen werden und erweitert auf Mutationen gescreent werden.

Niedrige Uveitisinzidenz unter Methotrexat bei frühkindlicher Oligoarthritis 28

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Ziel Die frühkindliche Oligoarthritis ist mit einer autoimmunen Uveitis vergesellschaftet. Die Folgen der Uveitis sind mit einer erheblichen Einschränkung der Lebensqualität im Erwachsenenalter assoziiert. Die Inzidenz der Uveitis bei frühkindlicher Uveitis wird international mit 17–32 % angegeben. Die Therapieergebnisse bei der juvenilen idiopathischen Arthritis (JIA) im vergangenen Jahrzehnt haben sich seit Einführung des Methotrexats (MTX)gebessert. MTX wird oral oder subkutan in einer Dosis von 7,5–15 mg/m^2 (max. 20 mg) 1× pro Woche verabreicht. Auch Kinder mit frühkindlicher Oligoarthritis haben nach fehlendem Ansprechen auf nicht-steroidale Antirheumatika mit/ohne intraartikulären Kortikosteroiden eine Therapieerweiterung um MTX erfahren. Uns hat die Inzidenz der Uveitis bei frühkindlicher Oligoarthritis an einem Behandlungszentrum seit Einführung von MTX interessiert.

Methodik In einer explorativen Analyse wurde retrospektiv ab dem Jahr 2002 die Inzidenz einer Uveitis bei frühkindlicher Oligoarthritis an einem Kinderrheumazentrum evaluiert. Einschlusskriterien: Patienten der Kinderrheumaambulanz < 7 Jahre bei Beginn der Arthritis und eine Mindestbeobachtungsdauer von 6 Monaten. Ausschlusskriterien: Andere Formen der juvenilen idiopathischen Arthritis, Entwicklung einer Uveitis vor Diagnose der Arthritis und damit vor einer Basistherapie und ein Erkrankungsbeginn bei > 7 Jahre.

Ergebnisse 24 Kinder mit frühkindlicher JIA konnten eingeschlossen werden. Davon waren bei 22 Kindern im Serum antinukleäre Antikörper erhöht. Die Dauer vom Beginn der Gelenkerkrankung bis zum Beginn mit MTX war 1–30 Monate (im Mittel 5 Monate). Das Alter bei MTX Beginn war 1 $^8/_{12}$ – 5 ½ Jahre (im Mittel 3 $^4/_{12}$ Jahre). Nur eines von 24 Kindern (4,1 %) hat unter MTX eine Uveitis entwickelt, dies bereits nach 4 Monaten MTX-Therapie.

Schlussfolgerung Kinder mit frühkindlicher juveniler Oligoarthritis haben unter MTX-Therapie eine sehr niedrige Uveitisinzidenz zu erwarten.

Interleukin-6-Antikörper bei systemischer juveniler idiopathischer Arthritis und Makrophagenaktivierung – ein Fallbericht eines 13-jährigen Mädchens 29

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Wir berichten über ein 13-jähriges Mädchen mit schwerem Verlauf einer systemischen juvenilen idiopathischen Arthritis (sJIA). Die Diagnose wurde im August 2009 gestellt. Die Symptome begannen im April 2009 mit einem Exanthem und Fieber in immer kürzer werdenden Intervallen. Im Verlauf kam es zusätzlich zu Arthralgien und in Folge zur Arthritis der Finger- und Handgelenke, sowie zu einer Hepatosplenomegalie, Anämie und Lymphopenie. Die Befunde zeigten eine Makrophagenaktivierung (LDH 2200 U/l, GOT 390 U/l, Ferritin 71000 µg/l, Triglyceride 500 mg/dl). Nach dreimaliger Methylprednisolonstoßtherapie (30 mg/kg/Tag) kam es nur zu einer geringen Besserung, sodass die Therapie um Dexametha-

son und Cyclosporin A erweitert wurde. Die Entzündungsaktivität blieb dennoch sehr hoch (BSG nicht messbar, CRP 14 mg/dl, Ferritin 16000 µg/l, Serum Amyloid A 839 mg/l). Nach Umstellung der Therapie auf Methotrexat und NSAR wurde zusätzlich Anakinra (Interleukin-1-Rezeptorantagonist) subkutan verabreicht. Das Kortison konnte zu keinem Zeitpunkt abgesetzt werden. Unter einer Therapie mit 2× 2 mg/kg Anakinra war ein Rückgang der Entzündungsparameter zu vermerken (BSG 68/76 mm/h, CRP 5,06 mg/dl, Ferritin 9035 µg/l, Serum Amyloid A 176 mg/l), es kam jedoch nie zu einer Normalisierung der Werte. Im Rahmen eines Infektes mit Exazerbation der Grunderkrankung zeigten sich im Lungenröntgen und im HR-CT eine interstitielle Entzündung sowie eine milchglasartige Trübung der Unterfelder der Lunge. Die Lungenfunktion war massiv eingeschränkt und das Mädchen benötigte Sauerstoff. Die Therapie wurde schließlich von Anakinra auf hochdosiertes Methylprednisolon intravenös, dann täglich 2 mg/kg orales Prednisolon sowie intravenöses Tocilizumab (Interleukin-6-Rezeptorantikörper) umgestellt. Hierunter waren die Entzündungsbefunde weiter rückläufig (CRP 3,4 mg/dl, Ferritin 2880 µg/l). Die Lungenfunktion zeigte eine langsame Besserung der Vitalkapazität von 0,65 l (24,9 % I/S) auf 0,97 l (27,2 % I/S). Die Lungenbiopsie zeigte kaum Entzündungszellen, jedoch Ablagerungen von Eiweiß. Die Patientin wird von einer Lavage der Lungen wahrscheinlich profitieren. Der weitere klinische Verlauf wird präsentiert. Die Beobachtung zeigt, dass eine Beeinflussung von Interleukin 1 und Interleukin 6 bei sJIA eine Option ist, die Entzündung herabzuregulieren. Für ein Makrophagenaktivierungssyndrom mit Lungenbeteiligung gibt es derzeit noch keine standardisierte Therapie.

C. Klinische Studien und Präsentationen

Arthritis-Patienten mit TNF-Blockern und chirurgischen Eingriffen – ein systematischer Review 30

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Hintergrund Obwohl TNF-Blocker häufig verwendete Medikamente in der Behandlung von Arthritis-Patienten sind, gibt es Unterschiede, wie diese Präparate perioperativ gehandhabt werden.

Ziel Zu dieser Frage führten wir einen systematischen Review durch, um zu erheben, ob die Gabe von TNF-Blockern mit einer erhöhten Infektionsrate perioperativ assoziiert ist.

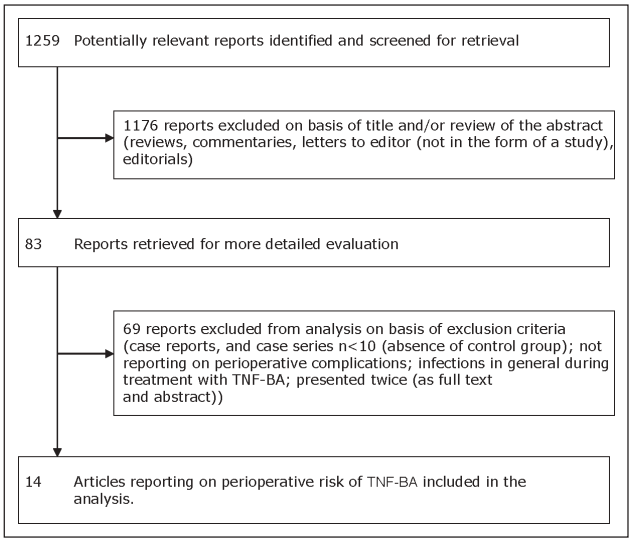

Abbildung 1: Pieringer H et al.: Literature review flow chart

Methoden PubMed Search mit den Begriffen „arthritis" und („surgery" oder „perioperative") und („infliximab" oder „adalimumab" oder „etanercept" oder „certolizumab" oder „golimumab" oder „tumour necrosis factor"). Zudem wurden die Online-Archive des Annual European Congress of Rheumatology und des Annual Scientific Meeting of the American College of Rheumatology durchsucht. Inkludiert wurden Vergleichsstudien sowie Fallserien mit einem Minimum von 10 Patienten. **Abbildung 1** zeigt den Suchablauf.

Ergebnisse 14 Studien wurden analysiert (13 retrospektiv): 6 verglichen TNF-Blocker- mit Nicht-TNF-Blocker-Therapie; 3 verglichen fortgesetzte TNF-Blocker-Therapie mit pausierter TNF-Blocker-Therapie; 3 inkludierten jeweils 3 Gruppen (beide erwähnten Vergleiche); 2 waren große Fallserien. 4 Studien (alle „TNF-Blocker ja/nein") zeigten ein erhöhtes perioperatives Infektionsrisiko bei Patienten mit TNF-Blockern, während sämtliche anderen Studien dies nicht zeigten. **Tabelle 1** zeigt sämtliche Ergebnisse.

Zusammenfassung/Schlussfolgerung Publizierte Daten unterstützen nicht konklusiv die Annahme, dass unter TNF-Blockern vermehrt perioperative Infekte auftreten. Es erscheint eher, dass Patienten, die diese Therapie erhalten, *a priori* ein höheres Infektionsrisiko haben.

Immunadsorption als Therapie bei steroidrefraktärer Dermatomyositis 31

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Hintergrund Glukokortikoide sind immer noch der therapeutische Goldstandard der Dermatomyositis (DM). Einige Patienten sprechen jedoch auf diese Therapie entweder nicht an oder es kommt nach Reduktion der Kortisondosis zu einem Relaps. Deshalb ist es wichtig, neue therapeutische Konzepte für diese Erkrankung zu finden.

Ziel Diese Studie wurde durchgeführt, um einen therapeutischen Effekt einer Immunadsorption (IAS) bei Patienten mit DM zu zeigen.

Methoden 5 Patienten mit aktiver DM, trotz Therapie mit Aprednislon als Monotherapie oder in Kombination mit MTX oder Azathioprin, wurden mit IAS behandelt.

Ergebnisse Vor Beginn der Therapie mit IAS war in allen Patienten die CPK deutlich erhöht (MW ± SD: 5212 ± 6142 U/ml). Nach einem Monat IAS-Therapie kam es zu einem Absinken der CPK in allen Patienten (283 ± 317 U/ml), und zu einer Normalisierung in 3 Patienten. Die mittlere Dosis von Aprednislon konnte von 135 mg auf 37,5 mg reduziert werden. In 3 Patienten konnte die IAS-Therapie wegen anhaltender Remission beendet werden. Die IAS wurde von allen Patienten gut toleriert.

Zusammenfassung/Schlussfolgerung IAS scheint als Therapiealternative bei steroidrefraktärer DM sicher und effektiv. Eine größere, kontrollierte Studie ist in Planung.

Herzfrequenz, kardiale Ejektionsdauer und „subendocardial viability ratio" bei Patienten mit Rheumatoider Arthritis verglichen mit Kontrollen 32

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Hintergrund In der Allgemeinbevölkerung geht eine höhere Herzfrequenz mit gesteigerter Mortalität einher. Bei der Rheumatoiden Arthritis (RA) treten gehäuft kardiovaskuläre (CV) Ereignisse auf. Es gibt nur begrenzt Untersuchungen, die Herzfrequenz bei RA- und Nicht-RA- (n-RA-) Patienten verglichen haben, und es ist offen, ob eine höhere Herzfrequenz bei RA-Patienten die gesteigerte Mortalität – zumindest in Teilen – erklären könnte.

Ziel Ziel war es, die Herzfrequenz bei RA- und n-RA-Patienten zu ermitteln. Zudem wurden Ejektionsdauer (ED) und „subendocardial

Tabelle 1: Pieringer H et al.: Übersicht über die Ergebnisse untersuchter Studien.

Study	P/R	Type	Pat. TNF-Block (n)/ Procedures (n)	Controls (n)/ Procedures (n)	Type of Surgery	Disc (n)/ cont (n)	Infections (%)+	Conclusion
Full text:								
Bibbo (2004)	P	y/n	16/72	15/69	Foot/Ankle-Surgery	n. a.	6/7	No increased risk
Giles (2006)	R	y/n	35/n. d.	56	Orthopaedic	n. a.	20/5	Increased risk
Talwalkar (2005)	R	c/disc	11/16	n. a.	Orthopaedic	12/4	0/0	No increased risk
Wendling (2005)	R	c/disc	30/50	n. a.	Orthopaedic & Non-orthop.	18/32	0/0	No increased risk
Den Broeder (2007)	R	y/n	n. d./196	n. d./1023	Orthopaedic	n. a.	7/4	No increased risk
		c/disc	n. d./196	n. a.		104/92	6/9	No increased risk
Ruyssen-Witrand (2007)	R	c/disc	92/127	n. a.	Mixed	n. a.	9	No increased risk*
Corrao (2008)	R	y/n	26/n. d.	210/n. d.	Mixed	n. a.	0/0	No increased risk
		c/disc	26/n. d.	n. a.	Mixed	21/5	0/0	No increased risk
Hirano (2010)	R	y/n	39/39	74/74	Orthopaedic	n. a.	5/7	No increased risk
Kawakami (2010)	R	y/n	49/64	63/64	Orthopaedic	n. a.	13/2	Increased risk
Abstracts:								
Shergy (2005)	R	Cases	63/76	none	Orthopaedic	n. a.	3	No increased risk
Matthews (2006)	R	y/n	30/n. d.	96/n. d.	Orthopaedic	n. a.	23/7	Increased risk
Arkfeld (2007)	R	y/n	n. d./11	n. d./11	Ellbow Arthropalsty	n. a.	36/9	Increased risk
Dixon (2007)	R	y/n	1348/1694	155/179	Mixed	n. a.	7/7	No increased risk**
		c/disc	1348/1694	n. a.	Mixed	337/1357	6/7	No increased risk**
Kanbe (2007)	R	Cases	43/43	none	Orthopaedic	n. a.	5	No increased risk

P = prospective; R = retrospective; y/n = „yes/no"-studies (comparison of patients with and without TNF-blockers); c/disc = „continued/discontinued"-studies (comparison of patients who continued or discontinued treatment with TNF-blocking agents); n. d. = not determined; n. a. = not applicable.

* c/disc is stratified in 3 groups (depending on duration of discontinuation), infections are mentioned only for the total group, the total complication rate was not influenced by time of discontinuing the drug; ** according to the p value no increased risk; + Infections: in c/disc-studies percentages for infections are given as: „discontinued/continued"; in y/n-studies percentages for infections are given as: „with TNF-BA/without TNF-BA".

viability ratio" (SEVR), ein Marker für kardiale Workload, untersucht.

Methoden In dieser Cross-sectional-Studie wurde die Herzfrequenz bei insgesamt 282 Patienten (131 RA, 151 n-RA) mit dem Sphygmocor-Apparat gemessen. Weiters wurden kardiale ED und SEVR mittels nicht-invasiver Pulswellenanalyse (PWA) ermittelt. SEVR wird wie folgt berechnet: Druckintegral über die Zeit in der Diastole („diastolic time index", DTI) durch Druckintegral in der Systole („tension time index", TTI). Patienten mit chronotropen Medikamenten wurden exkludiert.

Ergebnisse Patienten-Daten sind in **Tabelle 2** dargestellt. RA-Patienten waren älter und hatten höhere Cholesterinwerte ($p < 0,05$). In der n-RA-Gruppe waren mehr Diabetiker ($p < 0,05$) und grenzwertig mehr Raucher ($p = 0,05$). Die Herzfrequenz war in beiden Gruppen quasi ident (Median 70 Schläge/Minute in beiden Gruppen; $p > 0,05$). Des Weiteren zeigte sich kein signifikanter Unterschied zwischen den Gruppen hinsichtlich ED (RA 321 ± 24 ms vs. n-RA 318 ± 24 ms) und SEVR (RA 144 ± 25 % vs. n-RA 147 ± 27 %).

Zusammenfassung/Schlussfolgerung Der CV-Risikofaktor „Herzfrequenz" ist bei RA-Patienten im Vergleich zu Kontrollprobanden nicht erhöht und wird daher die erhöhte Rate an CV-Ereignissen bei RA-Patienten nicht erklären können.

Tabelle 2: Pieringer H et al.: Patienten-Charakteristika.

	RA (n = 131)	n-RA (n = 151)	p
Alter (a)	54,3 (12,6)	46,3 (11,4)	0,01
Frauen (n, %)	115 (87,8)	137 (90,7)	> 0,05
RA-Dauer (a)	13,2 (9,2)		
RF positive (%)	74		
BSG (mm/h)	25,8 (23,3)		
DAS28	3,37 (1,6)		
Diabetes (n, %)	2 (1,5)	34 (22,5)	0,01
Raucher (n, %)	22 (16,8)	43 (28,5)	0,05
Cholesterin (mg/dl)	216 (41)	192 (49)	0,025
Herzfrequenz (bpm)	71,9 (11,2)	72,3 (11,7)	> 0,05
ED (ms)	321 (24)	318 (24)	> 0,05
SEVR (%)	144 (25)	147 (27)	> 0,05
DTI (ms × mmHg)	3490 (475)	3379 (592)	> 0,05
TTI (ms × mmHg)	2484 (478)	2375 (499)	> 0,05

BSG = Blutsenkungsgeschwindigkeit; ED = Ejektionsdauer; DAS28 = Disease Activity Score 28; DTI = diastolic time index; RF = Rheumafaktor; SEVR = subendocardial viability ratio; TTI = tension time index.

Sicherheit und Verträglichkeit von Methotrexat bei älteren Patienten mit Rheumatoider Arthritis 33

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Ziel Methotrexat (MTX) stellt in der Behandlung der Rheumatoiden Arthritis (RA) die First-line-Therapie dar. Studien zeigen, dass ältere Patienten mit RA oft nicht adäquat behandelt werden. Einer der wesentlichen Gründe scheint die Sorge der behandelnden Ärzte zu sein, dass unerwünschte Arzneimittelwirkungen (UAW) unter MTX bei älteren Patienten häufiger auftreten könnten als bei jungen. Wir analysierten die Häufigkeit von UAW unter einer Monotherapie mit MTX, die zum Abbruch der Basistherapie führten, und verglichen dabei Patienten mit RA im Alter > 70 Jahren mit jenen < 70 Jahren.

Methoden In diese retrospektive Analyse wurden all jene Patienten erfasst, die im Zeitraum vom 1. 1. 1993 bis zum 1. 1. 2009 an der Ambulanz der Klinischen Abteilung für Rheumatologie der Universitätsklinik für Innere Medizin III wegen einer RA mit einer MTX Mono-Th in Behandlung waren. Neben MTX-Dosis, Th-Dauer, Komedikation und den für die Th relevanten Laborwerten (Blutbild, Leberfunktionsparameter, Serum-Kreatinin, glomeruläre Filtrationsrate) wurden die Abbruchraten und Abbruchgründe erfasst.

Ergebnisse Insgesamt konnten Daten von 504 Patienten ausgewertet werden. Das Durchschnittsalter des Gesamtkollektivs lag bei 58 Jahren. Davon waren 388 < 70 Jahre (Gruppe I) und 116 > 70 Jahre alt (Gruppe II). In 77 Fällen traten UAW auf, die zum Therapieabbruch führten. Therapieabbrecher (ABB) nahmen mit 18,2 mg/Woche eine signifikant niedrigere Maximal-Dosis von MTX ein als Nichtabbrecher (NAB) mit 20,7 mg/Woche ($p = 0,05$). Die Therapiedauer war bei ABB mit 15 Monaten signifikant kürzer als bei NAB mit 30 Monaten ($p = 0,001$). Zwischen den Altersgruppen fanden sich aber keine Unterschiede in der Häufigkeit eines Therapieabbruchs (p = n. s.). Umgekehrt war auch der Altersdurchschnitt von ABB (mean 58,7 Jahre) mit jenem der NAB (mean 56,6 Jahre) vergleichbar (p = n. s.). Die Häufigkeit begleitender NSAR-Einnahme und die durchschnittliche Steroiddosis waren ebenso gleich verteilt. 94,6 % aller Patienten erhielten eine Folsäure-Substitution.

Schlussfolgerung Bei RA Patienten > 70 Jahre kommt es mit einer Häufigkeit von rund 15 % unter MTX-Monotherapie nicht

häufiger als bei jüngeren zu UAW, die zum Th-Abbruch führen. Die häufigsten UAW waren dabei Übelkeit und Stomatitis.

Immediate Access Rheumatology Clinic: Efficiency and Outcomes 34

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Background & Objective It was shown that early application of disease-modifying antirheumatic drugs (DMARD) improves the outcome of RA. The delay from symptom onset to the first visit with a rheumatologist or start of therapy ranges from several months up to more than 1 year. This delay has several reasons: neglect or negation of rheumatic diseases in general, lack of information, lack of knowledge about available therapies, limited availability, and (geographical) proximity of specialists, or a mix thereof. In order to facilitate access and shorten waiting times to rheumatologist assessment, an immediate access clinic (IAC) was established. In this study we evaluated the effectiveness of the IAC and we describe the spectrum of patients' diagnoses and clinical characteristics at presentation and after 6–12 months.

Methods Patients for this study were first seen in the IAC between February and December 2009. In the IAC an experienced rheumatologist takes a brief history regarding duration and clinical symptoms. In addition, a short symptom-centred physical examination is performed and a preliminary decision is made to assign the patient to one of 2 groups: Patients in group A are referred to the regular outpatient clinic for further work-up; patients in group B are assigned to other specialist care/work-up or back to the referring physician with appropriate recommendations for further care. Demographic data, tentative diagnoses, symptom duration, and pain (assessed using a 100 mm visual analogue scale; VAS) as well as the time between the date of referral and the day of assessment were recorded at baseline (first presentation to the IAC) and entered into an electronic spreadsheet. For follow-up after 6–12 months, group A patients had to be divided into 2 subgroups: Group A1 were patients who were regularly followed in the outpatient rheumatology clinic data regarding diagnoses and pain were extracted from the patients' charts. Patients initially allocated to group A who did not return for follow-up visits within the 6–12-month timeframe (group A2) were called for a telephone interview. Group B patients were also interviewed by telephone.

Results From February to December 2009, 1036 patients were assessed. 223 (21.5 %) patients had symptoms for 3 months or less. 660 were available for re-assessment after 6–12 months. Initial tentative diagnoses were confirmed in > 75 % of patients suspected of having rheumatoid arthritis (RA), spondylarthropathy, and osteoarthritis. Men suspected of having spondylarthropathy had a significantly longer symptom duration than women (median [IQR] 54.0 [18.0–120.0] vs 24.0 [6.0–66.0] months; p = 0.0082). There was no significant gender difference regarding pain. At follow-up, the visual analogue scale for pain in RA patients admitted to further care in the clinic (n = 61) had significantly decreased by a median (IQR) of 37.5 mm (10.5–50.5), whereas this improvement was only 6 mm (–26–33.5) in the 22 RA patients followed outside the clinic (p = 0.0083).

Conclusions The IAC resulted in considerable waiting time reduction for rheumatology assessment. A substantial minority was seen before 3 months' symptom duration. "Positive predictive correctness" of the assessing rheumatologists regarding the presence of inflammatory rheumatic conditions was > 75 %. Patients with RA cared for in the clinic had substantially lower pain levels after 6–12 months' follow-up than patients treated elsewhere. The IAC presented here may thus serve as a model for other institutions to reduce overall waiting times for appointments and at the same time allow early recognition and timely appropriate therapy for patients in need of a rapid intervention, such as RA or CTD.

Assessing the Impact of TNF-Blocking Agents on Male Sperm Characteristics and Pregnancy Outcomes 35

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Aim Published data were analysed to determine if the use of tumour necrosis factor- (TNF-) blocking agents in male patients during time of conception is associated with an increased risk of fetal abnormalities or complications during pregnancy. Moreover, we were interested in the impact of TNF-blocking agents on sperm quality characteristics.

Methods We performed a systematic literature review (Medline, online archives of Annual European Congress of Rheumatology and the American College of Rheumatology). 139 articles of potentially relevant reports were identified and screened for retrieval and 9 articles were included in the final analysis.

Results Overall, there were 60 cases where expectant fathers used TNF-blocking agents shortly before conception. The outcomes of the pregnancies are documented in 28 events. We did not find any documentation of miscarriages or physical abnormities associated with TNF-blocking treatment and paternity; however we did find documentation evidence that sperm motility and vitality even may improve under TNF-blocking therapy. This improvement may be caused by a decrease in disease activity.

Conclusion From the studies, we believe that therapy with TNF-blocking agents in male patients does not affect reproduction ability.

Sonoelastography Detects Rigidity of Salivary Glands in Sjögren's Syndrome 36

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Objective To investigate the value of sonoelastography (SElasto) in patients with primary Sjögren's syndrome (pSS).

Methods Prospective study on 38 pSS patients fulfilling the American-European consensus group criteria (mean age 58 years; 92 % female; median duration of sicca symptoms 6 years, 65 % histological sialadenitis) and 11 healthy controls. B-mode sonography and SElasto of parotid and submandibular glands was performed using a GE Logiq E9 ultrasound device. Parenchymal homogenicity, echogenicity, hypoechogenic areals, hyperechoic reflections, and clearness of glandular borders were semiquantitatively scored (total score ranging from 0 to 48). SElasto was used to examine the elasticity of glandular parenchyma and a semiquantitative rating was performed with 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. The total score ranged from 0 to 16. Clinical assessments were performed at the same day of sonographic evaluation and included: Saxon test, Schirmer test, Xerostomia inventory (XI), and the Ocular Surface Disease Index (OSDI). Statistical analysis was performed using SPSS program (v18.0) and the Mann-Whitney-U and Spearman rank correlation test were performed as appropriate. Interobserver variability of sonography was tested in 30 % of pSS patients by intraclass correlation coefficient (ICC).

Results pSS patients had higher B-mode scores (median 25 [range 2.0–44.0] vs 2.0 [0–8.0]; p < 0.001) and SElasto scores (6.0 [2.0–12.0] vs 3.0 [1.0–4.0]; p < 0.001) than healthy controls. pSS patients showed a median salivary flow rate of 1.69 g/2 min (range 0.31–3.79), a median moisture on the filter paper (Schirmer test) of 4.0 mm/5 min (0–50.0), a median XI of 27.5 (8.0–43.9) and a median OSDI of 43.8 (0–77.1). In pSS patients, an inverse correlation was found between the result of the Saxon test and SElasto score (corr-coeff –0.426; p = 0.009), whereas B-mode ultrasound results were

not associated with saliva production. Neither disease duration nor duration of sicca symptoms influenced ultrasound results. A good reproducibility of B-mode and SElasto results was found as indicated by an ICC of 0.926 (95 % CI 0.565–0.983) and 0.934 (0.787–0.981), respectively.

Conclusion Increased rigidity of major salivary glands as demonstrated by sonoelastography in patients with pSS correlates with the impairment of saliva secretion.

Ultrasound Assessment of Elderly Onset Rheumatoid Arthritis (RA) Patients: Higher Scores of Inflammation but Similar Pattern of Joint Involvement Compared to Young Onset RA 37

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Background Musculoskeletal ultrasound is a sensitive means to detect joint inflammation in rheumatoid arthritis. Ultrasound findings in elderly onset rheumatoid arthritis (EORA) patients have not been compared so far with sonographic signs in young onset (YORA) patients.

Objective To compare sonographic scores of inflammation and the pattern of joint involvement between EORA and YORA patients.

Methods Retrospective analysis of 145 consecutive rheumatoid arthritis patients, routinely assessed by sonography of the wrists, metacarpo-phalangeal (MCP), and proximal inter-phalangeal joints (PIP) including semiquantitative scoring of synovial hypertrophy/effusion (SH/E) and power Doppler (PD) signals. Global ultrasound scores were calculated by the addition of SH/E and PD results. Sonographic disease activity was defined by the presence of PD signals in at least one joint. EORA was defined by a disease onset after the age of 60 years. The number of tender (TJ) and swollen joints (SJ), global assessment of disease activity on a visual analogue scale by the physician (VAS-phys) or patient (VAS-pt), disease activity score-28 (DAS-28), clinical disease activity index (CDAI), and simplified disease activity index (SDAI) were recorded. The respective values for disease activity were accounted for in group comparisons using the SPSS statistic software (version 18.0).

Results 70 patients were diagnosed with EORA (median age 73 [interquartile range 11] years, 81.4 % female) and 75 patients with YORA (54 [13] years, 86.7 % female). EORA patients had higher global ultrasound scores (median 18.5 [interquartile range 17.0] vs 12.0 [15.0]; $p = 0.009$) and SH/E scores (12.0 [10.0] vs 9.0 [9.0]; $p = 0.004$) than patients with YORA. Patients with EORA were more likely to show PD signals than patients with YORA (85 % vs 72 %; OR 3.9 [95 % CI 1.3–11.5]; $p = 0.015$). The groups did not differ regarding the sonographic pattern of joint involvement and the sensitivity of various reduced ultrasound joints counts to detect patients with ultrasound-defined active disease. Clinical disease activity parameters including DAS-28 (4.5 [1.4] vs 4.4 [2.0]; $p > 0.2$), CDAI, SDAI, the number of TJ, SJ, VAS-phys, and VAS-pt were comparable between EORA and YORA patients.

Conclusion EORA patients showed higher sonographic scores of inflammation despite similar clinical disease activity compared to YORA. The pattern of sonographic joint involvement as well as the sensitivity of reduced sonographic joint counts did not differ between the groups.

Sonography Verifies Active Inflammation in Erosive Hand Osteoarthritis 38

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Background Active inflammation as verified by sonography is associated with the occurrence of erosions in rheumatoid arthritis. For hand osteoarthritis (HOA) the association between sonographic, clinical, and x-ray findings remains elusive so far.

Objective To investigate the association between sonographic signs of active inflammation, clinical parameters, and erosions in HOA.

Methods Retrospective analysis of 114 consecutive HOA patients with routine sonographic assessment of the wrists, metacarpo-phalangeal, proximal, and distal inter-phalangeal joints. Semiquantitative scoring of synovial hypertrophy/effusion (SH/E) and power Doppler (PD) signals was performed, and active inflammation was defined by the presence of PD-signals in at least one joint. X-rays of the hands were routinely performed within 4 weeks of sonography and rated by an experienced radiologist (H. W.). Number of tender (TJ) and swollen joints (SJ), global assessment of disease activity by the physician (VAS-phys) and patient (VAS-pt), C-reactive protein (CRP), erythrocyte sedimentation rate (ESR), and health assessment questionnaire (HAQ) were recorded. This analysis was accepted by the local ethics committee. Statistical analysis was performed using SPSS program (version 18.0) and the Mann-Whitney-U and chi-square tests were performed as appropriate.

Results 32 out of 114 HOA patients (28.1 %) showed PD signals indicating active inflammation. Radiographic erosions were more prevalent among patients with ultrasound-verified active inflammation than among patients without hypervascularisation (22.6 % vs 6.3 %; $p = 0.013$). No differences were found between patients with and without PD signals regarding TJ, SJ, VAS-phys, VAS-pt, CRP, ESR, and HAQ.

Conclusion Active inflammation as detected by sonography is linked with higher frequency of x-ray-verified erosions in patients with HOA.

General Health Perception in Patients with Remission 39

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Background/Purpose In patients with rheumatoid arthritis (RA), reaching remission is the ultimate goal and recently new, stringent remission criteria have been defined by ACR and EULAR. However, it is not yet known if patients in stringent remission perceive their health status as optimal. We aimed to investigate the general health perception of RA patients who have achieved ACR-EULAR remission.

Methods In 716 consecutive patients with RA, we collected data on disease activity, including swollen and tender joint counts (SJC/TJC), pain (visual analogue scale; VASpain), patient and physician global assessment of disease activity (PGA/MDGA), simplified disease activity index (SDAI), disease activity score 28 (DAS28), physical function by health assessment questionnaire (HAQ), and quality of life by Short Form 36 (SF-36) and Euro-QoL 5D). Furthermore radiological damage was quantified using total Sharp van der Heijde Score (SvdH) including total erosions and joint space narrowing (JSN). The domain general health perception (GHP) of SF-36 was used as the measure of the patients' health perception. In patients with SDAI remission (SDAI ≤ 3.3; n = 172) we calculated tertiles of GHP and compared measures of function, pain, and QoL across the 3 groups using analysis of variance (ANOVA).

Results GHP of 716 patients (82 % female, 57 % rheumatoid factor positive, SDAI mean 9.3 ± 8) showed significant ($p < 0.01$) correlation with SDAI ($r = –0.46$), DAS28 ($r = –0.48$), PGA ($r = –0.58$), VASpain ($r = –0.58$), EGA ($r = –0.25$), and HAQ ($r = –0.60$). Patients in SDAI remission (n = 172) showed an average GHP of 60.97 ± 18.1 (range: 12–100). Those who still perceived themselves in bad health (bottom tertile of GHP, < 52/100) had poorer physical function and QoL, and higher pain levels as well as higher radiological scores – whereas there were no significant differences of MDGA in the 3 subgroups of GHP (0.81 vs 1.15 vs 1.19; $p = 0.51$).

Conclusion Even patients fulfilling stringent remission may have a poor health perception. Pain and functional disability that are considered unrelated to disease activity as well as joint damage are main determinants for this perception. These data call again for intensive treatment to prevent accumulation of damage, as well as for more consistent pain therapy in RA.

Biological Prescription in Every Day Routine – Longitudinal Analysis of a Prospective Database 40

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Background In rheumatoid arthritis (RA) treatment strategies focus more and more on biological agents, given that multiple clinical trials report effective reduction of disease activity.

Objective To investigate disease course of RA patients receiving biological agents at large Viennese outpatient clinics over the last 3 years (2007–2009).

Methods Clinical and laboratory parameters of every consecutive RA patient visiting our clinics are routinely entered in a longitudinal observational database (CARAbase). All patients receiving new biological therapy or were switched from one to another biological agent within the years 2007 to 2009 were identified and their disease course followed over 2 consecutive visits (follow-up 1 [FU1] and follow-up 2 [FU2]). Differences of clinical variables of baseline and follow-up visits were compared between the 3 years of prescription.

Results In total the CARAbase contains 21,645 visits of 2161 different patients. In the year 2007 to 2009, 336 out of 1114 RA patients (= 30.2 %) received at least once biological agent – the percentage of patients treated with biologicals increased over time (27.5 % to 31.2 % to 33.3 %; 2007–2009, respectively). In 113 patients (10.1 %) biological agents were prescribed for the first time in the time period investigated. Baseline characteristics of these patients are depicted in **table 3**, showing moderate disease activity according to CDAI (mean 17.7 ± 9.8) when treatment was started. We found no significant differences of baseline characteristics between the 3 years investigated (CDAI: 17.1 vs 19.1 vs 17.1; DAS28: 4.39 vs 4.22 vs 4.42; 2007 vs 2008 vs 2009 respectively). As shown in table 1 there was a significant reduction of all variables from baseline to FU1, and significant reduction of CDAI, DAS28, SDAI, and EGA from FU1 to FU2, though patients had still moderate disease activity according to CDAI (11.03 ± 8.6). 136 (12.2 %) patients were switched from one biological agent to another in time period investigated, showing slightly higher disease activity (CDAI 19.4 ± 10.5; DAS28 4.6 ± 1.2) at baseline visit when compared to patients starting biological treatment, again no differences were observed between 2007, 2008, and 2009. When comparing patients who were switched for the first time to those switched twice or more often, there were significant differences in disease activity at baseline visit (CDAI: 16.9 vs 21.1; DAS28: 4.2 vs 4.8; PGA 25.4 vs 37.1; SJC28: 4 vs 6.8; first vs second or more switches, respectively; other variables $p > 0.05$). Significant reduction of disease activity was observed (CDAI: 19.4 vs 16.9; DAS28: 4.6 vs 4.2) with no differences between 3 years investigated and number of switches.

Conclusion We found no differences in prescribing biological agents in the last 3 years. Though, reduction of disease activity in real time patients is notable lower when compared to typical clinical trials.

Aiming to Reach Remission – Is It worthwhile? 41

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Background Rheumatoid arthritis (RA) is a prevalent chronic inflammatory disease causing disability and a considerable burden for the single patient and society. Remission (REM) is one of the major goals of RA treatment. In this study, we investigated whether aiming for remission in patients with low disease activity is also effective from a socio-economic point of view.

Patients & Methods In 356 patients with established RA we obtained information about quality of life (Short Form 36 [SF-36]), utility (Short Form 6D [SF-6D]; Euro-Qol 5D [EQ-5D]), physical disability (Health Assessment Questionnaire [HAQ]), productivity (Work productivity and activity impairment Questionnaire [WPAI]), as well as disease activity (Clinical Disease Activity Index [CDAI]). In cross-sectional analyses we compared data obtained of patients in REM (n = 89) to those in LDA (n = 152) using Students T Test. We also compared patients who stayed in REM (n = 34) for a whole year and compared their values with those of patients in LDA (n = 66) for the same period.

Results In the cross-sectional analyses we found statistically significant differences of utilities when comparing patients in REM with those in LDA (SF-6D 0.75 vs 0.66; EQ-5D 0.89 vs 0.78), physical disability (HAQ 0.38 vs 0.75), and productivity (WPAI % overall impairment: 18.1 % vs 33.8 %; WPAI % impairment while working: 11.3 % vs 27.2 %) (all comparisons: $p < 0.05$?). Regarding quality of life we found significant differences in all domains except "role emotional" and MCS in favour of REM. Though, compared to healthy populations there are still significant differences in all domains except "mental health" (**fig. 2**). Preliminary longitudinal analyses showed significant differences of outcomes over one year

Table 3: Radner H et al.: Patient characteristics at baseline and follow-up visits (mean and standard deviation [SD] when applicable)

	Baseline visit	SD	Follow-up 1	SD	Follow-up 2	SD
Female (%)	86.70 %					
Rheumatoid factor pos. (%)	57.50 %					
Age (yrs)	53.6	17.9				
Disease duration (yrs)	12.8	7.3				
C-reactive protein (CRP in mg/dl)	1.58	2.39	1.03	2.00	1.91	6.43
Erythrocyte sedimentation rate (ESR in mm)	28.20	21.59	24.67	18.56	22.36	18.78
Swollen Joint Count 28 (SJC28)	5.35	4.20	4.01	3.96	3.31	3.91
Tender Joint Count 28 (TJC28)	4.88	5.11	3.51	4.58	2.79	4.03
VAS pain (mm)	42.27	22.34	31.95	23.02	28.96	21.78
Patient Global Assessment (EGA in mm)	46.25	22.79	35.50	23.67	31.47	24.04
Evaluator Global Assessment (PGA in mm)	28.25	17.60	21.92	18.11	16.90	17.23
Simplified Disease Activity Index (SDAI)	19.06	11.26	13.74	10.48	12.28	9.14
Clinical Disease Activity Index (CDAI)	17.68	9.77	13.11	9.57	11.03	8.64
Disease activity Index (DAS28)	4.35	1.10	3.73	1.17	3.48	1.05
Health Assessment Questionnaire (HAQ)	1.07	0.79	0.89	0.78	0.84	0.74

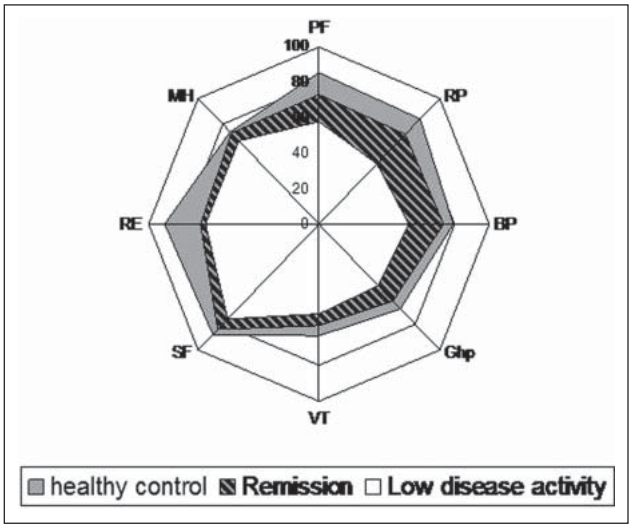

Figure 2: Radner H et al.: Domains of Short Form 36 in patients within REM compared to LDA and healthy control. BP = bodily pain; PF = physical function; RP = role physical; GHP = general health perception; SF = social function; MH = mental health; RE = role emotional; VT = vitality.

between patients in REM and those in LDA: QALY (SF-6D 0.89 vs 0.80; EQ-5D 0.80 vs 0.66), Quality of life over one year (PCS 48.7 vs 38.0), physical disability over one year (HAQ 0.22 vs 0.69), and percent of overall activity impairment per year (12.2 % vs 31.0 %). No significant difference of percent of activity impairment while working was found.

Conclusion From a socio-economic perspective including quality of life, disability, and productivity, REM seems to be still superior to any other state of disease, even LDA. Therefore aiming for REM seems worthwhile and should be the major target when treating RA.

RADAI-5 Remission Represents 2011 ACR/EULAR Proposal for Remission with High Specificity 42

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Background New remission criteria for rheumatoid arthritis were recently proposed by ACR and EULAR. It was of interest if a patient-centred disease activity score as the RADAI-5 meets these criteria.

Objective To approve RADAI-5 remission criteria with the recently proposed ACR/EULAR remission criteria for rheumatoid arthritis (RA).

Method 729 RA outpatients were assessed according to the RADAI-5 as well as the 2 approaches of the recently published ACR/EULAR proposal (Boolean-based and index-based) being in remission or not. 1844 assessments (mean interval of the single assessments 6.7 months, mean number of assessments/pat 2.5) were included in this study. Sensitivity, specificity, positive and negative likelihood ratio (+LR, –LR), and ROC-analysis (area under the curve [AUC]) were performed to illustrate the relation of the 3 different approaches defining remission.

Results Comparing the RADAI-5 remission group with Boolean-based definition showed a sensitivity of 83 %, specificity of 88 %, +LR 6.7, –LR 0.19, and AUC 0.85. Comparison with index-based definition showed 59 %, 91 %, 5.96, 0.46, and 0.75, respectively. Core set parameters were significantly different comparing assessments of the RADAI-5- and Boolean- as well as the index-based remission group except patient's global assessment compared with the index-based and ESR with the Boolean-based definition group.

Conclusion Although core set parameters are different, the RADAI-5 remission meets ACR/EULAR remission criteria showing high specificity with the index-based as well as Boolean-based definition on group level.

Characteristics of Patients According to the Two 2011 ACR/EULAR Proposals of Remission in Rheumatoid Arthritis 43

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Objective Recently an ACR/EULAR expert committee published new proposals of remission for rheumatoid arthritis (RA). 2 propositions have been made: The Boolean-based definition with ≤ 1 tender joint (TJ), ≤ 1 swollen joint (SJ), the patient global assessment on a 10 cm visual analogue scale (PATGA) ≤ 1.0, and the C-reactive protein (CRP) in mg/dl ≤ 1.0 or the index-based definition with a SDAI ≤ 3.3. The purpose of this investigation was to characterize patients according to both approaches.

Method 1844 assessments included a 28-joint count for TJ and SJ, PATGA, CRP, and physician's global assessment (MDGA) to calculate the SDAI and to identify patients in remission according to the ACR/EULAR remission definition. ESR 1st hr, VASpain and the HAQ were recorded. The mean of each core set parameter and the 95 % Confidence Interval were calculated in the respective group of remission and Student's T-Test was calculated for their relation. $P < 0.05$ was defined to be significantly different.

Results 184 assessments were identified to be in remission according to the Boolean-based definition, whereas 379 according to the index-based definition. 181 assessments fulfilled both criteria. PGA, VASpain, and HAQ (all patient related parameters) were statistically different in both groups.

Conclusion 198 more patients are identified to fulfil the index-based definition than the Boolean-based definition of remission. PGA, VASpain, and the HAQ score are statistically significantly different in both groups. This might be interpreted that patient's characteristics are different in both groups.

Empfehlung der Arbeitsgruppe Osteologie zur Prophylaxe und Therapie der Glukokortikoid-induzierten Osteoporose 44

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Arbeitsgruppe Osteologie der ÖGR

Einleitung Mehrere internationale Leitlinien zur Therapie und Prophylaxe der Glukokortikoid-induzierten Osteoporose (GIO) sind publiziert. Die Arbeitsgruppe Osteologie der ÖGR kam überein, diese zu sichten, zu diskutieren und zusammenzufassen.

Methode Die herangezogenen Leitlinien sind, gereiht nach deren Erscheinen, die Guidelines des Royal College of Physicians aus dem Jahr 2002, die Leitlinie zur GIO des DVO (Dachverband Osteologie) aus dem Jahr 2006, die EULAR-Empfehlungen zur Therapie mit Glukokortikoiden aus dem Jahr 2007, die DVO-Leitlinie 2009 zur Prophylaxe, Diagnostik und Therapie der Osteoporose bei Erwachsenen und das Update zur Prävention und Behandlung der GIO aus dem Jahr 2010 des American College of Rheumatology.

Resultat 4 Schwerpunkte wurden erarbeitet: Überlegungen vor einer geplanten Glukokortikoidtherapie, eine Empfehlung zur Diagnostik, eine Empfehlung zur (prophylaktischen) Therapie und was nach Absetzen einer Glukokortikoidtherapie zu beachten ist.

Zusammenfassung Die Empfehlungen wurden in der Wiener Klinischen Wochenschrift publiziert [Wien Klin Wochenschr 2011; 123: 1–12] und werden bei der ÖGR-Jahrestagung diskutiert.

Radiologische Progression von AS-Patienten unter TNF-Blocker-Therapie 45

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Ziel Klinische Studien deuten darauf hin, dass bei Patienten mit ankylosierender Spondylitis (AS) auch unter einer Therapie mit TNF-Blockern eine radiologische Progression der Erkrankung beobachtbar ist [1, 2]. Wir gingen deshalb der Frage nach, ob auch im klinischen Alltag bei Patienten mit AS unter einer Therapie mit TNF-Blockern eine radiologische Progression eintritt.

Methoden Nachdem die Methodik der Studie durch die lokale Ethikkommission genehmigt worden war, wurden alle Daten von Patienten mit gesicherter AS aus der seit 2004 bestehenden digitalen Datenbank RCQM retrospektiv extrahiert. Patienten, von denen projektionsradiographischen Aufnahmen der HWS, der LWS und der Sakroiliakalgelenke (SIGs) in einem Mindestabstand von 2 Jahren vorlagen, wurden in die Studie eingeschlossen. Die projektionsradiographischen Aufnahmen der Wirbelsäule (WS) und der SIGs wurden von 2 Radiologen unabhängig voneinander nach dem modifizierten Stoke Ankylosing Spondylitis Spine Score (mSASSS, normaler Range 0–72) ausgewertet und die Daten mit dem Software-Programm JMP 9.0 analysiert und die Ergebnisse in Abhängigkeit von der Verteilung mittels ANOVA- beziehungsweise Wilcoxon-Rangsummentest verglichen. Die Krankheitsaktivität der Patienten wurde im Röntgenintervall im Mittel 11 ± 9 Mal klinisch anhand des BASDAI und des AS-DASCRP bestimmt und mittels ANOVA ausgewertet.

Resultate Bei der Analyse der Datenbank wurden 170 AS-Patienten identifiziert, wobei bei 55 AS-Patienten (18 Frauen, 37 Männer; mittleres Alter 48,7 ± 10,5 Jahre; mittlere Krankheitsdauer 14,8 ± 11,5 Jahre; 87 % HLA-B27 positiv) projektionsradiographische Aufnahmen der WS und der SIGs im Abstand von 3,3 ± 1,2 Jahren vorlagen. Während des Beobachtungszeitraumes standen 21 Patienten (38 %, Gruppe 1) unter einer permanenten Therapie mit TNF-Blockern und NSAR bei Bedarf und 34 Patienten (62 %, Gruppe 2) unter einer Therapie mit NSAR bei Bedarf. Zum Zeitpunkt des ersten Röntgens bestand zwischen den 2 Therapiegruppen kein Unterschied im medianen mSASSS (14,5 [0,5–72,0] vs. 13,5 [1,0–72,0]; $p > 0,80$). Die mediane radiologische Progression war unter einer TNF-Blocker-Therapie tendenziell, aber nicht signifikant niedriger als unter einer NSAR-Therapie bei Bedarf (2,5 [0,0–9,0] vs. 3,3 [0,0–27,0]; $p = 0,32$) und auch die mittlere radiologische Progression pro Jahr war nicht signifikant unterschiedlich (1,0 [0,0–3,2] vs. 1,1 [0,0–6,7]; $p = 0,37$). Die mittlere Krankheitsaktivität der AS zwischen den Röntgenaufnahmen, gemessen bei jeder Visite anhand des BASDAI (3,7 ± 0,3 vs. 3,5 ± 0,4) und anhand des AS-DASCRP (2,2 ± 0,7 vs. 2,2 ± 0,9), war zwischen den Gruppen ebenfalls nicht unterschiedlich. Es bestand aber eine signifikante, wenn auch schwache Korrelation zwischen dem AS-DASCRP und dem mSASSS ($r = 0,28$; $p < 0,05$).

Zusammenfassung Auch im klinischen Alltag konnte bei AS-Patienten eine radiologische Progression der Erkrankung unter einer laufenden Therapie mit TNF-Blockern beobachtet werden. Ob die Suppression der klinischen Krankheitsaktivität nicht ausreichend war oder ob alternativ der Wirkmechanismus der TNF-Blocker überhaupt imstande ist, eine strukturelle Progression in einem klinisch relevanten Ausmaß zu verhindern, muss in großen, prospektiven Kohorten untersucht werden.

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Evaluation of Fluid in Knee Recesses at Varying Degrees of Flexion by Ultrasound 46

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Objective Various methods are utilized in daily practice to obtain optimal information on effusion in the knee. Our aim is to investigate which scanning position provides the best information about synovial fluid in the knee by using ultrasound and to evaluate the magnitude of difference for measuring synovial fluid in 3 major recesses (suprapatellar, medial and lateral parapatellar recess) of the knee according to various degrees of flexion.

Methods Sonographers in 14 European centres documented bilateral knee joint ultrasound examinations on a total of 148 knee joints. The largest sagittal diameter of fluid was measured in scans corresponding to the 3 major recesses at different (0, 15, 30, 45, 60, and 90°) degrees of flexion of the knee. Difference of measurement of effusion according to transducer position, knee position, and interaction between them was investigated by analysis of variance, followed by Tukey's test.

Results No correlation was noted between patient characteristics and ultrasound detection of effusion. Sagittal diameter of synovial fluid in all 3 recesses was greatest at 30° flexion. Analysis of variance and Tukey's test revealed that the suprapatellar scan and 30° flexion is the best association for detecting effusion, confirmed by receiver operator characteristic curve analysis.

Conclusion The suprapatellar scan of the knee in 30° flexion was the most sensitive position to detect fluid in knee joints. Sagittal diameter of fluid in all 3 recesses increased with the knee in the 30° flexed position as compared to the extended position.

Pulmonary Sonography: A New Tool for Lung Screening Patients with Systemic Sclerosis 47

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Introduction In systemic sclerosis, interstitial lung disease and pulmonary hypertension are highly associated with mortality. The time point of detecting manifestations like PAH and ILD is of vital importance. High resolution computed tomography to date is the gold standard to diagnose ILD. In addition ultrasound of the lung is suggested as a non-invasive and radiation-free method of structural monitoring of the lung. We tested the reliability of lung sonography for the assessment of patients with systemic sclerosis.

Materials & Methods In 28 patients with systemic sclerosis and 40 healthy volunteers, we screened the pleura and the pulmonary parenchyma for sonographic abnormalities. The occurrence of B lines, comet tail phenomena, and pleural irregularities was scored. All SSc patients were subjected to computed x-ray tomography of the chest.

Results We used a convex 3.5 MHz transducer for the parenchyma and a linear probe for the pleural changes (LOGIQ 7, General Electric). 44 % of SSc patients, but only 7 % of controls showed B-line phenomena and pleural thickening. The diagnosis of ILD in these patients was confirmed by HRCT scan. B-line phenomena and pleural irregularities were significantly more common in SSc patients. Patients with ILD had higher pleural scores and comet scores when compared to systemic sclerosis patients without radiographic ILD.

Conclusion Transthoracic ultrasound of the lung is suggested as a cheap and safe tool to screen patients with systemic sclerosis for

incipient peripheral pulmonary structural changes. In case of abnormalities, computed tomography has to be performed before initiation of immunosuppressive treatment.

Rituximab: New Hope in Severe Systemic Sclerosis 48

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Introduction Systemic sclerosis (scleroderma) is a chronic autoimmune disease with interstitial lung disease as the main cause of death. There is no curative treatment so far. Hypothetically, B cell depletion may be a promising treatment for refractory systemic sclerosis. There was a significant decrease (mean ± SD) in mRSS (32.8 ± 5 vs 10.0 ± 2) and of the diffuse capacity of the lung for carbonmonoxide (DLCO) in all patients (40.5 ± 0.6 % vs 62.7 ± 2.3 %; $p < 0.05$). A reduced dosage of rituximab was administered in the following cycles of rituximab treatment, because of an increase of disease activity after 3 months. 4 female patients with progressive systemic sclerosis refractory to standard immunosuppressive therapies were treated with > 2 courses of rituximab over a minimum of 6 months. 1000 mg of rituximab were administered at week 0 and 2 and 500 mg every 3 months. Extent of skin sclerosis was monitored by Rodnan Score (mRSS), pulmonary diffusion capacity was measured by DLCO.

Conclusion B cell depletion therapy using rituximab effectively reduced skin and pulmonary involvement in 4 subsequent systemic sclerosis patient's refractory to conventional immunosuppressive therapy.

Near Misses of ACR/EULAR Criteria for Remission: Effects of Patient Global Scores on the Boolean- and Index-Based Definitions 49

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Background & Objective The ACR/EULAR criteria allow definition of remission by 2 means: The Boolean approach requires swollen and tender joint counts (SJC, TJC), as well as C-reactive protein (CRP in mg/dL) and patient global assessment (PGA in cm) to be ≤ 1; the index-based definition requires the Simplified Disease Activity Index (SDAI, linear sum of SJC, TJC, CRP, PGA, and physician global [MDGA]) to be ≤ 3.3. It has been argued that high PGA, if unrelated to RA disease activity, may prevent patients from fulfilling these criteria. We aimed to quantify the relevance of PGA in the definition of remission by the new ACR/EULAR criteria in a rheumatoid arthritis patient cohort from clinical practice.

Methods We identified all visits of RA patients from an observational, prospective RA outpatient database. We investigated the proportion of patients who fulfilled only 3 of the 4 required Boolean criteria at one visit ("near misses"). Among those near misses, we identified the proportion of patients who did not reach the criteria because of PGA, SJC, TJC, or CRP, and looked at the proportion of patients fulfilling the index-based definition (which allows scores of some variables to be > 1 through compensation by other variables with lower scores). We estimated the impact of PGA that is potentially unrelated to RA disease activity (eg, related to secondary fibromyalgia) by looking at how many patients would fulfil the criteria if MDGA were used instead of PGA in the Boolean criteria system. By logistic regression analyses we identified variables which would predict the probability of being a "near miss" concerning PGA (PGA > 1 despite fulfilling the other 3 Boolean criteria).

Results We identified 8242 visits of 795 RA patients (80 % female, 67 % rheumatoid factor [RF] positive, 79 % anti-citrullinated peptide [ACPA] positive, mean disease duration: 8 years). Half of these patients (52 %) had at least one visit, where they fulfilled just 3 of the 4 required Boolean criteria: Among those, PGA was the major reason for not achieving the criteria (61 %; n = 249; mean PGA = 3.6 cm), followed by SJC (20 %), CRP (13 %), and TJC (7 %). 44 patients (17.7 %) who failed the Boolean criteria because of PGA fulfilled the index-based definition of remission. The characteristics of these patients are shown in table 1. 166 patients (66.7 %) with Boolean criteria failure due to PGA had a MDGA ≤ 1 cm (mean discrepancy: 3 cm). 1/4 (24.7 %) of those patients did fulfil the index-based remission criteria (**tab. 4**) These patients showed significantly lower pain, PGA (mean PGA = 1.8 cm), and less discrepancy between PGA and MDGA than those not fulfilling index-based criteria (mean PGA = 4 cm). Similar results were obtained when using the Boolean- and index-based definitions for clinical practice which exclude CRP from the respective formulae (data not shown). When using a logistic model to predict near misses, increasing pain and EGA evaluations and decreasing SJC, TJC, and CRP seem to increase the probability of PGA being > 1, although the other 3 Boolean criteria are fulfilled.

Conclusion 2/3 of patients who fail to reach the Boolean definition of remission due to PGA are assessed as < 1 cm on the physician global. By means of the index-based criteria, 1 out of 4 of these patients were classifiable as being in remission, because a slight elevation of the PGA above 1 was compensated by other variables in the index being ≤ 1. Thus PGA elevations unrelated to RA disease activity may need to be considered in clinical practice in patients who fail to classify as remission by both, the Boolean- and, to a somewhat smaller extent, the index-based criteria.

Therapie von kutanen Rheumaknoten bei seropositiver Rheumatoider Arthritis mit Rituximab – ein Fallbericht 50

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Ziel Es existieren wenige Fallberichte über den Rückgang von pulmonalen Rheumaknoten unter Rituximabtherapie (RTX). Unser Ziel war es, kutane Rheumaknoten bei einer Patientin mit Rheumatoider Arthritis (RA) mit RTX zu behandeln.

Methoden Eine 39-jährige Patientin stand wegen einer seropositiven, usurierenden RA mit SLE-Overlap seit 2005 in unserer ambulanten und stationären Betreuung. Basistherapeutisch wurden bereits MTX, Infliximab und zuletzt Etanercept eingesetzt. Unter Etanercept/MTX-Kombination war die Patientin klinisch in Remission (DAS28: 2,08). Abseits der zufriedenstellenden Gelenkssitua-

Table 4: Studenic P et al.: Characteristics of 249 patients who fail Boolean criteria because of PGA > 1

	Fulfilling index-based criteria		Remission on Boolean criteria using MDGA ≤ 1 instead of PGA ≤ 1		MDGA ≤ 1 + fulfilling index-based criteria
	No	Yes	Yes	No	Yes
N	205 (82.30 %)	44 (17.70 %)	166 (66.70 %)	83 (33.30 %)	41 (24.70 %)
PGA (cm)	3.99 (1.83)	1.74 (0.49)	3.33 (1.76)	4.12 (2.0)	1.78 (0.49)
MDGA (cm)	1.16 (1.40)	0.16 (0.35)	0.29 (0.29)	2.38 (1.5)	0.08 (0.18)
SJC	0.47 (0.50)	0.09 (0.29)	0.40 (0.49)	0.42 (0.5)	0.10 (0.30)
TJC	0.42 (0.50)	0.02 (0.15)	0.33 (0.47)	0.39 (0.5)	0.02 (0.16)
CRP (mg/dl)	0.45 (0.25)	0.40 (0.22)	0.38 (0.23)	0.56 (0.22)	0.40 (0.23)
Pain (cm)	3.50 (1.90)	1.79 (0.93)	3.05 (1.74)	3.48 (2.1)	1.84 (0.93)

tion litt die junge Patientin sehr unter ausgeprägten kutanen Rheumaknoten, vor allem an den Händen und oberen Extremitäten, die an mehreren Stellen rheumaorthopädisch entfernt wurden, aber rezidivierten bzw. neu auftraten. Die zusätzliche Gabe von Resochin hatte ebenfalls keinen diesbezüglichen Benefit gebracht. 2009 wurde der Patientin deswegen ein Therapieswitch auf RTX vorgeschlagen.

Ergebnisse Unter der Therapie mit RTX/MTX kam es zu einer beinahe kompletten Rückbildung der vorhandenen kutanen Rheumaknoten und zu keinem Neuauftritt von Knoten, die Patientin ist nach wie vor in klinischer Remission (DAS28: 1,86).

Zusammenfassung RTX erwies sich – entsprechend den positiven Fallberichten bei pulmonalen Rheumaknoten – auch in der Therapie von kutanen Rheumaknoten als wirksam.

Attending and Non-Attending Patients in a Real-Life Setting of an Early Arthritis Clinic – Why do People Leave Clinics and Where do They Go? 51

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Objectives Rheumatologist assessment as early as possible is considered essential for patients with inflammatory joint disease. In our Very Early Arthritis Clinic (VEAC), a substantial proportion of initially included and followed patients later stop attendance in the clinic. We questioned attending (AP) and non-attending patients (NAP) regarding current health status and satisfaction with care as well as reasons for discontinuation and current care received by NAP.

Methods VEAC patients first seen between 1996 and 2003 were included. Assessment included the RADAI, HAQ, and visual analogue scales for pain, disease activity, fatigue, and satisfaction with current health care. Current (DMARD-) treatment was recorded.

Results Among AP, 87 % had rheumatoid arthritis (RA) and 13 % non-RA. Of NAP, 37 % had RA, 23 % non-RA, and 40 % no more rheumatic disease. Satisfaction with health care concerning the rheumatic disease was better in AP than NAP. Likewise, most outcome parameters were better in AP. Substantially more RA patients in the AP than in the NAP group received DMARDs. Apart from disappearance of arthritis, logistic reasons were given most frequently for discontinuation of attendance. Less than 10 % of NAP indicated dissatisfaction with medical care.

Conclusions We found advantages in both disease activity measures and satisfaction with health care for patients receiving continuous care in a highly specialized rheumatology clinic. Furthermore, difference of DMARD usage in RA in AP and NAP may indicate significant deficits in treatment quality outside specialist care. Logistic issues associated with access to continuous rheumatology care for early arthritis patients need improvement.

X-Ray in the Diagnosis of Hand Osteoarthritis – A Must-Have? 52

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Objective There is no clear consensus whether to employ plain radiography in the classification/diagnosis process of hand osteoarthritis (OA). This might be due to a lack of scientifically proven data on the relationship between structural/histological joint damage and radiographic alterations. Here we tested whether histopathologic features of distal and proximal interphalangeal (DIP and PIP) joints would be reflected by radiographic changes in the very same joints. Furthermore a hand OA patient's cohort was examined for clinical and radiographical features of hand OA.

Methods DIP and PIP joints were obtained from corpses (n = 40). Plain radiographies (posterioranterior and lateral images) of the dissected DIP and PIP joints were taken and scored according to the Altman atlas of radiographic features and scoring system. Joint samples were prepared for histological analysis and the grade of cartilage damage was evaluated according to the Mankin scoring system. 217 patients were included in a hand OA cohort and assessed clinically according to the current ACR classification criteria as well as radiographically.

Results We found a highly significant correlation between histological and radiographic changes in the investigated DIP and PIP joints. Sensitivity and specificity of x-ray examinations was high for both DIP and PIP joints (92.3 %/81.8 % and 75 %/100 % respectively). Moreover, for a reliable radiographic diagnosis regarding OA in DIP joints the presence of ≥ 2 radiographic features is necessary, while for PIP joints a single feature would suffice. Finally, a subgroup of patients, displaying advanced structural damage but no clinical signs of bony joint swelling, could be identified by the use of x-ray examinations. In parallel to the data on *post mortem* specimens, we were able to identify a subgroup of patients from the hand OA cohort which did not fulfil the ACR classification criteria, however, displayed classical x-ray features of hand OA.

Conclusion On the basis of histopathological changes of DIP and PIP joints our investigation demonstrates the reliability and usefulness of x-ray examinations in the classification/diagnosis of hand OA and these findings were fostered by the examination of the hand OA patient's cohort. This study, however, supports the use of plain radiography as a criterion to define hand OA and represents a complementary piece linking recommendations and clinical practice.

BioReg – ein österreichisches Biologikaregister mit zunehmender Teilnahme durch Rheumatologen in Österreich 53

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Einleitung Seit Sommer 2010 werden in das neu geschaffene Biologikaregister für entzündlich rheumatische Erkrankungen (BioReg; www.bioreg.at) Daten eingegeben. Die anfangs erwartungsgemäß nur zögerliche Dateneingabe ließ einen Erfolg des Registers noch nicht sicher vorhersagen.

Ziel Das österreichische nationale Biologikaregister ist eine prospektive Beobachtungsstudie. Dokumentiert werden unter anderem Krankheitsaktivität beurteilt mit validierten Messinstrumenten, Therapiekontinuität und unerwünschte Ereignissen.

Methode Dokumentiert werden Patienten mit chronisch entzündlich rheumatischen Erkrankungen, die mit den für die entsprechenden Erkrankungen (Rheumatoide Arthritis [RA]; Spondylarthritis [SpA] und Psoriasisarthritis [PsA]) zugelassenen Biologika behandelt werden.

Ergebnisse Zum Stichtag 17. August 2011 waren 415 Patienten (RA 254, SpA 110, PsA 51) mit den Basisdaten registriert, 155 Patienten (RA 102, SpA 35, PsA 18) mit 1. Folgevisite nach etwa 6 Monaten und 51 Patienten (RA 30, SpA 15, PsA 6) mit 2. Folgevisite nach etwa 12 Monaten. Von Krankenhausbetreibern wird zunehmend das Einverständnis gegeben (Allgemeines Krankenhaus Innsbruck, Schreiben vom 24. Juni 2011), Patienten der Krankenanstalt in das Register aufzunehmen.

Schlussfolgerung Österreich ist zwar eines der letzten europäischen Länder, in denen ein Biologikaregister begonnen wurde. Dennoch wird die Notwendigkeit erkannt und das Register zunehmend akzeptiert. Im Vergleich zum deutschen Biologikaregister RABBITT, das 2002 begonnen wurde, sind im österreichischen Register BioReg mit Gründung 2009 und Beginn der Dateneingabe 2010 in Relation zur Einwohnerzahl bereits vergleichbar viele Patientenbögen dokumentiert.

Stollentherapie in Gastein bei Patienten mit axialer Spondylarthritis unter der Therapie mit TNF-Hemmern 54

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Einleitung Bei Patienten mit axialer Spondylarthritis (SpA), vorwiegend vom Typ einer Spondylitis ankylosans (Morbus Bechterew), ist die Radon-Stollentherapie im Gasteiner Heilstollen die bevorzugte nicht-medikamentöse Therapieform. Pro Jahr kommen etwa 2600 Patienten mit axialer SpA zur Stollentherapie nach Gastein. Nach Aussagen von Patienten kann nach dem Kuraufenthalt die symptomatische medikamentöse Therapie, zum Beispiel in Form von nicht-steroidalen Antirheumatika (NSAR), reduziert werden. Der Kurerfolg hält bis zu 6 Monate nach der Kur an.

Ziel Einfluss der Stollenkur auf die Gabe von TNF-Hemmern durch Vergleich der Applikationsintervalle der TNF-Hemmer vor und nach der Kur.

Methode Patienten mit SpA und Anti-TNF-Therapie wurden gefragt, ob sie ein Therapietagebuch führen und ob sie unter dieser medikamentöse Therapie zusätzlich noch Kuraufenthalte in Gastein mit Einfahrten in den Gasteiner Heilstollen durchführten. Wir konnten 12 Patienten (6 Humira, 3 Enbrel, 2 Remicade, 1 Simponi) finden, die uns ihr Therapietagebuch mit genauer Angabe der Anti-TNF-Applikation sowie den Zeitpunkt des Kuraufenthaltes zur Verfügung stellten.

Ergebnisse Nach einem Kuraufenthalt in Bad Gastein zeigt sich ein Trend, dass Patienten nach einer Stollenkur das Dosierungsintervall mäßig verlängern, sowohl bei Präparaten, die selbstständig subkutan verabreicht werden, als auch bei intravenöser Gabe durch den Hausarzt.

Schlussfolgerung Der Wirkmechanismus einer Stollentherapie in Gastein ist unklar, der Therapieerfolg wird aber von Patienten berichtet. Neben einer Besserung der Beschwerden werden auch symptomatisch wirkende Medikamente nach einer Kur zumeist reduziert. Ähnlich wie für NSAR scheint es auch für Biologika zuzutreffen, dass nach erfolgreicher Stollentherapie die Dosis des TNF-Hemmers durch Verlängerung des Applikationsintervalls nach dem Kuraufenthalt verringert wird. Die bisher vorliegenden Patientenzahlen reichen allerdings noch nicht aus, um konkrete Berechnungen über Kosteneinsparungen anzustellen.

Rituximab (RTX) Therapy for Psoriatic Arthritis (PsA) 55

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Background/Objective Psoriatic arthritis is a chronic and frequently destructive arthropathy which, in contrast to rheumatoid arthritis (RA), is usually negative for autoantibodies including rheumatoid factor (RF). The current treatment armamentarium comprises several synthetic disease modifying antirheumatic drugs (DMARDs) and TNF inhibitors. In contrast, several other biological agents are available for the treatment of RA. RTX is one of them, but it is apparently primarily effective in RF-positive patients, although some efficacy has been reported also in RF-negative individuals. It has not yet been assessed in PsA and there have been reports on reactivation of psoriasis in some RTX-treated patients. Therefore it deemed appropriate to assess the potential benefit of RTX in PsA initially in an open label study. Here we evaluated the efficacy and safety of RTX in an exploratory open-label study of patients with PsA.

Patients & Methods 9 patients with PsA underwent RTX at 1000 mg twice within 14 days and were evaluated, among other traditional variables, by DAS28, DAPSA, BASDAI, HAQ, and PASI. Patients were followed monthly for 6 months. Changes in scores were calculated using a lineal model.

Results Baseline demographics showed an age of 50 ± 11, disease duration of arthritis 9 ± 7 and psoriasis of 12 ± 7 years; mean swollen and tender joint counts (SJC 66, TJC68) were 12 ± 7 and 23 ± 10, respectively. RTX was tolerated well and there were no serious adverse events. Over 6 months, DAS28 improved from a median (IQR) of 6.2 (5.9; 6.4) to 4.9 (4.3; 5.4), DAPSA from 52.0 (39.5; 58.5) to 32.5 (21.5; 54.3), and HAQ from 1.5 (1.3; 1.6) to 1.0 (0.75; 1.6) (all $p \leq 0.05$). C-reactive protein and PASI did not change significantly. BASDAI decreased from 6.2 (5.2; 7.4) to 5.3 (3.8; 6.9; p = n. s).

Conclusion In this exploratory open-label study, RTX therapy exhibited significant efficacy in PsA patients with long-standing disease. In particular, composite scores decreased and physical function improved beyond the minimal clinically important difference. Over the 6 months of observation, RTX was well tolerated and there was no reactivation of psoriasis. These data suggest that RTX may have efficacy in PSA and warrant testing this hypothesis in a double-blind controlled clinical trial.

D. Physikalische Medizin

Blutdruck und Puls bei Extensionstherapie mit dem Gerät GammaSwing® 56

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Ziel Rückenschmerzen stellen in der industrialisierten Welt ein großes Gesundheitsproblem dar. Sie sind nicht nur Ursache für persönliches gesundheitliches Leid, sondern auch für enorme medizinische Kosten. Bei Kreuzschmerzen findet zunehmend die dynamische Extensionstherapie mit dem Gerät GammaSwing Anwendung. Dabei wird der Patient mittels Gamaschen am distalen Unterschenkel schrittweise (Phase 1 = Abhebung des Beckens, Phase 2 = Schulterstand) bis zur freien Hängelage (Phase 3) emporgehoben und eine therapeutische Schwingung (bis 100 pro Minute) in der Längsachse der Wirbelsäule appliziert. In der vorliegenden Untersuchung wurden die mit diesem Behandlungsablauf verbundenen Auswirkungen auf die Kreislaufparameter Blutdruck und Puls untersucht.

Methoden In die Auswertung wurden 19 Patienten (mittleres Alter 55,3 Jahre) einbezogen, die wegen eines lumbalen Vertebralsyndroms mit dem Gerät GammaSwing behandelt wurden. Die im Rahmen der Behandlungen bei jeder Lageänderung erhobenen Werte von Blutdruck und Puls wurden einer statistischen Analyse unterzogen.

Ergebnisse An 5 der 8 Behandlungstage ergab sich für einzelne Positionen des Behandlungsablaufs ein geringgradiger, jedoch statistisch signifikanter Abfall der Pulsfrequenz. Eine geringe, aber ebenfalls signifikante Reduktion des diastolischen Blutdrucks zeigte sich an 2 Behandlungstagen sowie für den systolischen Blutdruck an 1 Behandlungstag. Diese Unterschiede bei den verschiedenen Parametern traten an unterschiedlichen Behandlungstagen auf.

Zusammenfassung/Schlussfolgerung Während der Therapie mit dem Gerät GammaSwing zeigte sich zwar zu Behandlungsmitte (Phase 2 = Schulterstand) tendenziell eine Senkung der Werte für Blutdruck und Puls, jedoch waren diese Veränderungen von geringer Ausprägung. Auf Basis der vorliegenden Daten ist davon auszugehen, dass die Anwendung des Geräts GammaSwing nur mit einer geringen Belastung des Herz-Kreislaufsystems verbunden ist.

E. Rehabilitation

Rheumatoide Arthritis und Sturzrisiko (RAST-Studie) 57

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Ziel Ziel dieser Studie war es, den systematischen Zusammenhang zwischen der Krankheitsaktivität der Rheumatoiden Arthritis (RA) und dem Sturzrisiko der RA-Patienten zu untersuchen.

Methoden Insgesamt wurden 78 Patienten während ihres Ambulanzbesuchs untersucht. Die Krankheitsaktivität wurde durch Bestimmung folgender Parameter beurteilt: Blutsenkungsgeschwindigkeit (BSG), C-reaktives Protein (CRP), Rheumafaktor (RF), Antikörper gegen zyklisches zitrulliniertes Peptid (Anti-CCP-Ak), Swollen Joint Count (SJC), Tender Joint Count (TJC), Beurteilung des Schmerzes und der Krankheitsaktivität durch den Patienten und den Arzt mittels Visual Analogue Scale (VAS-Pain, VAS-Activity Patient, VAS-Activity Physician), Health Assessment Questionnaire Disease Index (HAQ-DI) und der zusammengesetzten Parameter Disease Activity Score 28 (DAS-28), Clinical Disease Activity Index (CDAI) und Simple Disease Activity Index (SDAI). Das Sturzrisiko wurde mittels eines Sturzassessments evaluiert. Dieses bestand aus Tinetti-Test, Timed-Get-Up-&-Go-Test (TUG), Chair-Rising-Test, Tandem-Walk- und Tandem-Stand-Test.

Resultate 26,9 % der Studienteilnehmer waren in den vorangegangenen 12 Monaten gestürzt, 46,2 % gaben an, Angst vor einem Sturz zu haben. Es zeigte sich eine starke Korrelation (Spearman [rs]) zwischen den Ergebnissen des Sturzassessments und folgenden Kranksheitsaktivitätsparametern: HAQ-DI (Chair-Rising: rs = 0,523, TUG: rs = 0,620, Tinetti-Test: rs = –0,676), CDAI (Chair-Rising: rs = 0,460, TUG: rs = 0,504, Tinetti-Test: rs = –0,472), VAS-Pain (Chair-Rising: rs = 0,441, TUG: rs = 0,616, Tinetti-Test: rs = –0,548) und VAS-Activity-Patient (Chair-Rising: rs = 0,473, TUG: rs = 0,577, Tinetti-Test: rs = –0,520) und TJC (Chair-Rising: rs = 0,488, TUG: rs = 0,394, Tinetti-Test: rs = –0,385). Der Kruskal-Wallis-Test zeigte, dass Patienten mit mittlerer und hoher Krankheitsaktivität schlechter beim Sturzassessment abschnitten.

Zusammenfassung/Schlussfolgerung Der stärkste Zusammenhang zeigte sich bei Parametern, bei denen der Patient subjektiv seine Krankheit bewertet. Der Schmerz scheint der gemeinsame Nenner dieser Parameter zu sein. Der Schmerz wird wiederum von der Krankheitsaktivität beeinflusst. Die Ergebnisse dieser Studie legen nahe, bei Patienten mit Schmerzen oder erhöhter Krankheitsaktivität vermehrt auf das Sturzrisiko zu achten und bei Bedarf ergo- und physiotherapeutisch zu intervenieren.

The Dynamic Spinal Traction System GammaSwing Used During Inpatient Rehabilitation of Low Back Pain 58

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Background Inpatient rehabilitation may improve chronic unspecific low back pain demonstrably. In the rehabilitation programs active as well as passive therapies are implemented, such as traction treatment. The GammaSwing (GS) is a dynamic traction system for treating spinal problems with fixation and lifting of the distal lower leg up to a free-hanging position. The traction can be combined with an oscillating movement.

Aim Investigate the effectiveness and the compatibility of the traction device GammaSwing in the inpatient rehabilitation programs for patients suffering from low back pain.

Methods Three-week inpatient rehabilitation stay of 58 patients (46 male, 12 female, age 54.7 ± 10.1 years) with a standard program. Randomized allocation into the groups A (6 therapy units with the GammaSwing system) and B (6 therapy units spinal column massage). Study parameters: Pain at rest and on motion, disability using the Roland & Morris Questionnaire for low back pain and sleep disturbances conditioned by back pain using the Pittsburgh Sleep Quality Index.

Results During the inpatient rehabilitation both groups showed significant improvements regarding all parameters. In particular the pain on motion of the GS patients showed in comparison with the massage group statistical detectable difference ($p < 0.05$) and an improvement of the VAS from 5.5 to 2.2. The finger-to-floor distance also diminished significantly in the GammaSwing group from 13.5 to 9.3 cm. The improvement in the comparison group with 13.3 to 10.3 cm turned out not to be significant.

Conclusion Essential improvements of the complaints of low back pain can be attained by a multimodal rehabilitation program. Integration of the traction device GammaSwing resulted in beneficial supplementary effects.

Development of User-Focused Standards of Care for Osteoarthritis – The EUMUSC.net Project – Work Package 5 59

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Background The EUMUSC.net project facilitates cooperation between EU member states and promotes a comprehensive European strategy to optimise musculoskeletal health.

Objective The purpose of Work Package 5, as a part of the EUMUSC.net project, was to develop evidence-based and user-focused standards of care (SOC), initially for osteoarthritis (OA).

Method A systematic review of international documents covering SOC for OA was conducted. National scientific societies, social leagues, and health professional associations were contacted via the EULAR secretariat and asked to provide relevant documents. Documents concerning pharmacological and non-pharmacological interventions published after 2002 were included. The obtained documents were evaluated based on the AGREE criteria (www.agreecollaboration.org). All recommended methods to treat OA were extracted. Each of the extracted methods was discussed in a consensus group meeting of 16 EUMUSC.net researchers and patient representatives from different countries regarding priority and relevance in their home countries as well as possible interrelation with other methods; eg, the term, "therapeutic exercises" was found to relate to the term "physiotherapy" or "joint specific exercise". Paracetamol, topical analgesics, NSAIDS, and opioid analgesics were grouped under pharmacological methods for pain control. Thus, a scheme was developed with groups of interventions and formulated in a way that could be understood by users.

Results 46 methods, such as exercise or appropriate pain control, were extracted from the documents and could be grouped into 4 types of interventions, namely Non-Pharmacological (Lifestyle Interventions & Rehabilitative Interventions), Pharmacological, Surgical Interventions, and Prevention, Education, Information and Self Management (**tab. 5**). From these, 12 user-focused standards of care were formulated.

Table 5: Stoffer M et al.: Groups of interventions

Groups of Interventions				
I. Prevention & Education & Information & Self Management	II. Pharmacological	III. Non-Pharmacological Livestyle Interventions	III. Non-Pharmacological Rehabilitative Interventions	IV. Surgical

Conclusion The lay version of the user-focused SOC will be available in all 23 official languages of the European Union for the information of people with OA across all member states. This work should contribute to the harmonization of OA treatment in Europe.

F. Sozioökonomie/Berufspolitik

Optimierung der Zusammenarbeit zwischen Hausärzten und Rheumatologen 60

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Ziel Um die Zusammenarbeit zwischen Rheumatologen und Allgemeinmedizinern zu verbessern, wurde im Rahmen einer Fragebogenerhebung die Meinung österreichischer Rheumatologen, die entweder in Krankenhausambulanzen oder im niedergelassenen Bereich tätig sind, eingeholt. Auf diese Weise soll ein Beitrag dazu geleistet werden, die Schnittstelle Hausarzt-Rheumatologe zu optimieren, um die Arbeit für beide Seiten zu erleichtern und gleichzeitig auch die Behandlungsqualität und Sicherheit der Patienten zu erhöhen.

Methodik Der Fragebogen entstand durch Sammlung aller relevanten Aspekte in der Zusammenarbeit zwischen Rheumatologen und Hausärzten und wurde von R. Puchner und E. Mur unter Mithilfe der Vorstandsmitglieder der österreichischen Gesellschaft für Rheumatologie entwickelt. Der Befragungszeitraum war zwischen 18. August und 20. September 2011. Die Dateneingabe und Auswertung erfolgte durch das Ärztliche Qualitätszentrum. Der Rücklauf beträgt 46 auswertbare Fragebögen bei 98 ausgesandten Fragebögen, was einer Rücklaufquote von 47 % entspricht.

Ergebnisse Auf die Frage, welche Vorabklärung bei Mono-, Oligo- und Polyarthritis durch die Hausärzte erfolgen sollte, antworteten > $^3/_4$ der Rheumatologen, dass vor Überweisung zur Erstuntersuchung folgende Laborparameter bestimmt werden sollten: Blutsenkungsgeschwindigkeit, C-reaktives Protein, Blutbild, Leberfunktionsparameter, Harnsäure, Kreatinin, Rheumafaktor und Antikörper gegen citrullinierte Antigene (anti-CCP/ACPA). 57,8 % der Befragten wünschen eine radiologische Vorabklärung der betroffenen Gelenke, 42,2 % wollen diese nicht. Bei Verdacht auf entzündlichen Rückenschmerz wünschen 66,7 % die Bestimmung von HLA-B27, 64,1 % ein konventionelles Röntgen der Sakroiliakalgelenke, aber nur 17,9 % eine Kernspintomographie durch die Hausärzte. Nur 22,2 % der Rheumatologen sind der Meinung, dass Fingerpolyarthrosen dem Rheumatologen immer vorgestellt werden sollten; 77,8 % wünschen eine Vorstellung bei der differenzialdiagnostischen Abklärung zu einer Arthritis. 31,1 % der Rheumatologen fühlen sich für die Behandlung der Fibromyalgie zuständig. 68,9 % der Befragten sind der Meinung, dass Patienten mit Fibromyalgie nicht oder nur zum Ausschluss einer entzündlich-rheumatischen Erkrankung dem Rheumatologen vorgestellt werden sollten. Die überwiegende Mehrheit der Befragten ist der Meinung, dass Patienten mit nachgewiesener Osteoporose dem Rheumatologen vorgestellt werden sollten. Der Beginn einer konventionellen Basistherapie sollte wenn möglich durch einen Rheumatologen erfolgen, die Kontrolle von Klinik und Labor durch den Hausarzt, aber alle 3–6 Monate durch den Spezialisten. 75 % der Rheumatologen sind der Meinung, dass die Folgeverordnung von Biologika, und 88,1 % sind der Auffassung, dass auch deren Verabreichung durch den Hausarzt erfolgen sollte. Das Vorgehen bei Verschlechterung der Gelenkerkrankung wird unterschiedlich beurteilt. 60,5 % sind für eine primäre Untersuchung beim Hausarzt, 39,5 % für eine unmittelbare Vorstellung beim Rheumatologen. Ähnlich unterschiedlich sind die Ergebnisse der Befragung hinsichtlich des Vorgehens bei einer Nebenwirkung der Behandlung.

Zusammenfassung Die Ergebnisse der Befragung sind in vielen Aspekten einheitlich und tragen aus unserer Sicht zu einer Erleichterung der Zusammenarbeit zwischen Rheumatologen und Hausärzten bei und damit auch zu einer Verbesserung der Versorgung der Patienten. Manche Fragen, insbesondere bezüglich des Vorgehens bei Verschlechterung der Erkrankung oder bei Auftreten von Nebenwirkungen, werden kontrovers beantwortet und bedürfen der weiteren Diskussion und der individuellen Abstimmung zwischen Hausarzt und Rheumatologen.

G. Sonstiges

Abatacept (CTLA-4Ig) Treatment Reduces Adhesion and Migratory Capacity of Monocytes in Patients with Rheumatoid Arthritis (RA) 61

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Background 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.

Aim 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.

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.

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 sign.

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.

Kardiale Beteiligung (Myokarditis) bei Polymyositis 62

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Hintergrund Kardiale Manifestationen wie eine dilatative Kardiomyopathie mit Herzmuskelentzündungen oder Herzgefäßentzündungen bei Polymyositis sind selten. Aufgrund der Klinik ist eine kardiale Beteiligung differenzialdiagnostisch schwer von einer ischämischen koronaren Herzkrankheit zu differenzieren. Bei Patienten mit entsprechender kardialer Symptomatik sollte immer an eine kardiale Beteiligung gedacht werden. Diagnostischer Goldstandard bietet das Kardio-MRT.

Ziel Rasche Diagnosefindung bei Patienten mit kardialer Beteiligung einer Polymyositis durch das Kardio-MRT, zur Einleitung einer suffizienten immunsuppressiven Therapie.

Methoden Kardio-MRT, Echokardiographie, Brain Natriuretic Peptide.

Ergebnisse Das Kardio-MRT ist diagnostischer Goldstandard bei kardialer Beteiligung einer idiopathischen Myopathie. Weiters zeigte sich bei unseren Patienten ein auffälliger Widerspruch zwischen massiver Erhöhung des NT-pro-BNP und guter (systolischer) Pumpfunktion der Ventrikel in der Echokardiographie.

Zusammenfassung/Schlussfolgerung Bei Patienten mit Polymyositis ist es differenzialdiagnostisch wichtig, vor allem wenn kardiale oder pulmonale Vorerkrankungen bestehen, an die kardiale Beteiligung der Polymyositis zu denken. Diagnostischer Goldstandard hierfür ist das Kardio-MRT, um eine entsprechende Therapie einzuleiten.

Infectious Non-Tuberculous Spondylodiscitis: A Retrospective Series of 23 Patients 63

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Objectives Infectious non-tuberculous spondylodiscitis causes severe symptoms with a reported in-hospital mortality reaching from 2 % to 19 %. There are only few and contradictory management recommendations for treatment of infectious spondylodiscitis. In general, initiation of antimicrobial therapy according to the results of blood cultures or percutaneous intervertebral biopsy is recommended, except in patients with severe sepsis. We describe the treatment strategy and functional outcome of our referral centre for rheumatology and osteology.

Patients & Methods We present a retrospective single centre study of 23 consecutive patients (14 male/9 female) with infectious non-tuberculous spondylodiscitis treated at our institution between 2004 and 2010. The mean age was 78 ± 11 years (mean ± SD).

Results Every patient showed at least one predispositional risk factor (eg, osteoporosis, current infection of the urinary or gastrointestinal tract, sacral decubitus, rheumatoid arthritis, diabetes mellitus, steroid therapy). Unspecific symptoms like diffuse back pain and sometimes fever started about 1–4 weeks before hospitalisation. 23 patients underwent MRI of the vertebral column. The sites of infections were as follows: 16 patients (69.5 %) lumbar spine, 5 patients (21.7 %) thoracal spine, 1 patient each (4.3 %) cervical spine, and sacral spine. In 15 patients (65.2 %) the causative microorganisms were detected using blood cultures or additional CT-guided vertebral disc biopsy (n = 4; 17.4 %). The following microorganisms were detected: Staph. aureus (n = 8; 34.7 %), E. coli (n = 2; 8.7 %), Staph. epid. (n = 2; 8.7 %), Klebs. pneum., Enterocc., Streptococc. sanguis (each: n = 1; 4.3 %). 1 patient with Staph. aureus suffered from concurrent Corynebacterium infection. 4 patients (17.4 %) presented with recurrent disease. In all patients, intravenous antimicrobial therapy with clindamycine and ciproxofloxacin together with adequate hydration was started for 3 weeks, followed by oral therapy for at least another 9 weeks. Because of unresponsiveness to the initial combination regime in 1 patient (Staph. aureus), antibiotic therapy was changed to fusidic acid and flucloxacilline. All patients were immobilized for 3–4 weeks with concurrent thromboembolic prophylaxis using LMW-heparine, followed by cautious mobilisation with a brace. In 9 patients (39.1 %) we observed additional abscess formation, localised epidurally and in the psoas region. In 2 patients with space occupying epidural abscesses and neurological deterioration, the abscesses were drained by open surgery. After a mean follow-up of 7.1 months, 8 patients (34.8 %) showed excellent recovery. 7 patients (30.4 %) suffered from mild/moderate functional deficits. 4 patients (17.4 %) had severe functional deficits. 4 patients (17.4 %) died.

Discussion & Conclusions Diagnosis was based on MRI of the spine in all patients. Blood cultures and in selected cases intervertebral biopsies are mandatory to find the causative microorganism. In our experience, clindamycine and ciprofloxacin proved to be a good first-line antimicrobial regimen. One should be aware of the high percentage of abscess formation which may require surgical intervention. Despite multidisciplinary treatment options, morbidity and mortality rates remain high and further research is required to optimize the outcome of infectious non-tuberculous spondylodiscitis.

Patientenkasuistik: Pulmonale Rheumaknoten bei chronischer Polyarthritis – erfolgreiche Therapie mit Abatacept 64

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Ziel Beurteilung des Therapieerfolges von Abatacept bei histologisch gesicherten pulmonalen Rheumaknoten.

Methoden Eine 64-jährige Patientin mit seropositiver (CCP AK und RF positiv) Rheumatoider Arthritis (Erstdiagnose 1986) wird im August 2010 aufgrund eines refraktären Verlaufs mit hoher Krankheitsaktivität unter Therapie mit Leflunomid 20 mg täglich und Adalimumab 40 mg s. c. alle 2 Wochen stationär aufgenommen. Im Rahmen eines Routine-Thorax-Röntgens zeigten sich dann neu aufgetretene multiple Rundherde über beiden Lungen. Die Patientin war aber völlig frei von pulmonalen Symptomen und ohne klinische Hinweise auf Infektzeichen. Aufgrund des pulmonalen Befundes wurde die Therapie mit Leflunomid und Adalimumab beendet und eine weiterführende bildgebende Diagnostik mit Computertomographie eingeleitet. In der CT-Untersuchung zeigten sich diese pulmonalen Raumforderungen als teilweise einschmelzende Prozesse mit unterschiedlicher Größe von 1 bis 4 cm. Zum Malignomausschluss wurde dann eine Bronchoskopie mit mehrfachen transbronchialen Biopsien durchgeführt. Die histologische Aufarbeitung zeigte eine zentrale Nekrose mit Epitheloidzell-Pallisaden und lymphozytärer Entzündung. Es gab keine Hinweise auf Verkäsungen oder maligne Zellen. Das histologische Bild war somit gut passend zur vermuteten Diagnose von multiplen pulmonalen Rheumaknoten im Rahmen der chronischen Polyarthritis. Ein ebenfalls durchgeführter IGRA-Test (QuantiFERON) und TBC-Kultur zeigten ein negatives Ergebnis. Nach Abschluss der diagnostischen Abklärungen wurde dann eine Monotherapie mit Abatacept 750 mg alle 4 Wochen begonnen. Auf Methotrexat musste aufgrund einer bekannten Unverträglichkeit und den neu diagnostizierten pulmonalen Rheumaknoten verzichtet werden.

Ergebnisse Von Februar bis Juni 2011 wurden insgesamt 7 Infusionen Abatacept appliziert. Neben einer relativ raschen Remission der chronischen Polyarthritis unter Abatacept zeigten die im Verlauf durchgeführten CT-Kontrollen der Lunge typische Regressionszeichen der pulmonalen Rheumaknoten.

Zusammenfassung/Schlussfolgerung Bei ca. 4 % der Patienten mit chronischer Polyarthritis können Rheumaknoten in der Lunge als extraartikuläre Manifestation gefunden werden. Differenzialdiagnostisch müssen die pulmonalen Rundherde von malignen und verschiedenen infektiologischen Erkrankungen unterschieden werden. In der aktuellen Patientenkasuistik präsentieren wir eine Patientin mit neu aufgetretenen pulmonalen Rheumaknoten und erfolgreicher Therapie mit Abatacept.

How do Gastrointestinal or Liver Comorbidities Influence the Choice of Pain Treatment in Inflammatory Arthritis – A Systematic Literature Review 65

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Objective To assess efficacy and safety of pharmacological pain treatment in patients with inflammatory arthritis and gastrointestinal (GI) or liver comorbidities.

Methods A systematic literature search was performed using MEDLINE, EMBASE, and Cochrane Controlled Trial Register up to June 2010, as well as ACR and EULAR Meeting abstracts (2007–2010). The population investigated was defined as patients with inflammatory arthritis and existing or prior reported GI or liver disease, treated with NSAIDs, opioids, or opioid-like drugs, paracetamol, antidepressants, neuromodulators, or muscle relaxants. Outcome of interests were efficacy, evaluated by common pain measures, and safety, evaluated by withdrawals due to adverse events, worsening of comorbidity, and mortality.

Results Out of 2866 identified studies only 1 article fulfilled inclusion criteria. This trial was a single-arm open trial at high risk of bias assessing efficacy and safety of naproxen (dosage not specified) in patients with RA and pre-existing GI dysfunction of varying degree. For safety the presence faecal occult blood was reported in 1/58 participants tested between weeks 1–26 and 2/32 participants tested between weeks 27–52. Over the course of the study, 7 patients (12.1 %) withdrew due to adverse events but of these, only 2 participants withdrew due to GI side effects (abdominal pain n = 1, nausea n = 1) and no serious adverse events were reported. Regarding efficacy significant reductions in the mean number of painful or tender joints (21.6; 13.5; 7.6), swollen joints (16.5; 11.4; 6.9), hot and/or red joints (8.7; 3.0; 0.3), and clinically active joints (21.9; 14.8; 9.8) from baseline to weeks 1–26 and weeks 26–52 respectively were reported. 14 patients withdrew due to lack of efficacy.

Conclusion Not much evidence regarding safety and efficacy of pain treatment in patients with IA and GI or hepatic comorbidities was found. Based on studies on mixed population with various rheumatic conditions NSAID should be used with caution in these patients.

Exogenous Hydrogen Sulphide Treatment Reduces the Expression of Matrix Metalloproteinases in Osteoarthritic Fibroblast-Like Synoviocytes 66

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In the pathogenesis of osteoarthritis (OA), which is the most common form of arthritis, fibroblast-like synoviocytes are of great importance. Activation of inflammatory pathways is caused by mechanically induced degradation of cartilage and bone leading to over-expression of matrix metalloproteinases (MMPs) and pro-inflammatory cytokine production. MMPs belong to the family of endopeptidases and are involved in numerous pathophysiological processes including degradation of extracellular matrix. Sulphur bath therapy is a frequently applied treatment in OA. Hydrogen sulphide (H_2S) is one of the most interesting members of the gasotransmitter family by showing multiple physiological effects on different disease models including OA. We investigated if treatment with exogenous H_2S donor sodium hydrogen sulphide (NaHS) has a positive impact on the aberrant expression of MMPs by OA-FLS. Quantitative RT-PCR was used to analyse the expression of MMP-1, MMP-2, MMP-3, MMP-14, and MMP-15. We found decreased expression of MMP-2, MMP-3, and MMP-14 when treated with low concentrations of NaHS. MMP-1 and MMP-15 were not affected by NaHS treatment. Furthermore, NaHS blocked the IL-1β-induced overexpression of MMP-2 and MMP-14, but not MMP-3. Long-term incubation after an one-hour NaHS treatment showed an increase in MMP-3 expression. Therefore we conclude that in these OA-FLS primary cell lines NaHS has a positive impact on inflammation by reducing the expression of MMPs in stimulated and unstimulated cells. Our results also indicate that NaHS treatment alters the expression of MMPs, although the impact on MMP-2 and MMP-14 expression strongly differ from those of MMP-3.

Vergleich der Effektivität von Biologika nach Versagen von Tumor-Nekrose-Faktor-α-Inhibitoren in Rheumatoider Arthritis: Systematischer Review und indirekte paarweise Metaanalyse 67

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Ziel Die optimale Behandlungsstrategie für Patienten mit Rheumatoider Arthritis (RA) nach Versagen von TNFi ist unklar. Unser Ziel war es daher, die Effektivität und Sicherheit von Biologika im Einsatz nach TNFi zu untersuchen.

Methoden Ausgehend von einer systematischen Literatursuche in den elektronischen Datenbanken Medline, Cochrane und www.clinicaltrials.gov, wurden alle zur Verfügung stehenden randomisierten, placebokontrollierten Studien (RCTs) von Patienten nach TNFi-Versagen in einer indirekten Metaanalyse mit paarweisen Vergleichen einander gegenübergestellt. Es wurden die klinischen Effektivitäts-Outcomes (ACR-Response) und publizierten Nebenwirkungsraten extrahiert und Odds Ratios (OR) und Risk Differences (RD) in einem Random-Effects-Modell ermittelt.

Ergebnisse In 4 RCTs mit 24 Wochen Follow-up zeigten direkte Vergleiche von Abatacept, Golimumab, Rituximab und Tocilizumab signifikant bessere Ergebnisse als Placebo, mit ORs von 3,3–8,9 (ACR20), 5,5–10,2 (ACR50) und 4,1–13,5 (ACR70). Nebenwirkungsraten waren nicht signifikant höher als in den jeweiligen Placeboarmen. Der indirekte paarweise Vergleich der 4 Biologika ergab keinen signifikanten Unterschied der ACR50- und ACR70-Response-Raten (**Abb. 3**). Golimumab zeigte signifikant weniger ACR20-Response, dafür signifikant weniger Nebenwirkungen (RD 0,13–0,18). Die Effektivität der neuen Biologika nach einmaligem TNFi-Versagen unterschied sich nicht signifikant gegenüber dem Einsatz nach mehreren erfolglosen TNFi-Therapien.

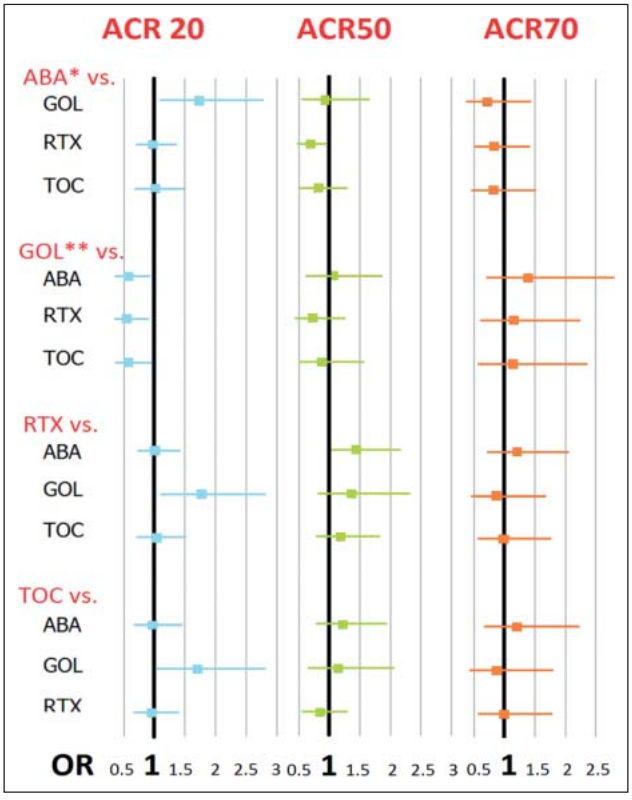

Abbildung 3: Schoels M et al.: Direkte Vergleiche von Abatacept (ABA), Golimumab (GOL), Rituximab (RTX) und Tocilizumab (TOC)

Zusammenfassung/Schlussfolgerung Bei Patienten, die sich als therapierefraktär unter einem oder mehreren TNFi erweisen, bringen Abatacept, Golimumab, Rituximab und Tocilizumab signifikante klinische Verbesserung bei zufriedenstellenden Sicherheitsdaten. Solange Head-to-head-Studien fehlen, ermöglicht die indirekte Metaanalyse den Vergleich von Effektivität und Sicherheit und zeigt ähnlich gute Resultate aller zur Verfügung stehenden Behandlungsoptionen.

Effects of TNF on Inflammmatory Osteoclastogenesis 68

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Introduction Rheumatoid arthritis (RA) is a systemic autoimmune disorder of unknown aetiology. RA is characterized by hyperplasia of the synovial membrane and degradation of articular cartilage and subchondral bone. Many proinflammatory cytokines are involved in the pathogenesis of inflammatory osteolysis among which tumor necrosis factor (TNF) alpha is one of the key players. However, the exact mechanisms whereby TNF influences inflammatory osteoclastogenesis remain unclear.

Objective We investigated the modulation of osteoclastogenesis by TNF and TNF inhibitors (TNFi) *in vitro* and *in vivo*.

Methods We analyzed the effect of various concentrations of TNF and TNFi on osteoclast precursor cells and mature osteoclasts *in vitro* using M-CSF and RANKL stimulated splenocytes. Moreover the effect of TNFi on osteoclast precursors as well as local bone destruction *in vivo* was analysed by treating TNF-transgenic mice with different doses of adalimumab.

Results We demonstrate that TNF stimulates osteoclastogenesis mainly by increasing the number of osteoclast precursor cells *in vitro*. This TNF effect is independent of the presence of RANKL. However, TNF can not substitute RANKL in the generation of mature multinucleated osteoclasts. As expected we found in the hTNFtg model of RA that TNF inhibition decreases dose-dependently synovial inflammation *in vivo*. However, local bone destruction and generation of osteoclasts is inhibited even at very low doses with no effect on the extent of synovial inflammation. This specific reduction of osteoclastogenesis is accompanied by a significant reduction of circulating osteoclast precursor cells in the blood of arthritic mice.

Conclusion TNFi reduces bone erosions by influencing osteoclast precursors even at very low doses. At this doses the effects is uncoupled from their anti-inflammatory action.

Health Promotion for People Living with a Disease of the Rheumatic Spectrum: Can It Be Possible? 69

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Introduction Chronic autoimmune diseases from the rheumatic spectrum, such as rheumatoid arthritis, systemic lupus erythematosus and systemic sclerosis are disabling diseases and can cause considerable problems in daily life. According to the WHO terminology, such disease may lead to activity limitations and participation restrictions in societal life for various reasons. Health is viewed as a state of optimal physical, mental, and social wellbeing, and not only as the absence of disease (WHO 1946). Diseases, complaints, and pain are understood as regular components of human lives, health is quantified besides others as the ability of maintenance and adaptation in crises. Disease, therefore, cannot simply be defined as the opposite of health or healthy life, but as an integral facet of it. Health promotion is defined as the process of enabling people to increase control over their health and its determinants, and thereby improve their health. We expect people living with a disease of the rheumatic spectrum promoting their health latest in the course of their disease. On the other hand, we question, people still have sources to care about their health, or even to promote their health, even if they have a severe course of disease.

Aim In the present project, we aimed to find out if people living with severe or moderate course of a rheumatic disease promote their health and, if so, how and what they do by promoting their health. Furthermore we wanted to identify which factors can contribute to HP in people a rheumatic disease such as rheumatoid arthritis, systemic lupus erythematosus, and systemic sclerosis.

Methods A qualitative biographic narrative study explores health promotion of people living with a rheumatic disease, within which 15 people per diagnose group (rheumatoid arthritis, systemic lupus erythematosus, and systemic sclerosis) were interviewed. People were asked to tell their life stories. Interviews were transcribed verbatim. The interview transcripts were analysed according to the biographical narrative interpretative method.

Results People living with rheumatic diseases such as rheumatoid arthritis, systemic lupus erythematosus, and systemic sclerosis promote their health. The way of how they promote their health differs. Also different factors are considered such as mental health, disease course, psychosocial connectivity, quality of life, and other health outcomes. Some of them had to come over hard times until they have developed strategies to promote their health, besides caring for their disease.

Conclusion Health promotion is possible for people living with a disease of the rheumatic spectrum. Additionally it is an important issue for their quality of life as well as for their health and wellbeing. Therefore people living with a rheumatic disease, such as rheumatoid arthritis, systemic lupus erythematosus or systemic sclerosis, should get more motivation and guidance – especially at the beginning of their disease – for health promotion. Health promotion therefore should get more attention from both health professionals and health promotion professionals. HP should become essential within the clinical routine.

Bestimmung von Autoantikörpern mit einem Random-Access-Analysengerät auf Basis von Magnetpartikel-basierten Chemolumineszenzassays 70

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Einleitung In der Autoimmunserologie kommen unterschiedliche Techniken (indirekte Immunofluoreszenz, Festphase-Enzymimmunoassay, Immonoblot, Westernblot) zum Einsatz. Die indirekte Immunfluoreszenz (iIF) stellt noch den Goldstandard im Screening von antinukleären Antikörpern (ANA) oder anti-neutrophilen zytoplasmatischen Antikörpern (ANCA) dar, gilt aber aufgrund ihrer hohen Anforderung an Erfahrung und Training der Befunder als schwer standardisierbar. Immunoassays mit definierten Zielantigenen werden zunehmend auch im Screening auf Autoantikörper eingesetzt. Laboratorien mit hohem Probendurchsatz drängen auf eine Vereinfachung der Diagnostik durch Immunoassayautomaten, auf denen eine Vielzahl von Autoantikörpern nachgewiesen werden kann.

Ziel Überprüfung der Richtigkeit von Autoimmunserologie-Ergebnissen eines Analysevollautomaten anhand von Rundversuchsproben.

Methoden 26 Serumproben von Patienten, zwischen November 2005 und Juli 2011 im Rahmen der Autoimmunologie-Rundversuche der ÖQUASTA ausgesandt, wurden auf dem neuen Random-Access-Chemilumineszenz-Analyzer Zenit RA der Firma Menarini Diagnostics, Florenz, auf das Vorliegen von Antikörpern der ENA-Gruppe (anti-SSA/Ro, anti-SSB/La, anti-U1nRNP, anti-Sm, anti-Scl-70, anti-Jo-1), Antikörpern gegen Zentromere, Antikörpern gegen dsDNA, Antikörpern gegen CCP sowie Antikörpern gegen PR3 und MPO getestet.

Ergebnisse Bei 23 von 26 Proben (308 von 312 Analysen) waren die Ergebnisse in Übereinstimmung mit dem erwarteten Ergebnis. Bei einer Probe wurden in Abweichung zum Zielwert schwach positive Antikörper gegen SSA/Ro (11,6 UA/ml, cut off 10 UA/ml,

ENA Screen ratio 1,2) gemessen (Zielwert negativ), eine Probe lieferte ein falsch-positives Ergebnis bei den PR3-Antikörpern (50,8 UA/ml, NW 10–20 UA/ml) und eine Probe ein falsch-positives Ergebnis bei den MPO-Antikörpern (91,9 UA/ml, NW 10–20 UA/ml). Bei Anti-dsDNA- und Anti-CCP-Antikörpern lieferte das Gerät bei allen Proben korrekte Ergebnisse.

Schlussfolgerung 308 von 312 Ergebnissen (98,7 %) wurden mit dem neuen Immunoassayautomaten richtig beurteilt. Die Ergebnisse des neuen, auf Magnetpartikel-basierten Chemolumineszenzassays-basierenden Analysenautomaten stehen in hoher Übereinstimmung mit jenen anderer weitverbreiteter Immunoassays (Immunoblot, Festphasen EIA, Fluorenzymimmunoassay) verschiedener in Österreich vertretener Hersteller und bietet die Möglichkeit, Autoimmunserologie in kurzer Zeit auf einem Random-Access-Vollautomaten abzuarbeiten.

Klinische Wertigkeit von Anti-Sa-Antikörpern 71

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Einleitung Antikörper gegen zitrullinierte Peptide (ACPA) haben einen hohen Stellenwert bei der Diagnose der Rheumatoiden Arthritis (RA). Ziel dieser Studie war es zu evaluieren, ob eine Anti-Sa- (= zitrulliniertes Vimentin) Antikörper-Bestimmung ergänzende Informationen zu anderen bereits routinemäßig eingesetzten und kommerziell erhältlichen ACPA-Tests liefern kann.

Methoden Aus 1769 anti-CCP-positiven Patienten wurden jene ausgewählt, die zum Zeitpunkt der Anti-CCP-Bestimmung trotz eines positiven Anti-CCP-Befundes nicht als RA (= Non-RA) diagnostiziert worden waren. Diese wurden mithilfe eines kommerziell erhältlichen ELISAs (anti-Sa ELISA Fa. Euroimmun, Lübeck) auf das Vorliegen von Anti-Sa-Antikörpern getestet. Für das klinische Follow-up aller auf Anti-Sa getesteten Patienten wurde zur Re-Evaluation der Diagnose der Hausarzt telefonisch kontaktiert. Zur Abschätzung der Sensitivität des verwendeten ELISAs wurden bei 18 anti-CCP-positiven Patienten mit gesicherter RA Anti-Sa-Antikörper gemessen. Weiters wurden die zugehörigen Rheumafaktorwerte mit dem Anti-Sa-Befund verglichen.

Resultate Bei 16 von 1769 anti-CCP-positiven Patienten wurde zum Zeitpunkt der Blutabnahme eine andere Diagnose als RA gestellt. Bei 10 dieser 16 Patienten konnten keine Anti-Sa-Antikörper nachgewiesen werden (cut-off: 20 RE/ml). 4 dieser Proben waren nach Anti-CCP-Nachmessung anti-CCP-negativ und wurden eliminiert. Von den 6 verbleibenden anti-CCP-positiven, anti-Sa-negativen Patienten entwickelte keiner im klinischen Follow-up eine RA. Von den 6 anti-Sa-positiven Non-RA-Patienten hatten 3 im klinischen Follow-up eine RA und 3 keine RA entwickelt. Die Sensitivitätstestung des anti-Sa ELISAs ergab eine Sensitivität von 52 %. Der Vergleich der Höhe der Rheumafaktorwerte mit dem Anti-Sa-Antikörper-Status zeigte keinen signifikanten Zusammenhang.

Schlussfolgerung Anti-CCP-positive, anti-Sa-negative Patienten scheinen keine RA zu entwickeln. Die Anti-Sa-Testung kann zusätzlich zur Anti-CCP-Bestimmung eine nützliche diagnostische Ergänzung bei anti-CCP-positiven, klinisch jedoch unklaren Patienten darstellen.

Evidence of an Aberrant Methylation Status of B and NKT Cells in Systemic Lupus Erythematodes 72

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Background Systemic lupus erythematosus is a chronic, multisystem autoimmune disease involving tissue damage resulting from autoantibody and immune complex deposition. Recent studies provided evidence that the invariant Natural Killer T (iNKT) cell is involved in immunoregulation processes associated with autoimmunity. Patients with active lupus have significantly reduced proportions of iNKT cells. There is evidence that epigenetic mechanisms play a crucial role in the pathogenesis of SLE. T cells from patients suffering from active lupus were shown to contain globally hypomethylated DNA. DNA methylation patterns of B and iNKT cells in the pathogenesis of SLE have not been investigated so far.

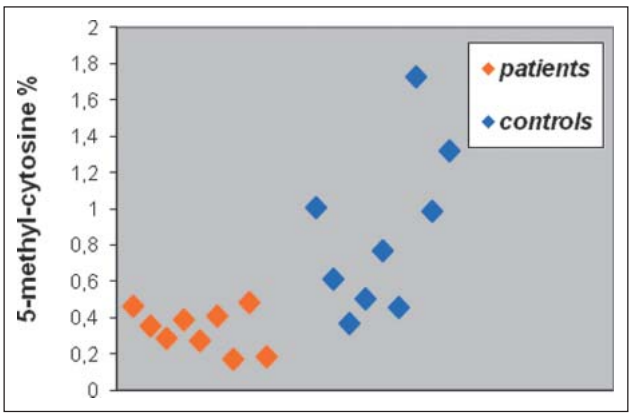

Figure 4: Felber A et al.: 5-methyl-cytosine index in patients and controls

Aim We intended to prove that iNKT cells and B cells of patients with activated SLE exhibit a different 5-methyl-cytosine (5-mC) Index compared to healthy controls.

Methods We enrolled 9 female patients (age 30 ± 5) suffering from systemic lupus erythematosus (SLEDAI 5–7), none of them received corticosteroids. B lymphocytes and iNKT cells were purified from peripheral blood using MACS separation. Methylated DNA was quantified by the MethylFlash Kit (Epigentec, Farmingdale, NY). We compared the relative methylation status of the B and the iNKT cell genome of SLE patients and 9 healthy female volunteers.

Results Patients suffering from SLE had an average 5-mC proportion of 0.29 % in B cells compared to healthy controls showing an average 5-mC proportion of 1.09 %. Within the iNKT cell population from SLE patients we determined an average genomic methylation of 0.33 %, which was significantly diminished in comparison to iNKT cells of healthy controls (**fig. 4**).

Conclusion B cells and iNKT cells of patients with SLE exhibit globally hypomethylated DNA alluding to a possible preactivation of these cell populations.

Fallbericht: Solitärer Fibröser Tumor (SFT) der Pleura bei Rheumatoider Arthritis unter Therapie mit Abatacept und Methotrexat 73

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Einleitung Der solitäre fibröse Tumor (SFT) stellt eine seltene Tumorentität des mesenchymalen Gewebes dar, der in den Weichteilgeweben wie auch pleural auftreten kann. Entsprechend der rezenten WHO-Klassifikation handelt es sich um eine Tumorentität intermediärer Dignität, wobei Malignitätskriterien definiert sind durch zytologische Atypien, und mitotische Aktivität. Wir berichten über eine zum Diagnosezeitpunkt 58-jährige Patientin unter Therapie mit Abatacept und Methotrexat (MTX), bei der im Rahmen einer Routinekontrolle ein großer Tumor im Thoraxröntgen entdeckt worden war. Zuvor wurden Leflunomid, Methotrexat und Infliximab über 7 Jahre verwendet.

Methode Klinischer Fallbericht.

Ergebnisse Nach primärer, erfolgreicher Resektion des gestielten Tumors wurde die Patientin vorerst mit MTX behandelt und aufgrund des hohen Leidensdruckes und der Krankheitsaktivität wurde etwa 8 Monate später mit Tocilizumab begonnen (non-response). Bei wiederum starker Krankheitsaktivität wurde ab 7/2011 mit Golimumab/MTX therapiert. Die Patientin zeigt sich hinsichtlich der RA ab 9/2011 in Remission. Derzeit besteht kein Hinweis für ein Tumorrezidiv.

Schlussfolgerung Im Einzelfall kann eine Biologikatherapie in Absprache mit dem Patienten und nach interdisziplinärem Konsilium auch kurz- bis mittelfristig nach Tumorextirpation unter Berücksichtigung der Krankheitsaktivität indiziert sein, um die Lebensqualität und Mobilität zu erhalten. In unserem Fall war die Therapie mit Tocilizumab und in Folge mit Golimumab bei vorbekanntem rezentem SFT über 1 ½ Jahre sicher und erfolgreich möglich.

The Use of TNF-Inhibitors in Ankylosing Spondylitis in Austria 74

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Objective The introduction of anti-tumor necrosis factor-alpha agents (TNF-inhibitors), offered new dimensions of symptom palliation and alteration of disease progress for patients with Ankylosing Spondylitis (AS). In 2007, infliximab, etanercept, and adalimumab were approved for AS in Austria. Drug expediture data of 2007 were retrieved to evaluate frequency of prescription, preferred substance, and data on switching therapies.

Methods Data from 8 sickness funds covering 5.4 million insured people, which correspond to 64 % of the population, were analyzed linking 2 databases, combining data on therapy of individual patients and their diagnosis.

Results A total of 694 patients with AS on TNF-inhibitors in 2007 were retrieved for data analysis. Yearly costs for TNF-inhibitors were highest for adalimumab (14,399 Euro per patient/year) followed by infliximab (11,685 Euro per patient/year) and etanercept (10,184 Euro per patient/year). The choice in drug for new prescriptions in 2007 showed that adalimumab was prescribed most often, with a tendency towards prescription of adalimumab and etanercept in the younger and infliximab in the older population. In the first year of prescription, 11.5 % already switched substance with etanercept showing the least switching rate. 1-year drug survival in our data was 0.89 for etanercept, 0.79 for infliximab and 0.77 for adalimumab, while 2-year drug survival was 0.69 for infliximab, 0.63 for adalimumab and 0.61 for etanercept.

Conclusions In 2007, AS patients on TNF-inhibiting therapy in Austria were treated most often with adalimumab, while etanercept showed the lowest switching rate and the longest 1-year drug survival, while infliximab showed highest 2-year drug survival.

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