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1 Pathophysiologie

1.1
Expression of distinct negative immune checkpoint molecules characterizes t regulatory cells in RA, SLE and healthy controls

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Aim: T regulatory cells (Tregs) play a crucial role in the regulation of the immune response and are of utmost interest when studying autoimmune diseases, such as rheumatoid arthritis (RA) and systemic lupus erythematosus (SLE). Therefore, targeting specific Treg markers in therapy is now widely discussed. Expression of T cell immunoglobulin 3 (TIM-3) is associated with an enhanced immune suppression and are currently discussed as target in cancer therapy. Fc receptor-like protein 3 (FCLR-3), which regulates Treg proliferation, was shown to be associated with the susceptibility in juvenile RA. Other surface markers, like CD161 enable Tregs to produce IL-17A, IFNg and IL-2, hence promoting inflammation. The aim of this study was to distinguish between RA and SLE using anti-and pro-inflammatory cell markers on Treg subsets.
Methods: Peripheral blood samples from 66 RA patients (mean ± SD; age 60 ± 10 years, female ratio: 0.68, disease duration 18 ± 14 years), 40 SLE patients (age 42 ± 13 years, female ratio 0.85, disease duration 11 ± 13 years) and 72 age-matched healthy participants (age 46 ± 17 years, female ratio 0.68) were drawn over a sampling period of 2 years. Freshly isolated PBMCs were stained and Treg subsets were identified by the expression of CD25, CD127, FoxP3, CD45RA and CD15 on the surface of CD3 and CD4 positive T cells. CD25+CD127+CD45-Tregs were further subclassified by the expression of TIM-3 (CD366) and FCLR-3 (CD307c). CD161 was used to identify Th17 type Tregs (CD15S-CD161-) and transitional Tregs (CD15S-CD161-). All cytometric measurements were performed using a standardized BD LSRFortessa platform.
Results: Transitional Tregs (CD15S-CD161-) were significantly higher ($p < 0.001$) in RA patients compared to the SLE and healthy cohort (40.5 ± 13.4% vs. 28.7 ± 9.6% and 29.7 ± 9.4% respectively). However, differences in the CD161+Th17 type Treg population could not be detected. Tregs expressing TIM-3 were higher in both RA and SLE patients compared to healthy controls (2.8 ± 2.3%, $p = 0.0105$ and 2.6 ± 1.6%, $p = 0.0031$ vs. 0.8 ± 0.7% respectively), but did not differ between the rheumatic diseases. On the other hand, FCLR-3+Tregs distinguished RA and SLE patients (17.8 ± 13.3 vs. 25.3 ± 13.1%, $p = 0.0036$), as well as SLE patients and healthy controls (16.8 ± 12.9%, $p = 0.0112$). No findings were correlated with the disease activity of RA or SLE patients.
Conclusion: Expression of negative immune checkpoints TIM-3 and FCRL-3 on Tregs not only distinguish healthy controls from RA and SLE patients but can be used to differentiate between different rheumatic diseases. These findings indicate that Tregs trigger the regulation of the immune response in RA and SLE, yet the activation of different Treg subsets is disease-specific.

1.2
Resveratrol-derivatives for the treatment of inflammatory and degenerative joint diseases: effects on fibroblast-like synoviocytes and chondrocytes

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Aim: Resveratrol, a naturally occurring polyphenol, is present in many plants and plant-derived products, e.g. red grapes and red wine. It is a free radical scavenger with potent antioxidant properties that influences many biological processes including cell division and inflammation. However, due to its poor water solubility, it can be hardly taken up by the human body. To improve the pharmacological efficacy of Resveratrol, we synthesized the Resveratrol-salicylate hybrid molecule compound 10 (C10). Recently, we observed anti-inflammatory properties of Resveratrol-salicylate hybrid molecules on human T lymphocytes in vitro, revealing an enhanced anti-inflammatory potential compared to the parent drug Resveratrol. Aim: In the present study, we investigated the role of Resveratrol and the Resveratrol derivative C10 on human fibroblast-like synoviocytes (FLS) and chondrocytes.
Methods: Primary human FLS or chondrocytes were isolated from synovia or cartilage specimens obtained from patients that underwent knee surgery for the treatment of rheumatoid arthritis (RA) or osteoarthritis (OA). Informed consent was obtained from all patients. 3D micromass cultures of FLS were established. FLS, micromasses and chondrocytes were treated in vitro with Resveratrol or C10, with or without subsequent stimulation with pro-inflammatory cytokines (TNF-α or IL-1β). IL-6 in FLS and 3D culture supernatants was analyzed by ELISA. Gene expression in OA chondrocytes was analyzed by RT-qPCR.
Results: Treatment of IL-1β-stimulated and unstimulated primary human OA chondrocytes with Resveratrol or C10 led to a decreased expression of IL-1β and matrix metalloproteinase-13 (MMP-13), C10 being about twice as effective as Resveratrol. Furthermore, both treatment with Resveratrol and C10 reduced IL-6 secretion by primary human FLS from RA and OA patients in a concentration-dependent manner. Interestingly, a more pro-

nounced effect on FLS was observed with Resveratrol. This result was verified by IL-6 secretion from RA FLS 3D cultures.
Conclusion: Resveratrol and its derivative C10 reduce cytokine secretion in FLS and chondrocytes from patients with RA and OA. Therefore, C10 has anti-inflammatory properties, which might be useful for the treatment of inflammatory and degenerative joint diseases in the future.

1.3
The novel hydrogen sulfide-releasing compound D-P* inhibits nitric oxide production and IL-6 synthesis via heme oxygenase-1 expression in the chondrogenic cell line ATDC5

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Aim: Osteoarthritis (OA) is a severe public health problem characterized by destruction and eventual complete loss of cartilage in joints. In the development of OA, inflammation has been reported to be a very early event contributing to cartilage breakdown by release of cytokines [1]. Therefore, the development of novel anti-inflammatory therapeutics is of great interest in OA research. Objectives: Lately, hydrogen sulfide (H2S) emerged as the third gasotransmitter- along with nitric oxide (NO) and carbon monoxide (CO). H2S exerts a diverse range of pharmacological effects and is reported to play an important role in the regulation of inflammatory processes [2,3]. Thus, the aim of this study was to examine and compare the effects of the common used H2S donor sodium hydrosulfide (NaHS) with the novel thiol-inducible H2S-releasing compound D-P* in the chondrogenic cell line ATDC5.
Methods: The chondrogenic cell line ATDC5 was stimulated with both IL-1β and IFNγ. Nitrite and IL-6 levels in cell culture supernatants were quantified by the Griess reaction and ELISA, respectively. Western blot analysis was performed to determine expression of inducible nitric oxide synthase (iNOS) and heme oxygenase-1 (HO-1). Reactive oxygen species (ROS) formation was monitored using fluorescence spectroscopy. HO-1 overexpression in ATDC5 cells was accomplished by transfection of a plasmid encoding the gene for HO-1.
Results: In ATDC5 cells, D-P* decreased both iNOS expression and nitrite production dose-dependently, while NaHS had no inhibitory effects. D-P*, but not NaHS, reduced IL-6 expression. In contrast to NaHS, D-P* strongly upregulated the stress-responsive enzyme HO-1. ROS measurement revealed that D-P* did not induce HO-1 expression by oxidative stress production. Overexpression of HO-1 in ATDC5 cells resulted also in a decline of nitrite and IL-6 levels.
Conclusion: Our findings indicate that in sharp contrast to NaHS, the novel slow H2S-releasing compound D-P* exhibits anti-inflammatory properties in the chondrogenic cell line ATDC5. D-P* decreased both iNOS and IL-6 levels. Moreover, compared to NaHS, the expression of HO-1 was strongly enhanced by D-P*. HO-1 is reported to exert its anti-inflammatory effects mainly by CO-release [4]. Since D-P* augmented HO-1 expression in ATDC5 cells, we suggest that the decline of iNOS and IL-6 by D-P* is mediated through CO production by HO-1. As a further proof, we observed that the CO-donor CORM-2 displayed similar anti-inflammatory effects in ATDC5 cells to D-P*.

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1.4
Diminished Memory B-cells in Systemic Lupus Erythematosus Patients with Low Disease Activity

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Aim: B-cells play a pivotal role in the initiation and perpetuation of systemic lupus erythematosus (SLE). Recently, it has been demonstrated that in active SLE patients, the peripheral blood is enriched in CD27+IgD- post-switched memory B-cells. The aim of our study was to delineate the B-cell repertoire of SLE patients with low disease activity (SLEDAI – 2K ≤4).
Methods: Peripheral blood samples from 42 patients suffering from SLE (mean±SD; age 42±13 years, 88 % females, disease duration 10.9±7 years) and 74 age-matched healthy controls (HC; age 46±17 years, 80 % female) were drawn over 2 years. All SLE patients were in remission or with low disease activity (SLEDAI of 2.0±1.7). B-cells were characterized using CD19-, CD20-, CD5-, CD27-antibodies and grouped in naïve (IgD+27-), non-switched memory (IgD+, CD27+), memory (IgD-, CD27+), B1 (CD5+27-) and MBL-like (CD5++) B-cells. A quantitative flow cytometric bead-based assay (QuantiBRITE PE kit from Becton Dickinson) was used for the estimation of CD19 antibodies bound per cell. All cytometric measurements were performed using a standardized BD LSR Fortessa platform.
Results: SLE patients had significantly higher B1 type B-cells in comparison with HC (median±SE, 16.8±2.1 % vs. 9.9±0.7 %, p=0.001). In addition, naïve and MBL type B-cells were also significantly (p<0.005) more frequently in patients with SLE than in HC (77.2±3.6 % vs. 61.6±1.4 %; 0.3±0.1 vs. 0.2±0.1; respectively). In contrast, memory and marginal zone B-cells were significantly reduced (p=0.001) in SLE patients with low disease activity (10.2±1.8 % vs. 16.6±1.0 %; 2.9±0.9 % vs. 9.9±0.7 %; respectively). Interestingly, also non-switch memory B-cells were significantly lower in SLE patients compared to HC (2.1±0.7 % vs. 6.5±0.5 %; p<0.0001). No significant difference was seen for the number of CD19 molecules on the surface of B-cells of SLE patients or HC (7432±449 vs. 7900±225; respectively). In addition, the percentage of CD86+ B-cells were similar between SLE patients and HC (9.3±1.1 % vs. 8.4 ± 0.4 %; p =0.421).
Conclusion: Our results suggest that a successful SLE therapy leads to alterations in the B-cell population, which are characterized by naïve and inactive B-cells. Further studies are needed to elucidate whether our findings are limited to certain therapies or not.

1.5
Identification of novel metabolic regulators of Th17 pathogenicity

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Aim: Th17 cells play diverse roles in immunity and health: promoting inflammation under autoimmune disease conditions while maintaining tissue homeostasis in mucosal sites in healthy individuals. Understanding the molecular mechanisms that can restrict proinflammatory functions of Th17 cells while sparing their functions in tissue maintenance can be of great therapeutic benefit. Our previous work using single-cell transcriptomic analysis of Th17 cells has revealed that CD5Like, a regulator of lipid biosynthesis, is critical in maintaining the regulatory state of Th17 cells by regulating the balance of saturated and polyunsaturated fatty acid, suggesting lipid metabolism plays a critical role in regulating Th17 cell function.
Methods: Here, we describe COMPASS, an algorithm for comprehensive, data-driven characterization of metabolic states of T cells using scRNA-seq data-sets of Th17 cells. Using COMPASS we aimed to identify novel

metabolic drivers of Th17 pathogenicity. COMPASS pointed to the known association of the glycolytic pathway with Th17 activation, and further revealed novel metabolic targets, which were seldom studied in relation to autoimmunity and Th17 pathogenicity.
Results: To validate the findings of COMPASS we performed targeted metabolomics as well as carbon-tracing experiments thereby showing differential use of these pathways by non-pathogenic and pathogenic Th17 cells respectively. Interference in these pathways in Th17 cells, using genetic deletion and small molecular weight inhibitors of metabolic targets, resulted in alteration in cell pathogenicity in cell culture experiments in vitro and in an autoimmune disease model in vivo. In order to explore potential mechanisms for the observed effects we performed RNA-seq as well as ATAC-seq and noted distinct alterations in the Th17 program of the targeted cells.
Conclusion: Overall, this study establishes a central role of these newly identified pathways in regulating pathogenicity of Th17 cells.

1.6
Rituximab treatment significantly reduces circulating CD86+ b cells in systemic sclerosis

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Aim: Rituximab (RTX) is a monoclonal antibody that targets the CD20 surface marker. This results in a reduction of CD20+ immune cell populations, foremost B cells. B cell depletion via RTX was found to be beneficial for patients suffering from systemic sclerosis (SSc), leading to an improvement of skin fibrosis and autoimmunity. However, little is known about the influence of RTX on specific B subsets in SSc. The purpose of this study was to further characterize the effect of RTX on B cell populations in patients with SSc.
Methods: Peripheral blood samples from 37 patients suffering from SSc (mean age: 54 years ± 1.64 SEM, female ratio: 0.78) and 10 age-matched healthy participants were drawn over a sampling period of 2 years. 20 SSc patients in this study group were at the time under RTX treatment and the modified Rodnan Skin score (mRSS) was measured before and after treatment start. The percentage of CD19±, CD20± lymphatic cells and CD19+CD20+ B cells co-expressing either CD5, CD24, CD27 or CD86 on their surface was done by staining freshly isolated PBMCs. A quantitative flow cytometric bead-based assay (QuantiBRITE PE kit from Becton Dickinson) was used for the estimation of CD19 antibodies bound per cell. All cytometric measurements were performed using a standardized BD LSRFortessa platform.
Results: RTX induced a significant decrease in mRSS from 19.7 ± 2.8 to 8.1 ± 1.7 (mean ± SEM, p <0.000). In addition, the CD19-CD20+ cells were significantly reduced as a result of the treatment. Thus, the frequency of CD19-CD20+ cells in the group without RTX treatment was 1.3 % ± 0.3 % compared to 0.7 % ± 0.2 % (p = 0.048). In some patients and healthy controls a B cell population was identified which had a higher than average CD19 and CD20 expression. These highly positive CD19+ CD20+ B cells were further screened for co-expression of CD5, CD24, CD27 and CD86. Within this B cell population, an average of 33.3 % ± 3.8 % was positive for CD86, a checkpoint molecule for activation of T cells during an immune response. RTX treatment significantly reduced this B cell population to 11.2 % ± 4.7 % (p = 0.039).
Conclusion: The administration of RTX not only showed a reduction of CD20-positive B cells in SSc patients, but also a reduction of active CD86+ B cells. The reduction in this specific B cell population could mean that B cells in RTX-treated SSc patients are no longer able to efficiently activate T cells. The further characterization of T and B cell subsets and their association in these patients should therefore be the subject of further investigations.

1.7
STAT signaling profiles in peripheral leucoyctes stratify patients with rheumatoid arthritis

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Aim: In rheumatoid arthritis (RA) stratification is considered an important step towards the development of patient-tailored therapeutic concepts. The fact that less than 50 % of RA patients experience a substantial improvement in response to any single biologic therapy has brought up the idea that yet unidentified subtypes of RA (endotypes) might exist. This concept is in line with distinct microscopic patterns of synovitis found in biopsies of RA joints. Furthermore, a subset of RA patients has leucocytes with interferon driven gene expression, whereas the majority of RA patients does not. Interferons activate receptor associated Janus kinases leading to phosphorylation of STAT1 and STAT2. Other STAT family members are activated by cytokines such as IL-6 (STAT3) or IL-15 (STAT5). Therefore, the phosphorylation pattern of the different STAT molecules in circulating leucocytes might mirror the specific cytokine milieu of a given patient. Our objective for this study was to define endotypes of RA based on the phosphorylation patterns of the different STAT molecules in circulating leucocytes.
Methods: Cross-sectional study of 63 patients with established RA fulfilling the 2010 EULAR/ACR criteria (mean age: 64.5 ± 1.7 (SEM) years, female ratio: 0.79). Nine healthy subjects served as a control group. Flow cytometry was performed to detect the phosphorylated forms of STAT1-6 in Monocytes, Granulocytes, B cells, naïve-, effector-, and memory-T cells of the CD4+ and CD4- lineage. All steps from blood draw to cell fixation were performed at 4 °C to prevent auto-activation of leucocytes. The mean fluorescence intensity (MFI) of fluorochrome labeled antibodies against phosphorylated STATs in the different leucocyte populations was used for statistical analysis. MFIs were correlated with disease activity measured by the cDAI. MFIs of populations with elevated STAT phosphorylation not associated with disease activity were analyzed by unsupervised hierarchical clustering. The resulting groups were validated by principal component analysis. Finally, criteria for patient assignment to specific groups by MFI were generated by calculating ROC-curves.
Results: Pronounced ex vivo phosphorylation of STAT1-6 in any leucocyte population was detected in 30 of 63 (48 %) RA patients but not in healthy subjects (n=10). Active STAT5 signaling in Monocytes, naïve CD4+ T cells and CD4+ effector T cells was significantly associated with disease activity. Unsupervised hierarchical cluster analysis of RA patients based on pSTAT MFIs not associated with disease activity resulted in 3 groups: 1) Patients with active STAT1 and STAT3 signal in Monocytes and Granulocytes (n=14/63, 22 %), 2) Patients with active STAT5 signal in naïve CD8+ T cells, CD8+ effector T cells and CD4+ memory T cells (n=16/63, 25 %) and 3) Patients without active STAT signal in any leucocyte population (n=33/63, 52 %). cDAI, CRP, ESR, current treatment, RF and ACPA status did not differ significantly between the groups. To test if the assignment to a group changed over time, we performed a second analysis of STAT phosphorylation after 3–6 months. Seventy percent of the patients tested (11/16) were re-assignment to their initial group.
Conclusion: We identified three distinct RA endotypes based on active STAT signal. Whether patients within different endotypes respond differently to a given therapy will be subject to further research.

1.8
The emerging regulatory function of microRNA146a in bone biology and osteoporosis

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Aim: Micro RNAs (miRNAs) play a crucial role in the regulation of bone metabolism. MiR-146a, an important anti-inflammatory miRNA, was found to negatively impact osteogenesis and bone regeneration in vitro, by controlling the differentiation of mesenchymal stem cells. But to date the role of miR-146a in bone remodelling, its influence on bone stability and development of osteoporosis is not known.
Methods: Systemic bone, tibiae and femur, of wt, miR-146a-/- and miR-146a-/- TRAF6+/− animals was assessed histologically and via µCT analysis, over a period of 3 to 18 months of age. Serum cytokine levels were analysed by Elisa. Expression levels of MRNA in bone were analysed by qPCR. To induce osteoporosis, ovariectomy (OVX) induced bone loss was performed.
Results: When we analysed bone volume of long bones histologically as well as with µCT analysis we detected significantly increased trabecular as well as cortical bone mass in miR-146a deficient compared to wt animals, starting at an age of 6 months. Dose reduction of TRAF6, a main target of miR-146a, using miR-146a−/− TRAF6+/− animals could not change the observed bone phenotype. Analysis of serum in aged miR-146a deficient animals displayed elevated activity of bone resorbing osteoclasts as amounts of CTX I in miR-146a−/− mice were significantly increased compared to wt animals. Q-PCR analysis of important osteoclast as well as osteoblast marker genes in bones ex vivo displayed elevated expression of signature molecules of both cell types in aged miR-146a deficient mice, suggesting a regulatory role of miR-146a in both cell types. Moreover, expression level of Wnt5a, a known target of miR-146a, influencing bone forming as well as bone resorbing cells, was strongly elevated in miR-146a−/− bones, possibly responsible for this deregulated bone growth. When we induced osteoporosis using the OVX disease model, histological analysis of long bones showed significant trabecular bone loss in ovariectomized wt mice. In contrast, we could not detect trabecular bone loss in ovariectomized miR-146a knock out animals, suggesting that loss of miR-146a deficiency protects bone loss induced by estrogen deficiency.
Conclusion: MiR-146a seems to control bone turnover and miR-146a deficient mice accrue bone over time. Moreover this miRNA has a negative influence on bone loss occurring during oestrogen loss induced osteoporosis. Therefore miR-146a could be possibly used as a therapeutic target in the treatment of osteoporosis.

1.9
Lymphopenia in primary Sjögren's Syndrome is associated with premature aging of naïve CD4+ T-cells

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Aim: To investigate peripheral lymphopenia, a frequent finding in primary Sjögren's syndrome (pSS) associated with higher disease activity and increased mortality.
Methods: Prospective, cross-sectional study of consecutive patients with pSS (n=66) and healthy controls (HCs, n=181). Lymphocyte subsets were analysed by flow cytometry, naïve (CD45RA+) and memory (CD45RO+) CD4+ T-cells were purified by MACS technology. In vitro proliferation and senescence associated β-galactosidase (SABG) were assessed by flow cytometry. Telomere length and T-cell receptor excision circles (TREC) were measured by real-time PCR. Telomerase activity was analyzed according to the telomeric repeat amplification protocols (TRAP).
Results: In pSS lymphopenia mainly affected naïve CD4+ T-cells. We noted a lower frequency of proliferating naïve CD4+ T-cells ex vivo and decreased homeostatic proliferation in response to IL-7 stimulation in vitro. Furthermore, naïve CD4+ T-cells exhibited signs of immune cell aging including shortened telomeres, a reduction in IL-7R expression and accumulation of SABG. The senescent phenotype could be explained by telomerase insufficiency and drastically reduced levels of T-cell receptor excision circles (TRECs), indicating a history of extensive post-thymic cell division. TRECs correlated with the number of naïve CD4+ T-cells linking the extend of earlier proliferation to the inability to sustain normal cell numbers.

Conclusion: In pSS extensive proliferation of naïve CD4+ T-cells earlier in life is associated with a senescent phenotype unable to sustain homeostasis. The resulting lack of naïve CD4+ T-cells forms the basis of lymphopenia frequently observed in pSS.

1.10
T-cell—Fibroblast interactions in patients with rheumatoid arthritis: partners in crime?

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Aim: Rheumatoid arthritis (RA) is a chronic debilitating autoimmune disease, which affects 1 % of the population and is characterized by synovial inflammation. The RA synovial tissue is composed of a variety of cell types, including fibroblast-like synoviocytes (FLS) and T-cells. Although previous publications point to a role of T-cell—FLS interactions, the main mechanism and the contribution to disease development and progression remains unknown. We therefore aimed to establish an experimental system, which allows studying T-cell—FLS interactions.
Methods: RA patient derived FLS were isolated from synovial tissue that was acquired during synovectomy. Using fluorescence activated cell sorting (FACS) of patient-derived PBMCs, naïve CD4+ T-cells were gathered to establish a co-culture that allows for examining consequences of T-cell—FLS interactions. By adding different pro-inflammatory cytokines, this system allows for deciphering the effects of the inflammatory synovial environment on T-cell—FLS interaction using automated fluorescence microscopy and downstream bioinformatic image analysis. Furthermore, by re-isolation of T-cells from co-culture, effects on T-cell activation and differentiation can be investigated using flow cytometry.
Results: We successfully established a co-culture system to visualize and quantify T-cell—FLS interactions. Our data confirmed enhanced T-cell—FLS interactions, in particular when T-cells were activated using CD3/CD28 stimulation. Re-isolated T-cells from co-culture showed increased upregulation of early and late T-cell activation markers especially after pretreatment of FLS with IFN-γ.
Conclusion: In conclusion, our data show that FLS interact with T-cells, which as a consequence leads to enhanced T cell activation. These data highlight a potential role of T-cell—FLS interactions as a major driver of local inflammation. A further understanding of T-cell—FLS interactions will help to develop new therapeutic strategies for the treatment of RA patients.

1.11
Histone deacetylase 1: (HDAC1): a key player of T cell-mediated arthritis

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Aim: Despite enormous efforts to develop new therapeutic strategies for treatment of rheumatoid arthritis (RA), the large number of non-responding patients to currently available drugs underlies the unmet need to identify new therapeutic targets. Certain CD4+T cell subsets, especially Th17 cells, have been shown to be major drivers of inflammation in patients with RA. The expression of their key transcription factors is controlled by histone modifications which includes acetylation of lysine residues mediated by histone deacetylases (HDAC). Indeed, pan HDAC inhibitors have been shown to be a potential therapeutic strategy. However, major side effects limited the clinical use and underline the need of more specific HDAC inhibitors. We therefore addressed the individual role of HDAC1 on the development of collagen-induced arthritis model (CIA).
Methods: Mice with a T cell specific deletion of HDAC1 (HDAC1 cKO) were generated by using the CD4Cre/LoxP system. Collagen induced arthritis (CIA) was induced at week 8. Animals were scored for paw swelling and grip strength. After 10 weeks, mice were sacrificed and paraffin sections of the affected joints were analysed for histomorphologic signs of inflammation, cartilage and bone destruction. Anti-CII antibody levels were determined by ELISA. Serum samples were analysed for various cytokines by multiplex assays. CCR6 expression in CD4 T cells was analysed by flow cytometry.
Results: To address potential effects of HDAC1 in the pathogenesis of RA, CIA was induced in HDAC1cKO mice and WT mice. Surprisingly HDAC1cKO mice were completely protected from the development of arthritis. In line with the clinical data, histological analysis revealed no signs of inflammation, no bone erosion and no osteoclasts in the joints of HDAC1cKO mice. Anti-CII antibodies, including total IgG and igG2c were detected in HDAC1cKO and WT mice. Surprisingly, IL-17 was significantly decreased in the serum of HDAC1 cKO mice as compared to WT mice, suggesting a role of HDAC1 in the development of Th17 cells. To see whether HDAC1 is involved in the regulation of the chemokine receptor 6 (CCR6), the main marker of Th17 cells, we compared the upregulation of CCR6 in CD4+ T cells from WT and HDAC1cKO mice. Indeed, CCR6 could not be upregulated in CD4+ T cells from HDAC1cKO mice upon IL-6 in vitro. These data support the role of HDAC1 in the regulation of CCR6, an important chemokine receptor, which is necessary for the migration of pathogenic Th17 cells and therefore for the development of arthritis.
Conclusion: Our data show the importance of HDAC1 as a key immune regulator in the pathogenesis of T cell driven collagen induced arthritis. Therefore, it might be considered as an interesting novel therapeutic target in RA.

2 Klinische Studien und Präsentationen

2.1
Vaginal infection in pregnant women under immunomodulatory therapy during pregnancy with systemic autoimmune inflammatory conditions. A retrospective analysis

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Aim: Vaginal infections are a risk factor for preterm delivery. In this study, we sought to evaluate the vaginal flora of pregnant women who suffer from inflammatory rheumatic disease (IRD) and inflammatory bowel disease (IBD) in comparison to control women without these autoimmune conditions.
Methods: We collected the data from a total of 7748 women with singleton pregnancies who underwent routine screening for asymptomatic vaginal infections between 10 + 0 and 16 + 0 gestational weeks. Vaginal smears were Gram-stained, and microscopically evaluated for bacterial vaginosis, candidiasis, and trichomoniasis. In a retrospective manner, data of 195 women with inflammatory rheumatic or inflammatory bowel disease

(cases) were matched for age, parity, previous preterm delivery, and smoking status to the data of 7553 controls. The vaginal flora at antenatal screening served as the primary outcome measure. Secondary outcome measures were gestational age and birth weight.
Results: In the case group, 127/195 (65 %) pregnant women received immunosuppressive medications. Normal or intermediate flora was found in 145/195 women (74 %) and 6897/7553 controls [91 %; OR 0.49 (95 % CI, 0.33–0.71); $p < 0.001$]. Candidiasis occurred more frequently in pregnant women with inflammatory rheumatic and bowel disease than in controls [OR 2.11 (95 % CI, 1.26–3.27); $p < 0.001$]. Findings were inconclusive regarding bacterial vaginosis (± candidiasis) and trichomoniasis. The newborn of women with IRD and IBD had a lower mean birth weight [MD − 165.3 g (95 % CI, −283.6 to −46.9); $p = 0.006$] compared to infants of the control group.
Conclusion: Pregnant women with systemic autoimmune inflammatory conditions are at risk for asymptomatic vaginal infections. As recurrent candidiasis is associated with preterm delivery, the vulnerability of this patient population should lead to consequent antenatal infection screening and therapy at early gestation.

2.2
Ultrasound-verified enthesophytes are associated with radiographic progression at entheses in psoriatic arthritis

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Aim: The aim of this prospective study was to examine whether ultrasound or clinical abnormalities at enthesal sites predict radiographic progression at entheses in Psoriatic Arthritis (PsA).
Methods: Consecutive PsA patients were included and subjected to clinical and ultrasound assessments at 14 entheses at baseline, 6 and 12 months. Radiographs were performed at 0 and 12 months. By US, we investigated structural (erosions, osteophytes) and inflammatory changes (grey scale (0–32) and Power Doppler (0–14, range global ultrasound score 0–140), and radiographs were evaluated for enthesophytes and erosions (score range 0–56). Multivariate regression models were conducted to identify the possible association of clinical and ultrasound findings with radiographic progression.
Results: We examined 83 patients at baseline, of whom 43 (51.8 %) had complete clinical, ultrasound and x-ray data. Twenty-four of 43 patients (55.8 %) developed radiographic progression of entheses. These patients were younger (49.6 vs. 59.3, p=0.005), had shorter disease duration (9.7 vs. 17.9 years, p=0.015) and lower clinical disease activity at 6-months (DAPSA 6.7 vs. 17.0, p=0.018) as compared to patients without progression. Non-progressors had higher ultrasound enthesiophyte scores at baseline than progressors (20 vs. 15, p<0.05). The multivariate regression analysis revealed that 48.6 % of the variance of the x-ray score at 12-months FU (RegcoeffB=0.827, p=0.000) could be explained by the baseline US enthesiophyte score.
Conclusion: Our data indicate that radiographic progression at entheses is linked with age, disease duration and ultrasound verified enthesophytes at baseline. No other ultrasound parameter predicted radiographic progression at entheses.

2.3
A network meta-analysis to evaluate the efficacy of baricitinib and other treatments of rheumatoid arthritis in patients who are inadequate responders to methotrexate

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Aim: Baricitinib (BARI), an oral, selective inhibitor of Janus kinase (JAK)1/2, is used to treat moderate to severe rheumatoid arthritis (RA) in adults. To assess the comparative effectiveness of BARI 4-mg (background MTX) and other targeted synthetic/biologic disease modifying anti-rheumatic drugs in moderate-to-severe RA patients with inadequate response to methotrexate (MTX-IR).
Methods: A systematic literature review (SLR) of randomized controlled trials (RCTs; Phase 3) of interventions of interest was conducted (1999 to 2017) in Medline, Medline In-Process, Embase, Biosciences Information Service, the Cochrane Library, and trials registers. Network meta-analyses (NMAs) of RCTs reporting the American College of Rheumatology (ACR) response data were conducted using Bayesian mixed-treatment comparisons. Here, we present main results for the 24-week (±4) time point (fixed-effects simultaneous models).
Results: Totally, 24 trials met the SLR inclusion criteria. Analyses, using BARI RA-BEAM trial data, showed BARI 4 mg (background MTX) to be more effective than adalimumab (ADA) 40-mg (EOW; odds ratio [OR] 1.33; 95 % credible interval [CrI] 1.01–1.75), abatacept (ABA) 10-mg (IV/4 weeks; OR 1.47; 95%CrI 1.02–2.13), and infliximab 3-mg (IV/8 weeks; OR 1.61; 95%CrI 1.12–2.27) for ACR20. While no differences were found on ACR50, BARI 4-mg (background MTX) was found to be more effective than ADA 40-mg (OR 1.39; 95%CrI 1.02–1.89), ABA 10-mg (OR 1.85; 95%CrI 1.09–3.23), rituximab (RTX) 1000-mg (OR 2.38; 95%CrI 1.10–5.00) and 2000-mg (OR 2.44; 95%CrI 1.04–5.56) for ACR70. BARI 4-mg (background MTX) showed better results than etanercept monotherapy (50 mg/week or 25 mg/biweekly; OR 2.27; 95%CrI 1.04–5.26) for ACR20, and RTX 1000-mg monotherapy for ACR20/ACR70 (OR 1.82; 95%CrI 1.02–3.13)/(OR 2.70; 95%CrI 1.04–7.14). Sensitivity analysis including 10 additional trials with up to 20 % of patients with prior biologic use allowed comparison versus tofacitinib (TOFA), showing BARI 4-mg (background MTX) is more effective than TOFA 5 mg (BID) monotherapy for ACR20 (OR 1.92; 95%CrI 1.32–2.86).
Conclusion: The comparative analyses support BARI as an efficacious treatment option for moderate-to-severe RA patients with MTX-IR.

2.4
Efficacy of ixekizumab in different phenotypes of patients with active psoriatic arthritis: results from the SPIRIT trials

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Aim: Psoriatic arthritis (PsA) is a highly heterogeneous chronic inflammatory disease combining a range of musculoskeletal and extra-articular

manifestations. Ixekizumab (IXE) is approved for the treatment of moderate to severe psoriasis and more recently for active PsA. This post-hoc analysis describes the efficacy of IXE at week 24 in different phenotypes of PsA patients.

Methods: Biologic naïve patients (SPIRIT-P1) were randomized to IXE 80 mg (initial dose 160 mg) every 4 (Q4W; *N*=107) or 2 weeks (Q2W; *N*=103), to adalimumab 40 mg (Q2W; *N*=101), or to placebo (PBO; *N*=106). Patients who had an inadequate response or intolerance to TNF inhibitors (SPIRIT-P2) were randomized to IXE Q4W (*N*=122) or Q2W (*N*=123), or to PBO (*N*=118). Patients fulfilled the Classification Criteria for Psoriatic Arthritis (CASPAR) criteria and had active disease with ≥3TSJ and 3≥SJC. Patients were classified according to the following phenotypes of PsA: polyarthritis (≥5TJC and/or ≥5SJC), oligoarthritis (<5TJC and <5SJC), DIP joint only, enthesitis and dactylitis according to either the investigator's judgment or a scale-based definition. In each phenotype ACR 20, 50 and 70 response criteria, Minimal Disease Activity Psoriasis Area Severity Index (MDAPASI), and Disease Activity Psoriatic Arthritis (DAPSA) remission and low disease activity (LDA) response criteria were assessed to evaluate IXE effect at week 24 combining both doses. For each phenotype with a sufficient sample size, the IXE- and PBO-treated patients' baseline characteristics were assessed. Treatment effects of IXE and PBO were compared using Chi-square tests (or Fisher's exact tests if appropriate) within each phenotype.

Results: The most frequent phenotypes were polyarthritis (*N*=662), enthesitis (investigator: *N*=459; LEI>0: *N*=403), and dactylitis (investigator: *N*=220; LDI-B>0: *N*=155). Too small sample sizes due to inclusion criteria or low frequency were observed for "DIP joint only", oligoarthritis and arthritis mutilans phenotypes (*N*=22, *N*=17 and *N*= 15; respectively). Baseline patient characteristics were generally balanced between treatment arms and similar between the 3 most frequent phenotypes, with no difference in disease activity and duration. Efficacy of IXE was consistent across the different phenotypes for various outcomes at week 24: ACR20/50/70, MDAPASI, DAPSA remission and DAPSA-LDA in SPIRIT trials irrespective of previous biologic DMARD use (**Tab. 1**). Response rates were consistent to overall efficacy reported with IXE in SPIRIT trials.

Conclusion: Treatment responses with IXE at week 24 were consistent regardless of the phenotypes.

2.5
Ixekizumab significantly improves signs, symptoms and spinal inflammation of active ankylosing spondylitis/Radiographic axial spondyloarthritis: 16-week results of a phase 3 randomized, active and placebo-controlled trial

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Aim: COAST-V (NCT02696785) is the first Phase 3 study of ixekizumab (IXE), a high-affinity anti-IL-17A monoclonal antibody, in patients with active radiographic axial spondyloarthritis (r-axSpA) who are biologic DMARD (bDMARD) naive. We report the Week (Wk) 16 primary endpoint and key efficacy and safety data from this ongoing 52-wk study.

Methods: Adults with active r-axSpA per Assessment of SpA international Society (ASAS) criteria (sacroiliitis centrally defined by modified New York Criteria and ≥1 SpA feature), BASDAI ≥4, back pain ≥4 and inadequate response or intolerance to NSAID therapy, were randomized 1:1:1:1 to subcutaneous placebo (PBO), 80 mg IXE every 4 (Q4W) or 2 (Q2W) wks, with either 80-mg or 160-mg starting dose (assigned 1:1), or 40 mg adalimumab (ADA) Q2W (active reference arm) up to Wk 16. The primary endpoint was ASAS40 response at Wk 16. Major secondary endpoints included: ASAS20, BASDAI50 and change from baseline (CFB) in MRI spine and sacroiliac joint SpA Research Consortium of Canada

Tab. 1 Overall efficacy of ixekizumab in different phenotypes of patients at week 24 in the SPIRIT trials

Week 24	Polyarthritis		Enthesitis				Dactylitis			
ITT, NRI	≥5TJC and/or ≥5SJC		INV judgement		LEI >0		INV judgement		LDI-B >0	
	SPIRIT-P1 (*n*=306)	SPIRIT-P2 (*n*=356)	SPIRIT-P1 (*n*=186)	SPIRIT-P2 (*n*=273)	SPIRIT-P1 (*n*=182)	SPIRIT-P2 (*n*=221)	SPIRIT-P1 (*n*=86)	SPIRIT-P2 (*n*=134)	SPIRIT-P1 (*n*=93)	SPIRIT-P2 (*n*=62)
ACR20, %										
Placebo	43.7	29.9	33.3	29.4	33.3	26.1	41.0	40.0	50.0	42.9
Ixekizumab	63.1	52.7	62.8	52.7	61.6	49.3	64.2	51.5	70.8	50.0
p-value	0.0012	<0.0001	0.0002	0.0004	0.0004	0.0012	0.0137	0.3668	0.0548	0.6380
ACR50, %										
Placebo	19.4	11.1	14.0	9.4	14.0	11.6	17.9	20.0	21.4	28.6
Ixekizumab	44.8	34.3	43.4	35.6	43.2	32.9	47.4	36.4	53.8	39.6
p-value	<0.0001	<0.0001	0.0001	< 0.0001	0.0001	0.0009	0.0015	0.1713	0.0039	0.4530
ACR70, %										
Placebo	7.8	1.7	3.5	0.0	3.5	0.0	7.7	0.0	10.7	0.0
Ixekizumab	28.6	16.7	26.4	14.9	26.4	13.8	33.7	18.2	40.0	20.8
p-value	<0.0001	<0.0001	0.0003	0.0002	0.0003	0.0012	0.0019	0.0398	0.0052	0.0622
MDAPASI, %										
Placebo	18.4	5.1	7.0	2.4	7.0	1.4	15.4	0.0	17.9	0.0
Ixekizumab	36.0	25.1	33.3	23.9	33.6	21.7	40.0	27.3	47.7	27.1
p-value	0.0016	<0.0001	0.0001	< 0.0001	0.0001	0.0001	0.0058	0.0086	0.0067	0.0285
DAPSA Remission, %										
Placebo	5.8	1.7	0.0	1.2	0.0	1.4	0.0	0.0	0.0	0.0
Ixekizumab	19.7	10.0	18.6	9.0	18.4	8.6	23.2	13.6	30.8	14.6
p-value	0.0013	0.0045	0.0005	0.0153	0.0005	0.0445	0.0010	0.0809	0.0009	0.1292
DAPSA LDA, %										
Placebo	23.3	17.1	17.5	16.5	17.5	13.0	28.2	10.0	28.6	7.1
Ixekizumab	34.0	26.8	33.3	26.1	32.0	22.4	30.5	25.8	26.2	22.9
p-value	0.0547	0.0432	0.0279	0.0815	0.0427	0.1046	0.7897	0.1367	0.8094	0.1887

Results are expressed as proportions of patients in the intent-to-treat population calculated using non-responder imputation. *P-value* for differences between ixekizumab and placebo by Chi-square tests or Fisher's exact tests

Abbreviations: ACR20/50/70=20/50/70 % improvement from baseline in ACR criteria; *ACR* American College of Rheumatology, *DAPSA* Disease Activity Index for PsA, *INV* investigators, *ITT* intent-to-treat, *LDA* low disease activity, *LDI-B* Leeds dactylitis index-basic, *LEI* leeds enthesitis index, *MDA* minimal disease activity, *NRI* non-responder imputation, *PASI* psoriasis area severity index, *PsA* psoriatic arthritis, *SJC* swollen joint count, *TJC* tender joint count

(SPARCC) scores (all images were centrally read). In addition, the CFB is reported for high sensitivity C-reactive protein (hs-CRP) and the 4 patient domains used for calculation of the ASAS response: patient's global assessment (PGA), BASFI, spinal pain and BASDAI stiffness. Categorical endpoints were analysed by logistic regression with non-responder imputation for missing data. Continuous endpoints were analysed by a mixed-effects model of repeated measures. Safety was assessed.

Results: Of 341 subjects randomized, 97 % completed Wk 16. Baseline demographics and disease characteristics were comparable among study arms: mean age was 41.7 years; mean time since r-axSpA symptoms onset was 16.0 years, and mean BASDAI was 6.7. At Wk 16, significantly higher proportions of IXE-treated patients achieved ASAS40, ASAS20 and BASDAI50 vs PBO. Compared with PBO, both IXE regimens had significantly higher CFB improvements in MRI spinal and sacroiliac joint inflammation and hs-CRP at Wk 16 and, as early as Wk 1, significant CFB improvements in all ASAS components. At Wk 16, ADA showed significant improvements vs PBO for ASAS40 and for PGA, BASFI, NRS spinal pain and BASDAI stiffness CFB. Frequencies of treatment-emergent and serious adverse events are shown (**Tab. 1**). There was one opportunistic infection (Candida infection, ADA arm), one case of inflammatory bowel disease (IXEQ2W arm) and no malignancies or deaths.

Conclusion: The primary and all major secondary endpoints for IXE were met at Wk 16 with no unexpected safety findings. IXE was superior to PBO for improving r-axSpA signs and symptoms, with improvements in ASAS40, ASAS20 and BASDAI50, and CFB of inflammation on MRI, hs-CRP and individual ASAS components in patients with r-axSpA naïve to bDMARDs.

Tab. 1 Efficacy and Safety Results at Week 16

	Placebo (*N*=87)	ADA (*N*=90)	IXEQ4W (*N*=81)	IXEQ2W (*N*=83)
Responder Rate, *n* (%), Intent-to-treat population				
ASAS40[a,b]	16 (18 %)	32 (36 %)†	39 (48 %)‡	43 (52 %)‡
ASAS20[a,b]	35 (40 %)	53 (59 %)†	52 (64 %)†	57 (69 %)‡
BASDAI50[a,b]	15 (17 %)	29 (32 %)*	34 (42 %)‡	36 (43 %)‡
Change From Baseline, Least Squares Mean (Standard Error), Intent-to-treat population				
Spine SPARCC Score[b,d]	−1.5 (1.1)	−11.6 (1.1)‡	−11.0 (1.2)‡	−9.6 (1.2)‡
Sacroiliac joint SPARCC Score[d,e]	0.9 (0.6)	−4.2 (0.6)‡	−4.0 (0.6)‡	−4.3 (0.6)‡
PGA disease activity[c]	−1.4 (0.2)	−2.6 (0.2)‡	−2.5 (0.3)‡	−2.8 (0.3)‡
BASFI[b,c]	−1.2 (0.2)	−2.1 (0.2)†	−2.4 (0.2)‡	−2.4 (0.2)‡
NRS spinal pain[c]	−1.7 (0.2)	−2.7 (0.2)†	−3.2 (0.3)‡	−3.2 (0.2)‡
BASDAI stiffness[c]	−1.3 (0.2)	−2.7 (0.2)‡	−3.2 (0.2)‡	−2.9 (0.2)‡
High sensitivity C-reactive protein (mg/L)[c,f]	1.4 (1.9)	−7.2 (1.9)†	−5.2 (2.0)*	−6.6 (2.0)†
Safety Overview, *n* (%)	Placebo	ADA	IXEQ4W	IXEQ2W
Safety population	(*N*=86)	(*N*=90)	(*N*=81)	(*N*=83)
Treatment-emergent adverse events	34 (40 %)	44 (49 %)	34 (42 %)	36 (43 %)
Serious adverse events	0	3 (3 %)	1 (1 %)	1 (1 %)
Discontinued due to adverse event	0	1 (1 %)	0	3 (4 %)

[a]Logistic regression analysis with nonresponder imputation for missing data. [b]A primary or major secondary endpoint. Comparisons between each of the IXE treatment arms and placebo for primary and major secondary endpoints were all statistically significant as calculated using a graphical multiplicity testing method. [c]Mixed effects model of repeated measures analysis. [d]Analysis of covariance model based on observed case. [e]Sacroiliac joint SPARCC score at baseline was 5.2. [f]At baseline, 64 % of patients had CRP>5 mg/L. *$p<0.05$; †$p<0.01$; ‡ $p<0.001$ vs placebo.

All statistical comparisons were made between placebo and active treatment arms. ADA represents an active reference; the study was not powered to test equivalence or noninferiority of active treatment arms to each other, including IXE versus ADA. Intention-to-treat population: All randomized patients, analyzed according to the treatment to which they were assigned.

Safety population: All randomized patients who received ≥1 dose of study treatment, analyzed according to the treatment to which they were assigned.

ADA adalimumab, ASAS Assessment of Spondyloarthritis International Society criteria, *BASDAI* Bath Ankylosing Spondylitis Disease Activity Index, *BASFI* Bath Ankylosing Spondylitis Functional Index, *IXEQ2W* ixekizumab every 2 wks, *IXEQ4W* ixekizumab every 4 wks, *NRS* numeric rating scale, *PGA* patient's global assessment, *SPARCC* Spondyloarthritis Research Consortium of Canada

2.6

Goals: Baricitinib (BARI), an oral, selective inhibitor of Janus kinase (JAK)1/2, is used to treat moderate to severe rheumatoid arthritis (RA) in adults. We describe the drug's safety profile with updated data from an additional Phase (Ph) 3 trial and an on-going long-term extension (LTE) study

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Aim: Baricitinib (BARI), an oral, selective inhibitor of Janus kinase (JAK)1/2, is used to treat moderate to severe rheumatoid arthritis (RA) in adults. We describe the drug's safety profile with updated data from an additional Phase (Ph) 3 trial and an on-going long-term extension (LTE) study.
Methods: Long-term safety of once-daily BARI was evaluated in the All-BARI-RA dataset: all patients (pts) exposed to BARI from 9 randomized trials (5 Ph3, 3 Ph2, 1 Ph 1b) and 1 LTE (data to February 13, 2018). Placebo (PBO) comparisons were evaluated to Week 24 from 7 Ph2/3 trials: pts randomized to PBO, BARI 2-mg or 4-mg, with censoring at rescue/treatment switch. Dose responses were evaluated in the 2-mg/4-mg extended dataset from 4 Ph2/3 trials: pts randomized to 2-mg or 4-mg, LTE data included; data censored at rescue/dose change (as-treated analysis) and analyzed without
Results: Totally, 3770 pts received BARI (10,127 PYs); maximum exposure was 7 years. No significant differences were seen for BARI 4-mg vs PBO in adverse events leading to permanent drug discontinuation, death, malignancy, serious infection, or major adverse cardiovascular events. Herpes zoster IR was significantly higher for BARI 4-mg than PBO (3.8 vs 0.9) and numerically higher for BARI 2-mg (3.1). The IRs for deep vein thrombosis/pulmonary embolism were numerically higher in BARI 4-mg than PBO; IRs were similar by dose in 2-mg/4-mg extended dataset. Malignancy (excluding non-melanoma skin cancer) IRs were 0.8 (2 mg) and 1.0 (4 mg; as-randomized analysis). Fewer than 1 % pts discontinued for abnormal laboratory results.
Conclusion: BARI maintained a safety profile similar to that previously reported and acceptable in the context of demonstrated efficacy.

Tab. 1 Patient baseline demographics/characteristics

	IXE (*N*=283)	ADA (*N*=283)
Age, years	47.5 (12.0)	48.3 (12.3)
Male, *n* (%)	162 (57)	150 (53)
PsA duration since diagnosis, years	6.6 (7.4)	5.9 (6.4)
Concomitant csDMARD use, *n* (%)	193 (68)	199 (70)
TJC	19.1 (12.7)	21.3 (15.4)
SJC	10.1 (7.5)	10.7 (8.1)
PASI	7.9 (8.7)	7.7 (7.3)

Data are mean (SD), unless stated otherwise

Tab. 2 Patient reported outcomes

	IXE (*N*=283)		ADA (*N*=283)	
	Baseline	LS mean change at wk 24	Baseline	LS mean change at wk 24
HAQ-DI	1.20	−0.63	1.27	−0.56
SF-36 PCS	36.80	9.96	36.12	8.82
SF-36 MCS	45.40	4.47	44.85	3.93
Dermatology Life Quality Index	9.77	−7.81*	9.82	−6.48
Fatigue Severity Numeric Rating Scale	5.87	−2.66	6.46	−2.53

LS least square; *p<0.001 vs ADA

2.7
Multicentre, randomised, open-label, assessor-blinded, parallel-group head-to-head comparison of the efficacy and safety of ixekizumab versus adalimumab in patients with psoriatic arthritis naive to biologic disease-modifying anti-rheumatic drugs: 24-week results

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Aim: There have been few head-to-head clinical trials comparing different biologic disease-modifying anti-rheumatic drugs (bDMARDs) in patients (pts) with psoriatic arthritis (PsA). The objective of this study is to report 24-week (wk) results of a study directly comparing efficacy and safety of ixekizumab (IXE), an IL-17A inhibitor, and adalimumab (ADA), a TNF inhibitor, in bDMARD-naive pts with PsA.
Methods: The study (NCT03151551; SPIRIT-H2H) included pts with active PsA (≥3 TJC + ≥3SJC) and plaque psoriasis (BSA ≥3 %) who were bDMARD naive and inadequate responders to csDMARD therapy. Patients were randomised (1:1) to IXE or ADA for 52 wks (on-label dosing based on presence/absence of moderate to severe psoriasis). The primary objective was superiority of IXE vs ADA measured by the proportion of pts achieving both ACR50 and PASI100 responses at wk 24. Key secondary objectives versus ADA at wk 24 were (1) non-inferiority of IXE for ACR50 (noninferiority margin-12 %) and (2) superiority of IXE for PASI100. Additional PsA, skin, composite treat-to-target (T2T: MDA, DAPSA 4), PASDAS remission and patient-reported outcomes, and safety were assessed. Nine pts had PASI=0 and BSA≥3 % (a medical inconsistency) at baseline; these pts were considered PASI100 responders if PASI=0 and BSA=0 at wk 24. Categorical variables were evaluated using logistic regression analyses with NRI in the ITT population. Continuous variables were analysed using mixed models for repeated measure analysis.
Results: 566 pts were randomised (283 to IXE and 283 to ADA). Baseline demographics and disease characteristics were generally well balanced between groups (Table 1). All primary and key secondary efficacy endpoints at wk 24 were met (Figure). The proportion of pts achieving both ACR50 and PASI100 was significantly greater for IXE than ADA (36 % vs 28 %; p<0.05). IXE was non-inferior to ADA for ACR50 response and superior for PASI100 response (**Fig. 1**). While improvements from baseline were achieved with both treatments, significantly better results were seen with IXE vs ADA for skin and composite T2T outcomes, enthesitis resolution (Figure), and skin-related quality of life (Table 2). No unexpected safety signals were observed.
Conclusion: In bDMARD naive pts with active PsA and skin disease, IXE showed superior efficacy to ADA based on simultaneous achievement of ACR50 and PASI100 responses at wk 24. Greater improvements with IXE vs ADA were also attained in individual PsA domains and composite T2T outcomes.

2.8
Rheumatologic diseases impact the progression risk of MGUS to overt Multiple Myeloma

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Aim: Monoclonal gammopathy of undetermined significance (MGUS) is an asymptomatic pre-malignant condition with an inherent progression risk to overt multiple myeloma (MM) or related haematological disorders. Chronic inflammation is a known risk factor for cancer initiation and progression. The MGUS to MM transformation may be an excellent pathophysiological model to study the impact of inflammation owing to chronic rheumatologic diseases on cancer progression.
Methods: MGUS patients (pts.) diagnosed between 1/2000 and 8/2016 were identified and screened for concomitant chronic inflammatory rheumatic diseases. Rheumatic disorders (RDs) were grouped as follows: 1) Antibody (Ab-) mediated RDs (rheumatoid arthritis [RA]; connective tissue diseases including systematic lupus erythematodes, Sjögren syndrome, mixed connective tissue disease, systemic sclerosis; and ANCA-associated vasculitides) and 2) non-Ab-mediated RDs (including polymyalgia rheumatica [PMR], large vessel giant cell arteritis [LV-GCA], spondyloarthritis [SpA] and gout). Progression to MM was defined as categorial (yes/no) and continuous time-dependent (time to progression) variable.
Results: 255 (9 %) of 2935 MGUS pts. suffered from a concomitant RD. The progression-risk between MGUS pts. with versus without RD differs significantly. MGUS pts. suffering from non-Ab-mediated RDs have a doubled progression-risk when compared to MGUS pts. without a respective concomitant RD (HR=2.1 [95%CI 1.1–3.9], P<0.02). This data translates

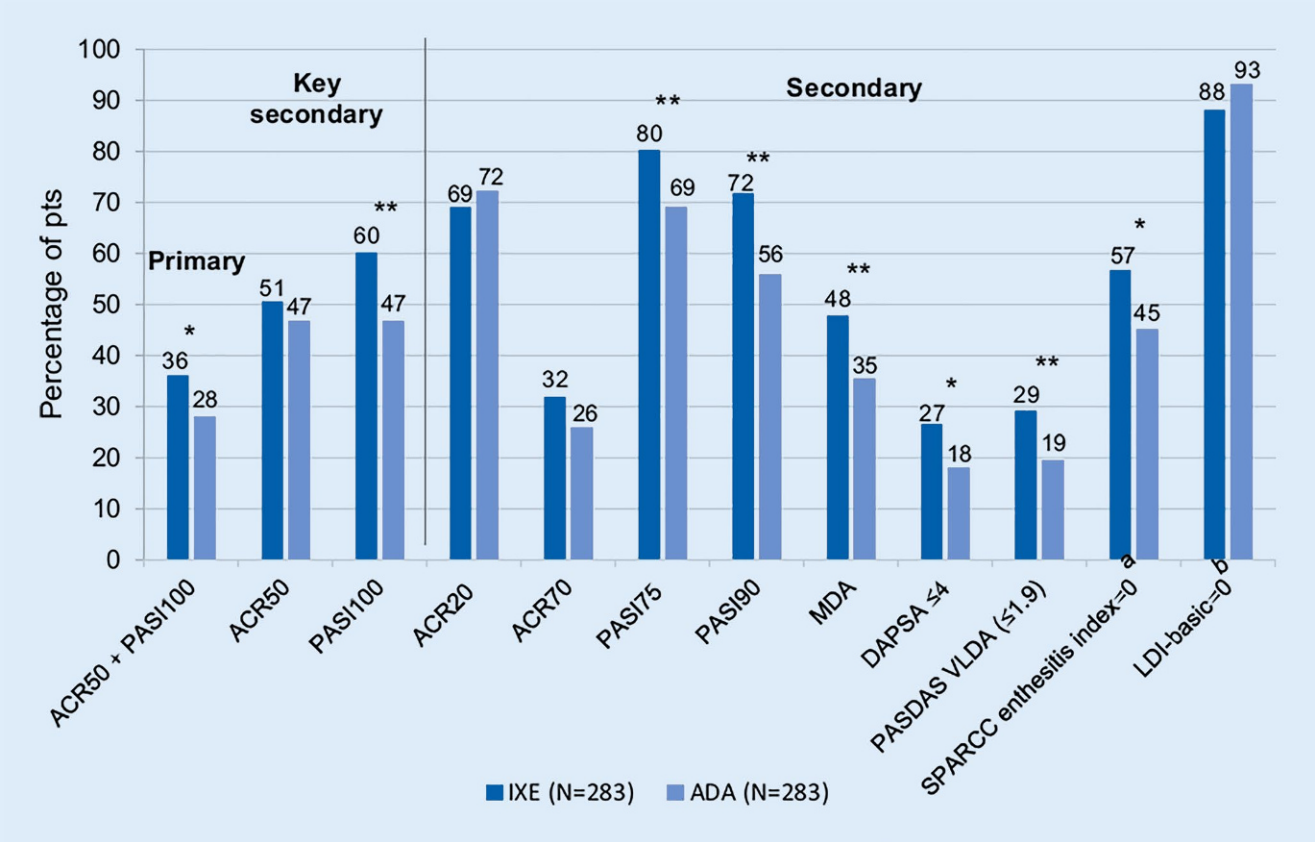

Fig. 1 ▲ Proportion of patients achieving primary and secondary outcomes at wk 24. Pts were stratified by conventional synthetic DMARD use and presence of moderate to severe psoriasis. [a]There were 189 IXE- and 171 ADA-treated pts with SPARCC enthesitis index scores >0 at baseline; these patients were evaluated at wk 24. [b]There were 42 IXE- and 58 ADA-treated pts with LDI scores >0 at baseline; these patients were evaluated at wk 24. ADA, adalimumab 80 mg wk 0 then 40 mg every 2 wk from wk 1 for pts with moderate to severe psoriasis or 40 mg wk 0 then 40 mg every 2 wk for pts without moderate to severe psoriasis; IXE, ixekizumab 160 mg wk 0, then 80 mg every 2 wk to wk 12 and every 4 wk thereafter for pts with moderate to severe psoriasis or 160 mg wk 0, then 80 mg every 4 wk for pts without moderate to severe psoriasis; ACR, American College of Rheumatology criteria; PASI, Psoriasis Area Severity Index score; MDA, minimal disease activity – PsA; DAPSA, Disease Activity for Psoriatic Arthritis; PASDAS VLDA, Psoriatic Arthritis Disease Activity Score very low disease activity; SPARCC, Spondyloarthritis Research Consortium of Canada; LDI, Leeds Dactylitis Instrument.*$p < 0.05$, **$p < 0.01$ IXE vs ADA

into a 5-year progression-risk of 4 %, 10 % and 2 % in MGUS pts. without rheumatologic co-morbidity, concomitant non-Ab-mediated and Ab-mediated RDs, respectively. Taking the complex risk-stratification model including, M-protein concentration, Ig-type and level of FLC ratio as variables, again the pts. strata with non-Ab-mediated RDs (n=57) faced the highest risk for progression (HR= 6.8 [95 % CI 1.5–30.7], P=0.02) versus pts. with Ab-mediated RDs (n=77).

Conclusion: Chronic inflammatory diseases impact the progression risk of MGUS into overt MM. However, the prognostic impact is not consistently negative, as some RDs (e.g. RA and connective tissues diseases) are even protective, whereas others clearly increase the risk of progression (e.g. gout, PMR, SpA). It remains unclear how the underlying inflammatory conditions and/or treatment of the RD impacts the progression risk. The ultimate goal is to further refine the currently applied prognostic scores in MGUS by considering autoimmune co-morbidities.

2.9
Prävalenz von Lungenveränderungen bei PatientInnen mit axialer Spondyloarthritis im transthorakalen Lungenultraschall

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Ziel: Die axiale Spondyloarthritis (axSpA) ist eine der häufigsten entzündlich-rheumatologischen Erkrankungen des Bewegungsapparates. Im Gegensatz zur rheumatoiden Arthritis (RA) wurden bei der axSpA nur in sehr alten Studien Lungenveränderungen nach langer Krankheitsdauer in den Oberlappen beschrieben. Ziel dieser Studie war die Erhebung von möglichen Lungenveränderungen mit der Lungensonographie.

Methoden: Die Untersuchung erfolgte mittels Esaote MyLab 70. Erhebung der B-Linien und AM-Linien mit dem Abdomenschallkopf (AC2541) und Messung der Pleuradicke mit den Linearschallkopf (L 4–15) in 18 Feldern (pro Lunge jeweils apikal, in der Mitte und basal von ventral, lateral und dorsal) anhand von 21 SpA-PatientInnen in einer Querschnittsanalyse.

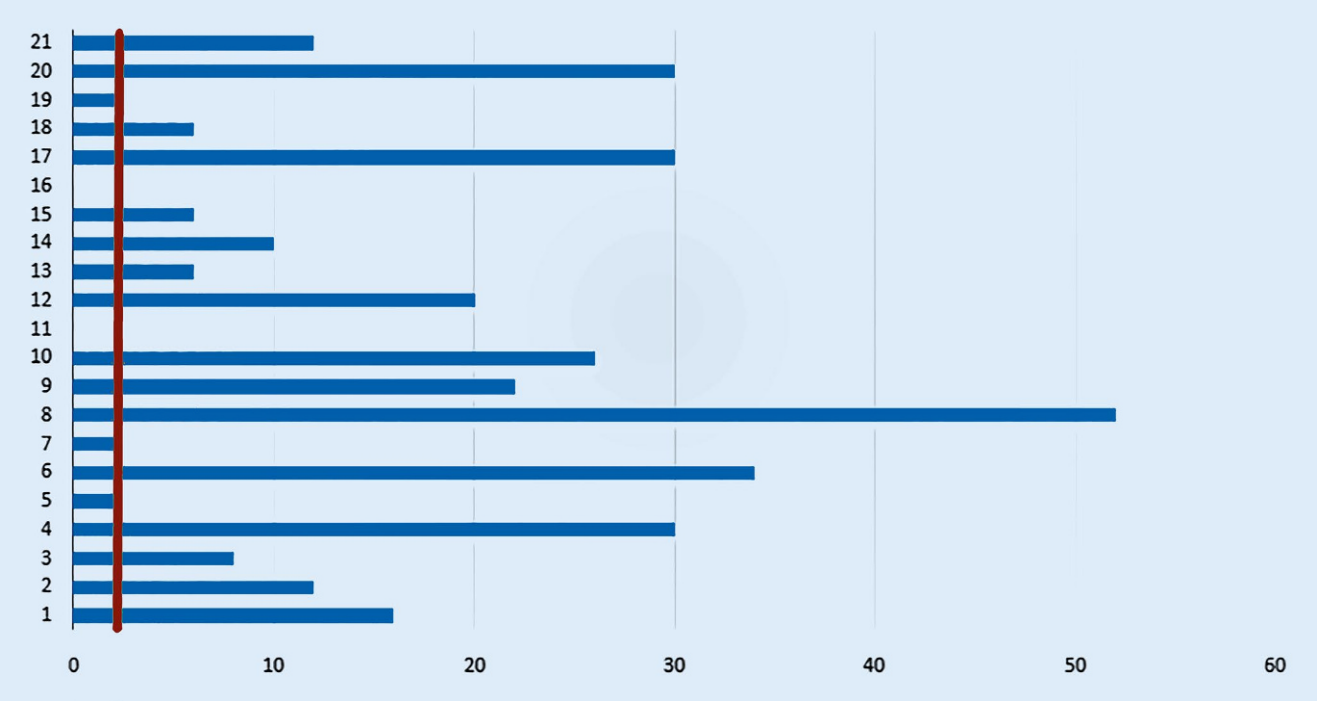

Abb. 1 ▲ Anzahl B-Linien 21 Patienten

Ergebnisse: Bei 21 PatientInnen (4 Frauen, 17 Männer; Durchschnittsalter 51 +/−11,8 Jahre, Krankheitsdauer 16,2 +/− 7,2 Jahre) fanden sich durchschnittlich 12 B-Linien (Range 0–52) (**Abb. 1**), wobei in der Literatur 0–2 B-Linien als normal angenommen werden und von Tardella bei einem Cut-Off von 10 Linien eine hohe Sensitivität und Spezifität beschrieben wurde [1]. In unserer Untersuchung wiesen nur 5 Patienten (23,8 %) eine normale Häufigkeit von B-Linien auf (0–2), während 9 PatientInnen (42,8 %) unter dem Cut-Off von 10 Linien waren. Apikal fanden sich 23,1 %, in der Mitte 39,2 % und basal 37,7 % der Veränderungen. Nur 3 PatientInnen wiesen AM-Linien auf und eine Verdickung der Pleura war nicht darstellbar (Median 1,05 mm). Wir konnten keinen signifikanten Zusammenhang der Häufigkeit der B-Linien mit bestehender TNF-Inhibition oder Raucherstatus finden.

Schlussfolgerung: In unserer Studie konnte gezeigt werden, dass nur 5 PatientInnen eine normalen Lungenultraschall aufwiesen und bei mehr als der Hälfte der PatientInnen sonographische Hinweise auf eine interstitielle Lungenveränderungen gefunden wurden.

Literatur

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2.10
Characterization of anemia in rheumatoid arthritis patients

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Aim: As seen in previous analysis, the prevalence of anemia in rheumatoid arthritis (RA) patients is decreasing due to new therapeutic options from between 30 and 66% to around 21% in our cohort. In a study cohort witch was designed to evaluate iron metabolism in chronic inflammation, we further analysed the characterization of anemia in RA patients. Therefore we investigated the type of anemia in RA outpatients at our tertiary centre and evaluated the iron state in monocytes. We also looked for the impact of disease activity and therapy strategies on the prevalence and type of anemia.
Methods: In the database we included patients with rheumatic diseases with or without biological treatment. Blood count, iron parameters (iron, ferritin, transferrin, and transferrin saturation), renal function, vitamin status, disease activity (CDAI, DAS-28), drug therapy and X-rays were collected at the time of initial diagnosis and at inclusion in the database during a routine follow-up. Anemia was defined as hemoglobin <12g/dl in women and < 13 g/dl in men. Monocytes were isolated from whole blood by Ficoll-Paque separation (rpm 1250), resuspended with CD 14 + MACS antibodies and separated via MACS columns. Wilcoxon and Mann-Whitney-U-test was performed to compare subgroups, Spearman-Rank-analysis was applied to analyse correlations with hemoglobin levels, routine laboratory parameters, disease activity and medical treatment.
Results: 261 RA-outpatients were evaluated. Most patients had IDA, followed by undefined anemia, ACD/IDA and then ACD. Over all, more than 57% had an atypical iron status. Atypical iron status was significantly associated with methotrexate ($p \leq 0.05$) and glucocorticoid ($p \leq 0.01$) intake. RT-PCR was performed in 83 patients, no significant correlation between serum ferritin levels and H-ferritin in monocytes ($p > 0.05$) were found. When comparing subgroups, there are no significant differences in H-Ferritin levels, compared to control.
Conclusion: Our data show that most patients with RA suffer from anemia with true iron deficiency which may emerge from occult (medication triggered) gastrointestinal bleeding, urogenital blood losses or insufficient dietary iron absorption which needs to be included in the diagnostic work up of such patients. Our study further shows that the majority of RA patients have a pathological iron status. Moreover, our molecular analysis indicated no association between circulating parameters of iron homeostasis such as ferritin with iron levels of monocytes which may be related to effects of DMARDS on iron homeostasis and hematopoiesis. Future studies have to identify novels biomarkers, which can better characterize anemia in RA patients, study the impact of DMARDs on iron regulation and hematopoiesis and analysis the impact of alterations of iron homeostasis and anemia type as well as their therapeutic correction on the course of diseases. References: Weiss G, Schett G: Anaemia in inflammatory rheumatic diseases. Nat Rev Rheumatol 2013, 9(4):205–215.

2.11
Diagnose der chronischen Großgefäß-Riesenzellarteriitis mittels Ultraschall

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Ziel: Das Ziel unserer Studie war die Bestimmung eines Ultraschall Cut-offs der Arterienwanddicke der Axillararterien, von Patienten mit chronischer/lang bestehender Riesenzellarteriitis (RZA), mit Frage nach Mitbeteiligung, im Sinne einer Großgefäß-Riesenzellarteriitis (G-RZA).
Methoden: Ultraschalluntersuchungen der Axillararterien wurden bei 127 RZA-Patienten zum Zeitpunkt der Diagnose und zu Follow-up Untersuchungen durchgeführt. Axillararterien von RZA-Patienten mit sonographischen Entzündungszeichen zum Zeitpunkt der Diagnose wurden mit Axillararterien von RZA-Patienten ohne sonographische Entzündungszeichen und mit Axillararterien 40 gesunder Kontrollen verglichen. Receiver operating curves (ROC) wurden berechnet, um den optimalen Arterienwand-Cut-off zu bestimmen, zur Diagnose einer G-RZA.
Ergebnisse: 148 Axillararterien von RZA-Patienten zeigten Zeichen einer Entzündung im Ultraschall zu Studienbeginn (G-RZA-Gruppe). Die Kontrollgruppe bestand aus 162 Axillararterien, darunter 82 (50,6 %) Axillararterien von RZA-Patienten ohne Zeichen einer Entzündung im Ultraschall und 80 (49,4 %) Axillararterien von 40 gesunden Kontrollen. Das Durchschnittsalter betrug 71 Jahre (S.D. 7,9) mit 69,9 % Frauen in der G-RZA-Gruppe bzw. 74 Jahre (S.D. 6,9) mit 59,8 % Frauen in der Kontrollgruppe. Die mittleren Intima Media Dicke-Werte (IMD ≙ Arterienwanddicke) in der G-RZA-Gruppe waren 1,14 (S.D. 0,38; *n*=78) für die rechten und 1,18 (S.D. 0,47; *n*=70) für die linken Axillararterien im Vergleich zu 0,60 (S.D. 0,11; *n*=77) für die rechten und 0,62 (S.D. 0,11; *n*=85) für die linken Axillararterien in der Kontrollgruppe. Die Intervalle von der Diagnose bis zur Follow-up Visite waren 0,5–3 Jahre, 3–6 Jahre und >6 Jahre, mit einer Verteilung von 96 (65 %), 32 (22 %) und 20 (13 %) Untersuchungen in der G-RZA-Gruppe und 29 (35 %), 41 (50 %) und 12 (15 %) Untersuchungen in der Kontrollgruppe (ausgenommen gesunde Kontrollen). Der optimale IMD-Cut-off für die Axillararterien bei Patienten mit chronischer RZA beträgt 0,87 mm mit 75,0 % Sensitivität und 99,4 % Spezifität.
Schlussfolgerung: Mithilfe des neuen IMD-Cut-offs, von 0,87 mm, kann bei Patienten mit chronischer RZA ein eventueller Mitbefall der Axillararterien evaluiert werden und dadurch die Diagnose einer G-RZA nachträglich gestellt werden.

2.12
Efficacy and safety of disease-Modifying drugs in psoriatic arthritis (PSA): a systematic literature review

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Aim: There is now an increasing range of drug options in PsA. To inform the update of the EULAR PsA management recommendations [1], we performed a systematic literature review assessing the efficacy and safety of pharmacological agents in PsA.
Methods: Original articles published since the last EULAR literature review (2015) until 2018 in English were searched in Medline, Embase and Cochrane Library, as well as ACR/EULAR abstracts (2015–2018). For efficacy, randomised controlled trials (RCTs) investigating pharmacological interventions, defined as biological (b)DMARDs, targeted synthetic (ts)/conventional synthetic (cs)DMARDs were analysed. The main efficacy outcomes were ACR response criteria, PASI75, enthesitis, physical function and radiographic progression. For safety, also cohorts and case-control studies were analysed with a focus on adverse events, infections, cancer and cardio-vascular events.
Results: Of 6380 articles (efficacy: 2191, safety: 4189), 76 (68 original articles and 8 abstracts) were analysed. The drugs most investigated over the timeframe of this search were TNFi (5 trials) and IL17i (5 trials) (**Tab. 1**). Other drugs with mechanisms not previously published on in this indication were especially IL23-p19 inhibitors and JAK inhibitors (**Tab. 1**). All trials of original drugs, except one open-label study comparing Ustekinumab to TNFi, were placebo-compared trials and met their primary endpoint, ACR20 (**Tab. 1**). Biosimilar comparison with bio-originator showed non-inferiority. Safety was evaluated in 32 articles. One article,

Tab. 1 Drugs investigated in PsA randomised controlled trials, 2015–2018

Drug target	Drug name (No. of Trials)	Population	Primary End-point met (*n*/*N*)
Biological DMARDs			
TNFi	Golimumab (1)	csDMARD/ NSAID-IR	Yes (1/1)
	Etanercept (1)[1]	MTX + DMARD naive	Yes (1/1)
	Adalimumab biosimilar (CT-P13) (1)	csDMARD-IR	Yes (non-inferiority; 1/1)
	CHS-0214 (1)[1]	csDMARD-IR	Yes (non-inferiority; 1/1)
IL17	Ixekizumab (2)	csDMARD-IR/ TNFi-IR	Yes (2/2)
	Secukinumab (3)	NSAID-IR/mixed csDMARD/TNFi-IR	Yes (3/3)
TNF/IL17A	ABT-122 (1)	csDMARD/TNFi-IR	Yes (1/1)
IL12/23	Ustekinumab (1)[2]	Patients with active enthesitis	Yes (1/1)
IL23-19p	Risankizumab (1)[1]	NSAID/csD-MARD/TNFi-IR	Yes (1/1)
	Guselkumab (1)	csDMARD/TNFi-IR	Yes (1/1)
IL6	Clazakizumab (1)	NSAID/csD-MARD-IR	Yes (1/1)
CD80/86	Abatacept (1)	csDMARD/TNFi-IR	Yes (1/1)
Targeted synthetic DMARDs			
PDE-4	Apremilast (4)	csDMARD-IR/ TNFi-IR/csDMARD naive	Yes (4/4)
JAK 1/2/3	Tofacitinib (2)	csDMARD-IR/ TNFi-IR	Yes (2/2)
JAK 1	Filgotinib (1)	csDMARD-IR	Yes (1/1)

csDMARD: conventional synthetic disease modifying anti-rheumatic drug; IR: insufficient responders

[1] Conference abstract

[2] open-label trial (Ustekinumab vs. TNFi)

investigating patients in the ARTIS and DANBIO registries did not show an increased risk of cancer with TNFi compared to TNFi naïve PsA patients and the general population. There was an increased risk of Candida infections and inflammatory bowel disease with IL17 inhibiting agents. Two longitudinal cohorts showed an elevated risk for major adverse cardiac events in PsA. One longitudinal cohort study showed no association of cardiovascular events with any treatment.
Conclusion: New drugs targeting IL17A, IL23-p19, JAK, CD80/86, TNF/IL17A and IL6 demonstrated efficacy for the treatment of PsA with varying responses across different disease domains. Efficacy of TNFi agents and other bDMARDs was confirmed. Investigated biosimilars were non-inferior to their reference products. No new major safety signals were identified, though long-term studies and more registry data are needed. This literature review informed the EULAR updated recommendations for management of PsA.

2.13
Tenderness is no sign of inflammation in rheumatoid arthritis, psoriatic arthritis or osteoarthritis

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Aim: In inflammatory joint diseases, joint swelling is regarded as a sign of inflammation, which is associated with structural progression. However, the significance of tenderness without swelling is unclear. The aim of this study was to determine whether clinical tenderness can be considered a sign of inflammatory joint activity in patients with rheumatoid arthritis (RA), osteoarthritis (OA), or psoriatic arthritis (PsA)
Methods: 34/26/31 patients respectively with RA, OA and PsA were included in the study. Each patient underwent clinical examination, followed by an ultrasound examination of bilateral MCP 1–5 (metacarpophalangeal), PIP 1–5 (proximal interphalangeal) joint and wrists; the sonographer was blinded to clinical data. On clinical examination synovial swelling and tenderness were evaluated using a binary scoring method, and tender, non-swollen joints (TNS) were identified. Grey-scale signs of synovitis (GS) and Power Doppler signal (PD) were evaluated using a semi-quantitative grading system. Differences of PD signals between groups (RA vs. OA, RA vs. PsA, TNS vs. non-tender non-swollen joints) were calculated by Chi-Square test. Furthermore, joints of RA and PsA patients were tracked back for up to 6 years to identify the time point of the last swelling of that respective joint. Kaplan-Meier estimates for the occurrence of the last time point of swelling were compared between PD positive and PD negative TNS joints.
Results: TNS joints more often showed PD signal in RA patients as compared to those with OA and PsA (14.2 % vs. 10.9 % vs. 9.1 %, respectively, p=0.46 for RA vs. OA; p=0.14 for RA vs. PSA). TNS joints were not more often PD positive as compared to non-tender non-swollen joints in RA (14.2 % vs. 10.2 % respectively, p=0.19) as well as in PsA (9.1 % vs. 8 %, p=0.65) and OA (10.9 % vs. 9.8 %, p=0.72). Kaplan-Meier analysis revealed a significantly shorter time period to last observed swelling in PD positive as opposed to PD negative TNS joints in both RA (52.04 vs. 67.65 months, p<0.01) and PsA (45.48 months vs. 105.01 months, p<0.001), however we found no difference in GS positive vs. negative TNS joints.
Conclusion: The results of this study suggest that tenderness might not be a sign of active inflammation in RA, PsA and OA. The fact that shorter time to last swelling was associated with positive PD in TNS joints suggests that, at least in RA, tenderness might reside after prior clinical swelling has resolved.

2.14
Efficacy and safety of ixekizumab in the treatment of radiographic axial spondyloarthritis: 16 week results of a phase 3 randomized, double-Blind, placebo-controlled trial in patients with prior inadequate response or intolerance to 1 or 2 tumor necrosis factor inhibitors

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Aim: TNF inhibitors (TNFi) are recommended for patients with axial spondyloarthritis (axSpA) who do not respond to or tolerate NSAIDs. Some patients have inadequate response (IR) or intolerance to TNFi and this axSpA population has not been exclusively studied in a clinical trial. In COAST-W (NCT02696798), we investigated the efficacy and safety of ixekizumab (IXE), a high-affinity monoclonal antibody that selectively targets IL-17A, in patients with active radiographic axSpA (r-axSpA) with prior IR or intolerance to 1 or 2 TNFi.
Methods: In this randomized, double-blind, placebo-controlled, Phase 3 trial, adult patients with IR/intolerance to 1 or 2 TNFi and an established diagnosis of r-axSpA (patients fulfilling Assessment of SpA international Society [ASAS] classification criteria for axSpA with radiographic sacroiliitis centrally defined by modified New York criteria) were recruited and randomized 1:1:1 to placebo (PBO) or 80-mg subcutaneous IXE every 2 (IXEQ2W) or 4 (IXEQ4W) weeks (wks), with either 80-mg or 160-mg starting doses (assigned 1:1). The primary endpoint was ASAS40 response rate at Wk 16. Secondary outcomes included ASAS20 and change from baseline (CFB) of spinal MRI inflammation, high sensitivity C-reactive protein (hs-CRP) and the four individual components used for calculation of the ASAS response: patient's global assessment (PGA), BASFI, spinal pain and BASDAI stiffness. Categorical outcomes were analysed by logistic regression with non-responder imputation. Continuous outcomes were analysed by mixed-effects model of repeated measures except MRI SpA Research Consortium of Canada (SPARCC) scores (analysis of covariance using observed case without imputation). Safety was assessed.
Results: 316 patients were randomized to PBO (N=104), IXEQ2W (N=98) or IXEQ4W (N=114). All patients possessed very active and longstanding disease (mean BASDAI, 7.4±1.3; median duration of symptoms, 16.7 years); 90 % had a prior IR and 10 % were TNFi-intolerant. At Wk 16, significantly higher proportions of IXE-treated patients achieved ASAS40 vs PBO, and ASAS20. Compared with PBO, both IXE regimens had significantly higher CFB improvements at Wk 16 for MRI spinal inflammation and hs-CRP. Significant CFB improvements vs PBO were observed as early as Wk 1 in PGA, BASFI, BASDAI spinal pain and BASDAI stiffness (**Tab. 1**). Most treatment-emergent adverse events (AEs) were mild/moderate (**Tab. 2**). Serious AEs were consistent across arms. There was one death (suicide; IXEQ2W) that was not attributable to study drug per the blinded principal investigator.
Conclusion: Both IXE regimens yielded rapid and significant improvements vs PBO at Wk 16 in ASAS40, ASAS20 and CFB of MRI spinal inflammation, hs-CRP, and individual ASAS components in patients with r-axSpA with previous IR or intolerance to 1 or 2 TNFi.

Tab. 1 COAST-W primary and secondary efficacy outcomes at Week 16 for the intent-to-treat population (N=316).[a] Baseline (Week 0) results included for continuous outcomes

	PBO (N=104)		IXEQ2W (N=98)		IXEQ4W (N=114)	
Responder Rate, Wk 16	**n (%)**		**n (%)**		**n (%)**	
ASAS40	13 (12.5)		30 (30.6)†		29 (25.4)*	
ASAS20	31 (29.8)		46 (46.9)*		55 (48.2)†	
CFB (LSM [SE]), ITT	**Wk 0**	**Wk 16**	**Wk 0**	**Wk 16**	**Wk 0**	**Wk 16**
Population	**Mean (SD)**	**LSM CFB (SE)**	**Mean (SD)**	**LSM CFB (SE)**	**Mean (SD)**	**LSM CFB (SE)**
MRI SPARCC spine score[b]	6.4 (10.2)	3.3 (1.4)	11.1 (20.3)	−4.0 (1.5)‡	8.3 (16)	−3.0 (1.4)†
Hs CRP (mg/L)	16.0 (22.3)	9.7 (2.7)	16.9 (19.8)	−8.1(2.9)‡	20.2 (34.3)	−11.1 (2.6)‡
BASDAI	7.3 (1.3)	−0.9 (0.2)	7.5 (1.3)	−2.1 (0.2)‡	7.5 (1.3)	−2.2 (0.2)‡
PGA	7.8 (1.6)	−0.7 (0.2)	7.8 (1.8)	−2.1 (0.2)‡	8.0 (1.6)	−2.4 (0.2)‡
BASFI	7.0 (1.7)	−0.6 (0.2)	7.4 (1.4)	−1.9 (0.2)‡	7.4 (1.8)	−1.7 (0.2)‡
BASDAI spinal pain	8.0 (1.4)	−0.9 (0.2)	8.3 (1.4)	−2.4 (0.2)‡	8.4 (1.3)	−2.5 (0.2)‡
BASDAI stiffness	7.2 (1.8)	−0.7 (0.2)	7.5 (1.7)	−2.4 (0.2)‡	7.2 (1.8)	−2.4 (0.2)‡

[a]Of 315 patients with prior TNFi experience, 205 (65.1 %) had an inadequate response to 1 TNFi, 78 (24.8 %) had an inadequate response to 2 TNFi, and 32 (10.2 %) were intolerant. One patient was inadvertently enrolled without prior TNFi experience.
[b]Number of patients observed at Wk 16, PBO: N = 46, IXEQ2W: N = 45, IXEQ4W: N = 49.
*$p<0.05$, †$p<0.01$, ‡$p<0.001$, all vs PBO
ASAS Assessment of Spondyloarthritis International Society criteria, *BASDAI* Bath Ankylosing Spondylitis Disease Activity Index, *BASFI* Bath Ankylosing Spondylitis Functional Index, *CFB* change from baseline, *hs CRP* high sensitivity C-reactive protein, *ITT* intent-to-treat, *IXEQ2W* ixekizumab every 2 wks, *IXEQ4W* ixekizumab every 4 wks, *LSM* least squares mean, *MRI* magnetic resonance imaging, *n* number of patients in analysis category, *N* number of patients in analysis population, *PBO* placebo, *SD* standard deviation, *PGA* patient's global assessment, *SE* standard error, *SPARCC* Spondyloarthritis Research Consortium of Canada, *Wk* Week

Tab. 2 Adverse events (AE) and treatment-emergent adverse events (TEAE) during the 16-week blinded treatment dosing period of COAST-W. Values presented as n (%)

	PBO (*N*=104)	IXEQ2W (*N*=98)	IXEQ4W (*N*=114)
TEAE (patients reporting ≥1 event)	51 (49.0)	59 (60.2)	73 (64.0)
Mild	18 (17.3)	23 (23.5)	34 (29.8)
Moderate	26 (25.0)	32 (32.7)	35 (30.7)
Severe	7 (6.7)	4 (4.1)	4 (3.5)
Discontinuation due to AE	2 (1.9)	3 (3.1)	10 (8.8)
Serious AE	5 (4.8)	3 (3.1)	4 (3.5)
Death	0 (0.0)	1 (1.0)[a]	0 (0.0)

[a]Cause of death was suicide which was determined to be unrelated to study drug by the blinded principal investigator. The patient had prior history of depression of about 1 year (reported as mild at study entry).
IXEQ2W ixekizumab every 2 wks, *IXEQ4W* ixekizumab every 4 wks, *PBO* placebo, *n* number of patients in analysis category, *N* number of patients in analysis population

2.15
Preliminary results from the nationwide Austrian register for reproduction and rheumatic disease (rhePro register)

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Aim: Data is limited regarding pregnancies and family planning with inflammatory rheumatic diseases. In May 2017, in the hope to collect more experience and data in this topic the nationwide Austrian Register for Reproduction and Rheumatic disease (RhePro Register) was established at the Medical University of Vienna.
Methods: The RhePro Register is a prospective nationwide, web-based longitudinal observational cohort study. Pregnant patients with confirmed diagnosis of inflammatory rheumatic disease are eligible to be enrolled until the 20th week of pregnancy or patients who wish to conceive. Clinical and laboratory course of rheumatic disease, the course of pregnancy, maternal and fetal complications during and after pregnancy and information of pharmaceutical treatment throughout the pregnancy and 3 years postpartal will be documented and collected. The collected data is pseudoanonymized and data handling is conform with the data protection policy.
Results: The RhePro Register started on 15th of May 2017. Until the end of January 2018, 89 patients were recruited. 36 pregnant women delivered their children, 17 women are currently pregnant and 36 women are in prae-

conceptional care. Of these patients 31 suffered from systemic lupus erythematosus, 11 from Sjögrens syndrome, 7 had other connective tissue diseases, 22 rheumatoid arthritis, 10 spondyloarthritis, 2 juvenile idiopathic arthritis, 2 psoriatic arthritis, and 3 systemic vasculitis. Average birthweight of the newborn was 2895 gr, average gestations week at delivery was 38 weeks. 9/36 (25 %) of the newborn were either small for gestational age (*n*=7 SGA) or had an intrauterine growth restriction (*n*=2 IUGR) and 75 % of the newborn were appropriate for gestational age (AGA) at delivery. Pregnancy complications included 1 HELLP syndrome, 6 patients experienced preterm delivery before gestational week 37, one patient had a postpartal deep venous thrombosis, 6 newborn were admitted to the neonatal intensive care unit postpartal, one child had a complex heart malformation.
Conclusion: The Austrian RhePro Register is launched. We hope to contribute to the present knowledge of patients with inflammatory rheumatic disease and pregnancy or present family planning.

2.16
Thickness of the pleura decreases significantly during therapy with rituximab and mycophenolate mofetil in systemic sclerosis

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Aim: Transthoracic lung ultrasound (TTLU) detects several sonographic artefacts that correlate with interstitial lung disease (ILD) in systemic sclerosis (SSC). Notably, an increase of the pleura thickness of about 2,8 mm is common in SSC. We investigated the thickness of the pleura in patients treated with rituximab and mycophenolate mofetil in comparison to patients without treatment.
Methods: A TTLU was performed in 37 consecutive SSC patients to monitor the occurrence and severity of sonographic changes. TTLU was performed with a linear and an abdomen sonography probe by an experienced investigator in lung ultrasound. The following ultrasound findings were documented in each study patient: B-lines, subpleural nodes and irregularities and thickness of the pleura on 24 areas at the right and left side of the lung. Group comparisons were performed between SSC patients under immunosuppressive therapy with rituximab and mycophenolate mofetil (*n*=12) and without therapy (*n*=25).
Results: The mean age of our SSC cohort was 53.2±9.4 years, 84 % were female and 48 % had lung involvement. There was no difference of disease duration between the treatment and non-treatment group (6.33±3.20 vs 6.5±5.53 years, $p>0.05$ [mean±standard deviation]). We found a statistically significant difference in pleura thickness between the groups without and after treatment with rituximab and mycophenolate mofetil (median [minimum-maximum] with vs. without treatment): left side of the lung (0.97 mm [0.6–2.7] vs. 1.6 mm [1.14–2.34], $p<0.001$) and right side of the lung (0.91 mm [0.64–2.38] vs. 1.68 mm [1.06–2.54], $p<0.001$).
Conclusion: Lung ultrasound might be a new, non-invasive and cheap imaging tool in the surveillance of ILD in SSC patients. Interestingly, the thickening of the pleura seems to be reversible; it might be an indicator of active, inflammatory lung involvement in SSC-ILD.

2.17
CRP changes during bacterial infections in baricitinib-treated patients with RA

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Aim: Baricitinib (BARI) is a selective inhibitor of Janus kinase 1/2, modulating responses to inflammatory cytokines, e.g. interleukin (IL)-6 or interferons (IFNs). During acute inflammation, including those caused by bacterial infections (BI), IL-6 induces hepatic C-reactive protein (CRP) synthesis; elevated CRP levels often represent a nonspecific, yet clinically useful marker of infections. IL-6 blockers can lead to blunting of CRP signals. This analysis evaluated CRP levels during BI in rheumatoid arthritis (RA) patients treated with BARI or placebo (PBO).
Methods: Using a high sensitivity (hs) assay, CRP values were obtained from patients with moderate to severe active RA pooled from the BEAM, BUILD and BEACON studies who were treated with BARI 4-mg or PBO for 24 weeks and had BI TEAEs (**Tab. 1**). Patient inclusion was based on the experience of ≥1 BI before rescue and availability of a CRP measure within ± 3 days of the start of the BI. Multiple CRP measures per patient were aggregated into the median resulting in 2 observations per patient

Tab. 1 Preferred Terms* for Bacterial Infectious Events

Acute tonsillitis, Arthritis infective, Atypical pneumonia, Bacterial infection, Bronchitis bacterial, Bronchopneumonia, Campylobacter gastroenteritis, Cellulitis, Cystitis, Ear infection, Escherichia urinary tract infection, Eye infection, Folliculitis, Gingivitis, Infected skin ulcer, Lobar pneumonia, Lung infection, Mycobacterial infection, Periodontitis, Pharyngitis bacterial, Pneumonia, Pulmonary tuberculosis, Sinusitis bacterial, Staphylococcal infection, Tonsillitis bacterial, Tuberculosis, Upper respiratory tract infection bacterial, Urinary tract infection, Urinary tract infection bacterial, Vaginitis bacterial, Wound infection, Wound infection staphylococcal

*Bacterial infections defined as per MedDRA Version 18.0

Tab. 2 Baseline Demographics and Disease Characteristics

Patients with bacterial infection and CRP data available (pooled from phase 3 studies BEAM, BEACON and BUILD)	Placebo (*n*=30/ N=892)	Baricitinib 4-mg (*n*=36/N=891)
Age, years	47.8 (12.6)	51.8 (11.8)
Female, n (%)	30 (100)	35 (97.2)
Duration of RA[a], years	8.2 (6.6)	8.8 (7.9)
Baseline MTX use, yes, n (%)	27 (90)	33 (91.7)
Glucocorticoid use, yes, n (%)	19 (63.3)	18 (50)
ACPA positive, n (%)	22 (73.3)	27 (75)
RF positive, n (%)	26 (86.7)	30 (83.3)
SJC, swollen joint counts of 66	14	16.2
CRP, mg/L	22.6	16
ESR, mm/hour	44.3	39.1
CDAI	39.2	39.9
DAS 28-ESR	6.5	6.4
DAS28-CRP	5.9	5.8

Data are mean (SD) unless otherwise indicated
[a]Time from RA diagnosis
ACPA anti-citrullinated peptide antibody, *BMI* body mass index, *CDAI* Clinical Disease Activity Index, *DAS28* Disease Activity Score 28 joints, *ESR* erythrocyte sedimentation rate, *CRP* C-reactive protein, *MTX* methotrexate, *N* overall population, *n* patient population, *RA* rheumatoid arthritis, *RF* rheumatoid factor, *SD* standard deviation RA studies
BEAM (MTX-IR study population), BEACON (bDMARD-IR study population), BUILD (cDMARD-IR study population)
bDMARD biological disease-modifying antirheumatic drugs, *cDMARD* conventional disease-modifying antirheumatic drugs, *IR* inadequate response, *MTX* methotrexate

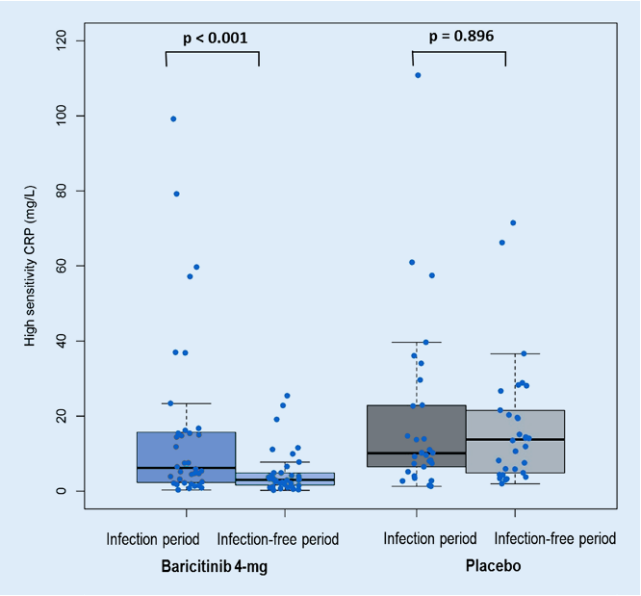

Fig. 1 ▲ Distribution of the CRP (mg/L) values per patient within treatment and infection status. CRP values during bacterial infection period (measured ± 3 days around the start of infectious TEAE) and during infection-free period (measured ± 2 weeks of bacterial infectious TEAE) are shown. During the infection period, only 3 patients (2 BARI, 1 PBO-treated) had 2 CRP measures; all others had 1 CRP. During the infection-free period, all patients had multiple CRP measures. Multiple CRP measures per patient were aggregated into the median, resulting in 2 observations per patient corresponding to the infection and infection-free period, shown as blue dots. For each treatment, the *p*-values correspond to the comparison of CRP within patients between infection and infection-free period from Wilcoxon Signed-Rank test

corresponding to the infection and infection-free period (Figure). Paired comparisons between CRP at infection and infection-free states were done within the same patients for each treatment group and *p*-values for the two differences were obtained from a Wilcoxon Signed-Rank test.

Results: Overall, 36 and 30 patients treated with BARI and PBO (**Tab. 2**) had CRP values during BI TEAEs, of which 60 % were urinary tract infections. For BARI, the median CRP were 6.2 and 3.0 mg/L in the infection and infection-free period, (p<0.001; **Fig. 1**) and the maximum values were 99.2 and 25.4 mg/L, respectively. For PBO, the median CRP were 10.1 and 13.7 mg/L for the infection and infection-free period (p=0.896); and the maximum values were 110.8 and 71.4 mg/L.
Conclusion: CRP remains a useful monitoring tool for BI in BARI-treated patients. CRP elevations were observed in BARI-treated patients during BI, with no apparent blunting of response. In the PBO patients, elevations of CRP also were observed in infection-free periods, in line with the presence of active RA, and these values may be comparable to the CRP values observed on those patients during a BI.

2.18
Efficacy of pharmacological treatment in rheumatoid arthritis: a systematic literature review informing the 2019 update of the EULAR recommendations for management of rheumatoid arthritis

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Aim: Via a systematic literature review of contemporary efficacy data of pharmacological therapies in RA we sought to inform the 2019 update of the EULAR recommendations for the management of RA.
Methods: A systematic literature review to investigate the efficacy of any DMARD (conventional synthetic (cs) DMARD, bDMARD, tsDMARD) or glucocorticoid (GC) therapy in patients with RA. MEDLINE, Embase and the Cochrane Library were searched for articles published between 2016 and March 8th 2019. Open-label studies were acceptable for strategy trials or trials investigating treatment changes.

Tab. 1 Head-to-head studies investigating biological DMARDs or tsDMARDs versus other biological DMARDs

Population	Study	Agent	Control	Type	RoB	PEP
Biological DMARDs						
MTX-IR	Burmester 2017 (MONARCH)	Sarilumab mono (Anti-IL6)	Adalimumab mono	S	Low	Met
	Smolen 2016 (EXXELERATE)	Certolizumab-pegol (anti-TNF)	Adalimumab	S	Low	Not met
	Genovese 2018	ABT-122 (anti-TNF/IL17A)	Adalimumab	S	Low	Not met
	Taylor 2018 (SIRROUND-H)	Sirukumab mono (anti-IL6)	Adalimumab mono	S	Low	Met
csDMARD-IR	Porter 2016 (ORBIT)	Rituximab (anti-CD20)	Anti-TNF	NI	High	Met
TNFi-IR	Blanco 2017 (NURTURE 1)	Secukinumab (anti-IL17)	Abatacept	S	Low	Not met*
Mixed cs/bDMARD-IR	Weinblatt 2018 (EARTH EXPLORER 2)	Mavrilimumab (anti-GM-CSF)	Golimumab	S	Low	Not met
Targeted synthetic DMARDs						
MTX-IR	Taylor 2017 (RA-BEAM)	Baricitinib+MTX	Adalimumab + MTX	S	Low	Met
	Fleischmann ACR 2018 (SELECT-COMPARE)	Upadacitinib+MTX	Adalimumab + MTX	S	Abstract	Met
	Fleischmann 2017 (ORAL-Strategy)	Tofacitinib mono Tofacitinib + MTX	Adalimumab + MTX	NI	Low	Not Met Met

RoB Risk of Bias, *PEP* Primary efficacy endpoint, *Type* Superiority (S), Non-inferiority (NI)
*superior to placebo, not superior to active comparator

Results: Of 7876 unique abstracts 234 were selected for detailed review with 136 finally included. Twenty-one studies investigated the efficacy of bDMARDs vs. placebo, with 14 studies meeting their primary efficacy endpoint (PEP). Seven head-to-head (H2H) trials comparing bDMARDs and three H2H trials comparing tsDMARD to bDMARDs were included (**Tab. 1**). Twenty placebo-controlled trials demonstrated efficacy of JAK inhibitors across different patient populations. Two studies investigated switching of bDMARD therapy in TNFi primary non-responding patients: one trial evaluated the superiority of switching to non-TNFi bDMARDs and met its PEP, while the second evaluated superiority of switching from adalimumab to certolizumab-pegol (CZP) but did not meet its PEP. Stopping or tapering of bDMARDs and/or csDMARDs/GCs was investigated in 22 studies. Using concomitant csDMARDs when tapering bDMARDs lowered the risk of flaring, while tapering csDMARDs in patients with ongoing bDMARD therapy increased the risk of flaring in most studies. All studies investigating biosimilars (n=17) showed non-inferiority compared to their reference products. Further, switching between bDMARD originators and their respective biosimilars showed non-inferiority across all studies (n=11). An open-label strategy trial compared an MRI-guided treat-to-target (T2T) strategy to a conventional T2T strategy (using DAS28-CRP) and failed to show any benefit regarding clinical outcome or radiographic progression.
Conclusion: The efficacy of many different bDMARDs as well as tsDMARDs was shown in studies included in this SLR. Switching to TNFi or non-TNFi bDMARDs after TNFi treatment failure seems to be feasible. Tapering of bDMARDs as well as csDMARDs is possible in patients achieving long-standing clinical remission but may increase the risk of disease flare. Biosimilars were non-inferior to their reference products.

2.19
Rheumatologische Versorgung im ländlichen Raum – das Rheumabus Projekt 2018

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Ziel: Rheumatologische Versorgung ist immer noch regional unterschiedlich verfügbar. Auf Initiative der Österreichischen Rheumaliga (Patientenliga) und der Österreichischen Gesellschaft für Rheumatologie und Rehabilitation (ÖGR) entstand das Projekt, 13 Jahre nach einem ähnlichen Projekt* (damals mit dem Focus auf Ballungszentren), Informationen betreffend Rheumatologie mit einem tourenden Bus direkt zu Betroffenen und Interessierten, diesmal im ländlichen Raum zu bringen. („Rheuma Bus on Tour"). Ein Team von RheumatologInnen und ehrenamtlichen MitarbeiterInnen stand im Bus zur Verfügung, um Informationen und Beratung vor Ort anzubieten.
Methoden: Im Zuge dieses Projekts erhoben die teilnehmenden Rheumatologen Art und Ausmaß der muskuloskelettalen Beschwerden bei Betroffenen, erstellten eine Verdachtsdiagnose und berieten bezüglich des Weiteren diagnostischen und therapeutischen Vorgehens. Die Erhebung erfolgte an Hand eines einseitigen anonymisierten Fragebogens.
Ergebnisse: Von 12. bis 17.10.2018 machte der Rheumabus in 16 österreichischen Städten für je 2 h Station. Insgesamt haben 647 Personen (im Durchschnitt 42 Personen pro Standort) die Gelegenheit zur Beratung genutzt. 75,7 % der Personen waren Frauen. 98 % der TeilnehmerInnen waren sehr zufrieden oder zufrieden mit der Veranstaltung bzw. der Beratung. 50 % hatten eine Beschwerdedauer bis zu 5 Jahren und 10 % bereits Beschwerden seit 18 Jahren und länger. 50 % waren in hausärztlicher Betreuung, 33 % bei einem Rheumatologen, weitere 15,5 % bei einem Facharzt für Orthopädie. 576 Personen haben das Schmerzausmaß angegeben, die häufigste Nennung in einer numerischen Skala von 0–10 war 5. 104 Personen (17 %) waren bisher noch nicht in ärztlicher Betreuung und gaben tendenziell ein niedrigeres Schmerzausmaß an.
Schlussfolgerung: Der Rheumabus wurde überwiegend von Frauen frequentiert. Rund 1/3 (33 %) der Befragten waren schon in rheumatologischer Betreuung und holten eine Zweitmeinung ein, was Rückschlüsse auf die Versorgungsdichte zulässt. Im Vergleich zu einem ähnlichen Projekt 2005, wo der Anteil der Personen, die bisher keinerlei ärztliche Betreuung hatten, 41 % betrug, war diese Gruppe 2018 mit „nur" 17 % deutlich kleiner.

Literatur

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2.20
Diagnostic performance of anti-cyclic citrullinated peptide (CCP) 2 and CCP3.1 assays in early rheumatoid arthritis

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Aim: Anti-cyclic citrullinated peptide (CCP) antibodies are the most specific markers for rheumatoid arthritis (RA). Different generations of assays (CCP1-CCP3) have been developed which show variability regarding their performance. This may have considerable impact on diagnostic decision making because serological testing is an important diagnostic tool especially in the early stages of disease. Therefore the comparability of different assays is an important issue to address.
Methods: This study aimed to investigate the diagnostic performance of IgG and IgA anti-CCP2 detected by EliATM (Thermo Fisher Scientific) compared to the combined IgG/IgA Quanta LiteR anti-CCP3.1 assay (Inova Diagnostics) in sera of 184 early RA patients, 98 healthy subjects and 360 disease controls.
Results: Anti-CCP2 IgG and IgA assays showed high specificity versus healthy subjects (98.9%; 98%) and disease controls (98.8%; 99.4%) (**Tab. 1**). Sensitivity was 52.2% for the IgG and 30.4% for the IgA assay, respectively, resulting in high positive likelihood ratios (LR+) of 47.5 (IgG) and 50.7 (IgA). However, IgA antibodies did not show an added diagnostic value since all positive patients were also IgG positive. The anti-CCP3.1 assay was slightly more sensitive than the anti-CCP2 IgG assay (55.4%) but specificity was markedly lower and amounted to 95.9% versus healthy subjects and 90.8% versus disease controls resulting in a LR+ of only 6.0. Out of 360 disease controls 33 (9.2%) were found to be positive for CCP3.1 but among these only four (1.1%) were positive for anti-CCP2 IgG (and 2 of these also for anti-CCP2 IgA). The most common diagnosis of CCP3.1 positive control patients was osteoarthritis (12 patients); six patients suffered from spondyloarthropathies, two patients had reactive arthritis, 10 patients were diagnosed with an autoimmune rheumatic disease (AI RMD) and two patients had osteoporosis. However, at a cut-off of 60 AU/ml only nine disease controls remained positive (3 OA, 1 SpA, 4 AI RMD, 1 ReA) and 3 of them were also positive in the anti-CCP2 as-

Tab. 1 Specificity, sensitivity and positive likelihood ratio (LR+) of CCP2 (IgG, IgA) and CCP3.1 assays

	CCP3.1	CCP2 IgG	CCP2 IgA
Cut-off (U/ml)	20	10	10
Patients positive (n)	102	96	56
Specifity % (healthy subjects)	95.9	99.0	98.0
Specifity % (disease controls)	90.8	98.9	99.4
Sensitivity %	55.4	52.2	30.4
LR+ (healthy)	13.5	52.0	15.2
LR+ (disease controls)	6.0	47.5	50.7

say (ReA, SpA, SLE). When applying 60 AU/ml (high positive) as cut-off value at the early RA cohort, sensitivity (52.7%) became comparable to the anti-CCP2 assay and both specificity (97.5%) and LR+ (21.08) increased substantially.
Conclusion: Thus, when interpreting the results of CCP assays disease specificity should be taken into account in order to reduce the risk of a false positive diagnosis.

2.21
Anti-RA33 antibodies as diagnostic markers in early rheumatoid arthritis

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Aim: Anti-RA33 antibodies have been observed in rheumatoid factor (RF) and anti-citrullinated protein antibodies (ACPA) negative patients, and thus may provide added diagnostic value of early rheumatoid arthritis (RA). This study aimed to investigate the prevalence and diagnostic value of RA33 antibodies in patients with early RA.
Methods: Sera from an investigation cohort (Vienna early RA cohort) comprising 134 early RA patients as well as a validation cohort (Leeds early RA cohort) of 131 early RA patients (both satisfying 2010 ACR/EULAR classification criteria) were tested for the presence of IgA, IgG and IgM isotypes of anti-RA33 antibodies, which were detected by newly developed prototype assays using the EliA™ platform (Thermo Fisher Scientific). The cut-off values were chosen to achieve specificities of ≥95 % against disease controls and 98 % against healthy subjects [1]. In addition, RF-IgM as well as ACPA-IgG was detected by EliA™ (Thermo Fisher Scientific).
Results: In the investigation cohort anti-RA33 antibodies were detected in 15.7 % of early RA patients. The anti-RA33 IgM isotype showed the highest sensitivity (10 %) followed by IgG (6 %) and IgA (3.7 %) isotypes. Importantly, anti-RA33 antibodies were detected in 8 out of 51 seronegative patients, reducing the 'serological gap' left by RF and ACPA routine testing by 15.7 %. Interestingly, the prevalence of anti-RA33 antibodies in the validation cohort was considerably higher with 37.4 % of patients positive for at least one anti-RA33 antibody isotype. The highest sensitivity was found for the anti-RA33-IgG isotype (20.6 %) followed by IgA (16 %) and IgM (14.5 %). 12 out of 49 seronegative patients had anti-RA33 antibodies, resulting in an added diagnostic value of 24.5 %.
Conclusion: This study suggests anti-RA33 antibody testing may aid in the diagnosis of (otherwise labelled seronegative) early RA. The wide-ranging prevalence in the tested cohorts however implies variable diagnostic power. Further investigation may clarify whether genetic and environmental factors influence anti-RA33 antibody development.

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3 Kinderrheumatologie

3.1
Paradoxical psoriasis in a child with CNO under adalimumab treatment—improvement of skin and bone symptoms under tofacitinib—case report and review of literature

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Aim: Paradoxical inflammatory reactions including psoriasis, Crohn's disease or uveitis related to TNF-inhibitors have been described. The diagnosis often reveals to be challenging, as well as treatment strategies.
Methods: We will present the case of a child with a long-term history of severe relapsing chronic non-bacterial osteomyelitis (CNO) that developed paradoxical psoriasis under treatment with adalimumab. The common therapy strategies for CNO (including methotrexate, TNF-inhibitors, bisphosphonates) did not bring significant and consistent improvement and control of disease activity.
Results: The initiation of tofacitinib brought a fast improvement of the skin affection and even led to a reduction of bone inflammation.
Conclusion: The JAK-inhibitor Tofacitinib developed to be a therapeutic option for severe autoimmune diseases including rheumatoid arthritis and psoriasis-arthritis. To date, no JAK-inhibitor is approved for the pediatric population. In special cases, that are resistant to other therapeutic options as described above, we assume that the treatment with JAK-inhibitors could be a contemplable off-label alternative for selected patients.

3.2
Fäkales Calprotectin zur Detektion Chronisch entzündlicher Darmerkrankungen bei Juveniler idiopathischer Arthritis

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Ziel: Die Assoziation chronischer Gelenks- und Darmentzündungen ist bekannt. Therapiestrategien bei juveniler idiopathischer Arthritis (JIA) und chronisch entzündlichen Darmerkrankungen (CED) sind ähnlich, jedoch sind nicht alle Therapeutika bei beiden Erkrankungen wirksam. Daher sollte eine CED vor Therapiebeginn der JIA ausgeschlossen werden. Gastrointestinale Symptome und serologische Entzündungsparameter sind dafür nur unzureichend geeignet. Fäkales Calprotectin (FCP) ist als sensitives, nicht-invasives Screeningtool zur Diagnose einer CED etabliert. Daten zum Einsatz von FCP zur Diagnose einer assoziierten CED bei JIA-PatientInnen sind rar. Das Ziel der Studie war, FCP als Screeningtool zur Frühdiagnose einer CED bei JIA zu untersuchen. Dazu wurde die Höhe des FCP von PatientInnen mit CED (JIA-CED) und ohne bestätigte CED (JIA-non-CED) verglichen sowie eine Assoziation zu den JIA-Subtypen untersucht.
Methoden: Retrospektive single-center Analyse von FCP-Werten aller, zwischen März 2012 und August 2019, vorgestellten PatientInnen mit der Diagnose JIA nach den ILAR-Kriterien, aller Subtypen, unter Ausschluss der systemischen Form, vor Einleiten einer DMARD-Therapie. FCP-Werte unter 100 µg/g wurden als normal eingestuft. Bei PatientInnen mit erhöhten FCP1-Werten erfolgten konsekutive Bestimmungen (FCP2, FCP3). Bei persistierend erhöhten Werten erfolgte die weiterführende Diagnostik mit Sonografie und Endoskopie mit histologischer Bestätigung einer CED.
Ergebnisse: 156 JIA-PatientInnen (w:134, m:41) wurden evaluiert. Subtypen: OligoA *n*=86, PolyA *n*=19, EAA *n*= 28, PsoA *n*=23, undiffA *n*= 1; ANA pos *n*=78, HLA-B27 pos *n*=28, RF pos *n*=9. 25/156 PatientInnen (16,0 %) hatten ein erhöhtes FCP1 (median: 25,5; range: 20–1123 µg/g). 9/25 hatten auch ein erhöhtes FCP2. Bei 5/9 PatientInnen wurde die Diagnose CED (Mb. Crohn, *n*=5) gestellt, entsprechend 3,2 % aller untersuchten PatientInnen. FCP-Werte der JIA-CED-Gruppe unterschieden sich von jenen der JIA-non-CED-Gruppe in der Höhe (median[range];

FCP1: 787[489–1123] vs 22,5[20–764] µg/g; FCP2: 1110[931–>1800] vs 20,5[20–332] µg/g) Im FCP3 lagen alle CED PatientInnen über dem messbaren Bereich (>1800) und die Kontrollen bei 20[x–y] (median[range]) und Dynamik. Während die konsekutiven FCP-Werte in der JIA-CED-Gruppe kontinuierlich anstiegen, sanken sie in der JIA-non-CED-Gruppe, mit Normalisierung bei allen bis zur FCP3-Bestimmung. 2 der 5 CED-PatientInnen hatten zum Zeitpunkt der Diagnose keine gastrointestinalen Symptome. Erwartungsgemäß zeigte sich eine Assoziation zwischen CED und EAA (n=3), PsoA (n=1) und ANA-neg. Oligoarthritis (n=1).
Schlussfolgerung: Initiale FCP-Werte über 489 µg/g, ansteigende konsekutive FCP-Werte und ein EAA-Subtyp waren mit einer CED assoziiert. Unsere Daten zeigen, dass die Bestimmung des FCP bei JIA-PatientInnen als Screeningtool zur Detektion einer CED geeignet ist.

4 Rehabilitation

4.1
Medizinisch-berufsorientierte Rehabilitation (RehaJET®): Korrelation Lebensqualität (EQ-5D) mit beruflich funktioneller körperlicher Leistungsfähigkeit (PACT/EFL)

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Ziel: Das Ziel der medizinischen berufsorientierten Rehabilitation liegt in der Wiederherstellung der Arbeitsfähigkeit des betroffenen Patienten und damit in einer nachhaltigen beruflichen Wiedereingliederung (Seidel et al., 2015). Innerhalb der Pensionsversicherungsanstalt in Österreich wird nun ein neues Konzept, basierend auf Job, Erwerbsfähigkeit und Teilhabe, der PVA-RehaJET®, in ein multidisziplinäres Rehabilitationsprogramm von berufstätigen PatientInnen mit besonderer Problemlage im Stütz- und Bewegungsapparat implementiert. Das RehaJET®-Programm gliedert sich in zwei Stufen. Stufe I betrifft alle aktiv versicherten PatientInnen und findet eingebettet in einem 3-wöchigen medizinischen stationären Reha-Aufenthalt statt. Die Stufe II ist ein medizinisch-berufsorientiertes Programm und dauert zwischen 4–6 Wochen. In Abhängigkeit von der Problemlage und der Arbeitsplatzsituation werden das Reha-Programm und das Training im speziell eingerichteten Workpark® (Fa. Matzka Rehatechnik) festgelegt und auf spezielle Belastungssituationen gezielt individuell eingegangen. Integriert sind valide Screening-Instrumente wie der SIMBO_C (Streibelt et al., 2007), welcher den Bedarf an beruflicher Rehabilitation analysiert, weiters die funktionelle Leistungsfähigkeit mittels EFL-Test (Frank et al., 2003) sowie der EQ-5D-Lebensqualitätsfragebogen (Herdman et al., 2011). Speziell die EFL-Testung dient als Basis für das Reha-Programm bzw. Abklärung einer beruflichen Wiedereingliederung.
Methoden: Zur Einschätzung der beruflichen Problemlage erfolgt die SIMBO_C-Befragung, eine Beurteilung durch das RehaJET®-Team (Ärzte, Therapeuten, Psychologen) und ein Gespräch mit dem eigenen Teilhabe- und Entlassungsmanagement. Alle aktiv versicherten PatientInnen erhalten RehaJET®-Stufe I. Unter Berücksichtigung aller Informationen und Fakten kann eine Zuteilung zur Stufe II, der medizinisch-berufsorientierten Reha, erfolgen. Am Beginn des aktiven berufsorientierten Reha-Programms (RehaJet Stufe II) wird neben dem SIMBO_C die funktionelle Leistungsfähigkeit evaluiert (EFL) und der Gesundheitszustand ermittelt. Bei PatientInnen der RehaJET® Stufe I (n = 640) und Stufe II (n = 50) wird am Beginn des Rehabaufenthaltes SIMBO_C und EQ-5D erhoben. RehaJET® Stufe II-PatientInnen erhalten eine EFL-Testung inklusive der Bestimmung einer Einschätzung der subjektiv wahrgenommenen Behinderung und der Leistungsbereitschaft eines Patienten (PACT—Standardisierter Fragebogen zur Selbsteinschätzung der körperlichen Leistungsfähigkeit) (Matheson et al., 1993).
Ergebnisse: Eine Charakterisierung potentieller RehaJET®-PatientInnen unter Verwendung der SIMBO_C-Daten ergab bei RehaJET® I-PatientInnen, die innerhalb eines Monats aufgenommen wurden (n = 140), dass 47 % der befragten aktiv Versicherten, aktiv im Krankenstand waren. 63,5 % der befragten PatientInnen gaben an, innerhalb des letzten Jahres 1–25 Wochen und 12,8 % länger als 25 Wochen in Krankenstand gewesen zu sein. Interessanterweise waren über 50 % der Patienten vollzeitberufstätig, 20 % teilzeitberufstätig und 12 % arbeitslos. Über 60 % der Befragten gaben an, in ihrem Beruf weiterarbeiten zu wollen. RehaJET® II-PatientInnen (n = 50) zeigten einen signifikant höheren durchschnittlichen Wert für SIMBO_C im Vergleich zu PatientInnen aus dem RehaJET® I (n = 640); Vergleichszeitraum war 10 Monate. Ebenso veränderte sich der allgemeine Gesundheitszustand (EQ-5D) zwischen den beiden Gruppen leicht. Der bei den PatientInnen im Zuge der EFL-Testung ermittelte PACT-Index korrelierte signifikant sowohl mit dem EQ-5D-Index wie auch dem EQ-5D VAS.
Schlussfolgerung: Die ersten Daten aus dem SIMBO_C zeichnen ein genaues Bild hinsichtlich der Arbeits- und Krankenstandsituation der Patientinnen im RehaJET® I. Der geeignete Einsatz der SIMBO_C-Befragung zur Unterstützung der Ermittlung von PatientInnen mit vorliegender beruflicher Problemlage lässt sich durch den im Durchschnitt erhöhten SIMBO_C-Wert bei RehaJET® II-PatientInnen belegen. Die beobachtete Korrelation zwischen dem PACT-Index und dem EQ-5D legt den Grundstein für weitere Untersuchungen der Selbsteinschätzung der körperlichen Leistungsfähigkeit in Abhängigkeit des allgemeinen Gesundheitszustands bei Berufstätigen. Durch gesetzliche Anhebungen des Pensionsalters und die Reduktion der Möglichkeiten eines frühzeitigen Arbeitsaustritts ist eine optimale Rückführung in den Arbeitsprozess und damit eine Aufrechterhaltung der Arbeitsfähigkeit unabdingbar. Die Etablierung der medizinischen berufsorientierten Rehabilitation steht dabei im Vordergrund und ihre Implementierung als wichtige Reha-Komponente innerhalb der Rehabilitationssysteme in Österreich ist daher von äußerster Wichtigkeit.

4.2
Influence of self-reported treatment expectations and motivations on treatment outcomes of a large cohort of patients with ankylosing spondylitis (AS), rheumatoid arthritis (RA), fibromyalgia (FM) and other chronic pain syndromes (CP) regularly attending the Gastein Healing Galleries

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Aim: The current literature on management of patients with musculoskeletal pain indicates that factors related to patient expectations and motivations are associated with both clinical outcomes, satisfaction with treatment, and influences behavior. The purpose of this study was to examine individuals' expectations and motivations with regard to their ability to predict health and well-being outcomes in a diverse sample of individuals many of which were diagnosed with rheumatological disorders and seeking treatment at the Gastein healing galleries.
Methods: Patients were 1444 individuals diagnosed with ankylosing spondylitis (23%), arthritis (22%), or fibromyalgia (9%) or individuals who were undiagnosed but seeking relief of chronic pain (46%). Average age was 58 years, about 52% were female, and almost three quarters (73%) had a high school education or less. One-third was employed, just over one-third was retired (37%), and the remaining percentage held other roles (e.g., homemaker, student, disabled, etc.). Expectations were measured using 5 items and motivations were measured using 6 items. Health and well-being measures included: pain, self-rated physical health, life-satisfaction, depression, anxiety, stress, fatigue, and sleep problems. Data were analyzed using

structural equation modeling where a latent variable was used to model the effects of expectations and motivations on health and well-being.
Results: Measurement models were used to first confirm that each construct was a unidimensional, well-fitting construct. Both one- and two-factor measurement models were estimated to determine if expectations and motivations scales were unique. The one-factor model did not fit the data well $\chi2 = 3493.64$, $p < 0.001$. The two-factor model fit the data significantly better, $\chi2 = 1208.31$, $p < 0.001$, $\chi2 = 2285.33$, $p < 0.001$ suggesting that expectations and motivations are unique constructs, though they are highly related, $r = 0.71$, $p < 0.001$. Structural models revealed that both expectations and motivations were significant predictors of health and well-being, after controlling age, sex, and education. Motivations were positively related to health and well-being (Beta = 0.33, $p < 0.001$) while expectations were negatively related to health and well-being (Beta = −0.14, $p = 0.001$). Further investigation of the paradox revealed that expectations were serving as a statistical suppressor of the relationship between motivations and health and well-being.
Conclusion: While weakly positively related to health and well-being at the bivariate level, the association between expectations and health and well-being reversed direction in the structural model and acted to increase the magnitude of the association between motivations and health and well-being. Hence, this is a classic example of net statistical suppression in which the key finding is that motivations for attending the healing galleries are an important predictor of actual health and well-being outcomes.

4.3
Self-reported treatment expectations and motivations of a large cohort of patients with ankylosing spondylitis (AS), rheumatoid arthritis (RA) and psoriatic arthritis (PA) attending the Gastein Healing Galleries regularly

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Aim: The Gastein Healing galleries combine several treatment factors such as low level radon exposure, high humidity and mild hyperthermia in a moderate altitude above sea level. Every year several thousands patients with a variety of diseases including rheumatic diseases seek treatment in this health facility. Our objectives were to assess and compare treatment expectations and motivations in a cohort of patients with AS, RA and PA attending the Gastein Healing galleries regularly.
Methods: We conducted an anonymous online survey with patients regularly attending the Gastein Healing Galleries in Bad Gastein. In this health facility approximately 12,000 patients with a variety of disease are being treated annually. Of those, 6465 patients were invited by email to fill out the survey. Socio-demographics and disease related variables (e.g. development of health condition until and since gallery sessions, pain, etc.) were assessed, including 2 blocks of questions (answer format: agree/mostly agree/slightly agree/disagree) such as `I am convinced that the Gallery sessions help me to …` (expectations) following 5 statements, e.g. ´reduce my pain` and `If I perform Gallery sessions, then I will again …` (motivations) following 8 statements, e.g. `be able to maintain my ability to work´.
Results: In total 2017 patients responded (=31 %) of which a subset of 503 respondents indicated a diagnosis of AS (73.8 %), RA (17.5 %), or PA (8.7 %). The mean age (SD) of the subset was 55.2 years (10.7) and 61.4 % were male. The current pain level was 4.1 (2.2) on a NRS. The majority attended the galleries once every year (61 %), every 2 years (13.7 %) or not regularly (10.5 %). Marked or moderate improvement of health condition until first gallery session was indicated by 16.9 % and since by 79.1 % of patients. Concerning the 5 items measuring expectations a large proportion of patients agreed or mostly agreed (62.3 % for ´strengthen my muscles´ –92.5 % for ´improve health condition`). The same picture was found for the 8 motivation items (58.6–85.8 %). Only in 4 of 13 items (expectation and motivation) there was a significant difference between the groups, i.e. patients with PA scored lower.
Conclusion: A high proportion of our cohort with AS, RA and PA reported considerable improvement in their health conditions since they perform regular visits to the galleries. Over 2/3 of all patients agreed or mostly agreed that their symptoms and pain and thus their health condition improve with gallery sessions. Patients are also highly motivated to take sessions because a large proportion feel that the galleries help them to improve physical functioning, participation and preserve their ability to work. To conclude, from our patients´ point of view regular gallery sessions have important positive effects on a variety of domains including symptoms, health status, functioning and participation and help them to improve their health condition in the future.

4.4
Stellenwert und Relevanz der Rehabilitation im Management von PatientInnen mit Rheumatoider Arthritis aus der Sicht von ÄrztInnen und Health Professionals

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Ziel: Aufgrund von effektiveren medikamentösen Therapien und damit einhergehend veränderten Krankheitsverläufen bei rheumatoider Arthritis hat sich der Stellenwert der Rehabilitation in Bezug auf die Anwendungsfelder verschoben. Waren es vor Einsatz der Biologika noch zunehmend Funktionsverluste, die im Fokus der Rehabilitation standen, sind es derzeit vor allem Themen wie Aktivität, Partizipation, Krankheitsmanagement oder PatientInnen-Edukation. Ziel dieser Studie ist es, Meinungen und Einstellungen von ProfessionistInnen in der Rheumatologie zum Thema Stellenwert und Relevanz von Rehabilitation für PatientInnen mit rheumatoider Arthritis (RA) zu erheben und darzustellen, inwieweit sich Einstellungen von Personen des Arbeitskreises (AK) Rehabilitation zu weiteren Mitgliedern der Österreichischen Gesellschaft für Rheumatologie (ÖGR) unterscheiden.
Methoden: 129 Mitglieder der ÖGR haben bei der Befragung zur Relevanz der Rehabilitation in der Rheumatologie teilgenommen. Die Fragen wurden 2017 im Rahmen einer Initiative des AK Rehabilitation der ÖGR ausgearbeitet und in einem Online Survey veröffentlicht. Neben den soziodemographischen und beschreibenden Daten zur Personen, wurden insgesamt zwei Themenblöcke erfragt: (1) Die Relevanz der Rehabilitation in Bezug auf verschiedene Interventionen, (2) der Stellenwert von Rehabilitationsmaßnahmen für die RA-PatientInnen hinsichtlich verschiedener Erkrankungszeitpunkte.
Ergebnisse: Insgesamt nahmen 129 Personen (50 % männlich, 50 % weiblich) aus ganz Österreich an der Befragung teil. Davon waren 12 Personen Mitglieder des AK Rehabilitation. 11 (8,6 %) Personen waren AllgemeinmedizinerInnen, 66 (51,6 %) FachärztInnen (FÄ) für Innere Medizin mit Zusatzfach Rheumatologie, 15 (11,5 %) FÄ für Innere Medizin, 14 (10,9 %) FÄ für Physikalische Medizin mit Zusatzfach Rheumatologie, 2 (1,6 %) FÄ für Orthopädie, 13 (10,2 %) Health Professionals und 7 (5,5 %) Personen sonstiger Berufsgruppen wie z. B. WissenschafterInnen. Die Mehrheit der Befragten (80 %) waren bereits mehr als 5 Jahre in der klinischen Betreuung von PatientInnen mit RA tätig und arbeiteten zum Großteil (51 %) im

Tab. 1 Ergebnisse Themenblock 1

Beurteilung der Relevanz bestimmter Maßnahmen und Interventionen in der Rehabilitation von RA PatientInnen von 0 (keine Relevanz) bis 10 (höchste Relevanz)	ÖGR Mitglieder			AK Rehabilitation		
	Ranking	MW	SD	Ranking	MW	SD
Ergo- und Physiotherapeutische Bewegungstherapie	1	9,4	1,00	1	9,2	1,03
Erlernen von Fingerübungen und Gelenksschutzmaßnahmen	2	9,0	1,51	2	8,5	1,73
Schulung/Information über die Erkrankung/Behandlung	3	8,4	2,05	3	8,3	2,14
Unterstützung durch PsychologInnen im Umgang mit der Erkrankung	4	7,8	2,10	4	7,5	2,15
Optimierung der medikamentösen Schmerztherapie	6	7,4	2,49	5	7,3	2,09
Begleitende Schulung durch Diätologen	7	6,3	2,77	6	6,8	2,69
Versorgung mit Schienen und Hilfsmitteln	5	7,7	2,29	7	6,7	2,87
Anwendung ergänzender passiver Therapien (Thermo- und Elektrotherapie)	8	6,0	2,71	8	5,3	1,49
Einstellung bzw. Umstellung einer bestehenden Basistherapie	9	5,3	3,52	9	4,8	3,35

Tab. 2 Ergebnisse Themenblock 2

Beurteilung des Nutzens für RA PatientInnen zu verschiedenen Erkrankungszeitpunkten 0 (keine Relevanz) bis 10 (höchste Relevanz)	ÖGR Mitglieder			AK Rehabilitation		
	Ranking	MW	SD	Ranking	MW	SD
PatientInnen mit Funktionseinschränkung	1	8,6	1,69	1	8,4	1,50
In den ersten Jahren der Erkrankung	2	7,43	2,30	2	7,3	2,38
In den ersten Monaten nach Diagnosestellung	4	6,2	3,20	3	7,3	2,00
Von einer regelmäßigen Rehabilitation im Abstand weniger Jahre	3	7,3	2,46	4	6,9	2,57
Nach einem Schub der Erkrankung	5	5,6	2,64	5	5,2	2,51
Effektivität der Rehabilitation bei PatientInnen, die im letzten Jahr eine Rehabilitation absolviert haben		7,1	1,91		7,7	1,43

stationären Bereich. Der Vergleich beider Gruppen zeigt, dass sich der AK Rehabilitation zu den weiteren ÖGR-Mitgliedern nur geringfügig unterscheidet (**Tab. 1**). Bei der Beurteilung des Stellenwerts von Rehabilitation für RA-PatientInnen zu spezifischen Zeitpunkten (**Tab. 2**) verlaufen die Einschätzungen beider Gruppen erneut ähnlich. Insgesamt schätzen beide Gruppen die Effektivität von Rehabilitationsmaßnahmen hoch ein.
Schlussfolgerung: Die Ergebnisse der Studie demonstrieren, dass sich die AK Mitglieder nur geringfügig von den anderen Mitgliedern der ÖGR in ihren Einschätzungen bezüglich Relevanz und Stellenwert der Rehabilitation unterscheiden. Folglich kann angenommen werden, dass insgesamt Rehabilitationsmaßnahmen bei RA behandelnden ÄrztInnen und Health Professionals sehr gut anerkannt werden und auch ein guter Wissensstand über Wirksamkeiten und Möglichkeiten in der Rehabilitation vorhanden ist.

4.5
Self-reported treatment expectations and motivations of a large cohort of patients with fibromyalgia (FM) and osteoarthritis (OA) attending the Gastein Healing Galleries regularly

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Aim: The Gastein Healing galleries combine several treatment factors such as low level radon exposure, high humidity and mild hyperthermia in a moderate altitude above sea level. Every year several thousand patients with a variety of diseases including osteoarthritis, rheumatic diseases and chronic pain conditions seek treatment in this health facility. Our objectives were to assess and compare treatment expectations and motivations in a cohort of patients with FM and OA attending the Gastein Healing galleries regularly.
Methods: We conducted an anonymous online survey with patients regularly attending the Gastein Healing Galleries in Bad Gastein. In this health facility approximately 12,000 patients with a variety of disease are being treated annually. Of those, 6465 patients were invited by email to fill out the survey. Socio-demographics and disease related variables (e.g. development of health condition until and since gallery sessions, pain, etc.) were assessed, including 2 blocks of questions (answer format: agree/mostly agree/slightly agree/disagree) such as `I am convinced that the Gallery sessions help me to …` (expectations) following 5 statements, e.g. ´reduce my pain´ and `If I perform Gallery sessions, then I will again …` (motivations) following 8 statements, e.g. `be able to maintain my ability to work.´
Results: In total 2017 patients responded (31%) of which a subset of 368 respondents indicated a diagnosis of FM (39.1%) or OA (60.9%) at different locations. The mean age (SD) of the subset was 61 years (10.7) and 41.3% were male. The current pain level was 4.3 (2.3) on a NRS (range 0–10). The majority attended the galleries once every year (50.3%), not regularly (27.4%) or every 2 years (10.3%). Marked or moderate improvement of health condition until first gallery session was indicated by 2.4% and since by 71.2% of patients. Concerning the 5 items measuring expectations a large proportion of patients agreed or mostly agreed (56.9% for ´strengthen my muscles´–86.6% for ´improve health condition`) with no significant differences between the patient groups. The same picture was found for the 8 motivation items (50.1–78.3%). Only in 2 items (´to perform moderate activities´/´to perform daily chores´) there was a significant difference between the patient groups.
Conclusion: A high proportion of our cohort with FM or OA reported considerable improvements in their health conditions since they perform reg-

ular visits in the galleries. Over 50% of all patients agreed or mostly agreed that their symptoms and pain and thus their health condition improve with gallery sessions. Patients are also highly motivated to take sessions because a high proportion feel that the galleries help them to improve physical functioning, participation and preserve their ability to work. To conclude, from our patients´ point of view regular gallery sessions have important positive effects on a variety of domains including symptoms, health status, functioning and participation and help them to improve their health condition in the future.

4.6
Geschlechtsspezifische Unterschiede und Erfolge in der Gesundheitsvorsorge Aktiv (GVA)

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Ziel: Die GVA wurde im April 2018 als stationäre, sekundärpräventive Gesundheitsmaßnahme für Patientinnen und Patienten mit Erkrankungen des Stütz-und Bewegungsapparates in ganz Österreich ausgerollt und ein neues Leistungsprofil etabliert. Ziel der Arbeit war die Evaluierung geschlechtsspezifischer Unterschiede hinsichtlich der Ausgangsdaten zu Beginn des Aufenthaltes sowie die Erfassung kurzfristiger Erfolge in der Medizinischen Ergebnisqualität bei Entlassung nach drei Wochen.
Methoden: Die vorliegende Arbeit stellt monozentrische Daten von Patientinnen und Patienten dar, welche zwischen April 2018 und Jänner 2019 im XXXX eine GVA absolvierten. Kennwerte der Medizinischen Ergebnisqualität (MEQ) wie Body-Mass-Index, Blutdruck und Puls, VAS-Schmerz, Alkohol- und Nikotinkonsum, Bewegungsverhalten, EQ5D und die Wattanzahl am Ergometer bei moderatem Ausdauertraining wurden zu Beginn und am Ende des Aufenthaltes erhoben. Das mittlere Alter der 1976 Patientinnen und Patienten betrug 51,2 ± 7,1 Jahre, der Frauenanteil lag bei 51,6 %. Die durchschnittliche Aufenthaltsdauer war bei 21,7 ± 1,8 Tagen.
Ergebnisse: Eine geschlechtsspezifische Betrachtung zeigte unterschiedliche Ausgangswerte zu Beginn des stationären Präventionsprogramms: Die Anzahl der übergewichtigen und adipösen Männer (79 %) überstieg jene der Frauen (62 %). Frauen berichteten über ein subjektiv höheres Schmerzempfinden (VAS: 4,9 vs. 4,6). Männer waren im Alltag körperlich aktiver (durchschnittlich 3,7 h pro Woche vs. Frauen: 3,1 h pro Woche) und wiesen eine höhere Leistungsfähigkeit am Fahrradergometer auf (92 W vs. 62 W). Mehr Männer (77 %) als Frauen (56 %) gaben an, zumindest gelegentlich Alkohol zu konsumieren. Kurzfristig verbesserten sich Frauen in subjektiven Parametern (EQ5D, EQ-VAS: Gesundheitszustand) etwas stärker und erzielten eine größere Zunahme der körperlichen Aktivität. Männer verzeichneten hingegen bei objektiv messbaren Kennwerten wie Blutdruck (−6 mmHG systolisch) und körperlicher Leistungsfähigkeit (+10 W) größere Erfolge als Frauen (−3 mmHG; +8 W). Insgesamt sprachen mehr Männer (80 %) als Frauen (75 %) auf das GVA-Programm an.
Schlussfolgerung: Die Ergebnisse bilden die Problematik von Übergewicht und Adipositas in unserem Patientenkollektiv ab. Insgesamt können durch die GVA Risikofaktoren bei beiden Geschlechtern reduziert werden. Leistungsfähigkeit und Lebensqualität verbessern sich bei mehr als zwei Drittel der Patientinnen und Patienten signifikant. Die geschlechtsspezifischen Ergebnisse zeigen unterschiedliche Bedürfnisse von Männern und Frauen auf und sollten daher im Behandlungskonzept Berücksichtigung finden.

5 Sonstiges

5.1
ÖGR-Summer School – effiziente Initiative zur Förderung des rheumatologischen Nachwuchses

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Ziel: Hintergrund: Rheumatologie ist ein Fachgebiet, das im aktuellen Medizincurriculum unterrepräsentiert ist, weswegen Studenten damit zu wenig oder gar nicht in Berührung kommen. Das ist ein wesentlicher Grund für ein sich in Österreich entwickelndes Nachwuchsproblem in der Rheumatologie. Ziel: Die Österreichische Gesellschaft für Rheumatologie und Rehabilitation (ÖGR) hat 2017 eine Summer School ins Leben gerufen, mit dem Ziel, nicht nur das rheumatologische Defizit im Ausbildungscurriculum zu schließen, sondern damit auch den rheumatologischen Nachwuchs zu fördern.
Methoden: Seit 2017 wird die ÖGR – Summer School an fünf österreichischen Medizinuniversitäten für Studierende des 5. und 6. Jahres über die Hauptvorlesung und die Studentenvertretung (Österreichische Hochschülerschaft) angekündigt, mit dem Aufruf, sich um eine Teilnahme zu bewerben. 2017 und 2018 wurden je 30 bzw. 36 Plätze an Studierende aus Österreich, Deutschland und Italien vergeben. Die Veranstaltung wurde mittels anonymer Fragebögen evaluiert und die weitere berufliche bzw. wissenschaftliche Entwicklung der Teilnehmer in Richtung Rheumatologie mittels Interviews nachverfolgt.
Ergebnisse: 2017 und 2018 beurteilten 93,3 % bzw. 100 % der Studenten die Veranstaltung insgesamt mit „sehr gut“. 2017 gaben 80 % der Studenten einen absoluten Wissenszuwachs durch die Summer School bzw. 16,7 % größtenteils an, 2018 waren es 71,4 % bzw. 28,6 %. 2017 gaben 13,3 % an, dass sich ihr Wunsch, Rheumatologe/Rheumatologin zu werden, „sehr verstärkt“ habe, 56,7 % gaben “eher verstärkt” an, 2018 waren dies 25,7 % bzw. 60 %. 2017 besuchten 14 (47 %) der Teilnehmer in Folge der Summer School die ÖGR-Jahrestagung, 2018 waren es 18 Teilnehmer (50 %). Es konnten 2017 und 2018 je 4 (13,3 % bzw. 11 %) Teilnehmer für wissenschaftliche Projekte bzw. die rheumatologische Ausbildung gewonnen werden. 2017 und 2018 gaben 100 % der Teilnehmer an, die Summer School anderen Studenten weiter empfehlen zu wollen.
Schlussfolgerung: Die ÖGR Summer School wurde von der großen Mehrzahl der Studenten mit „sehr gut“ evaluiert. Das Ziel, Studenten mit der Rheumatologie vertraut zu machen und Jungmediziner für die Rheumatologie zu begeistern, wurde erreicht.

5.2
Dose-dependent cannabidiol-induced elevation of intracellular calcium and apoptosis in human articular chondrocytes

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Aim: Osteoarthritis (OA) is a major public health problem among the increasing aged and obese population, therefore development and investigation of new therapeutics is a major focus of OA research. Endocannabinoids (ECs), cannabinoids derived from the Cannabis sativa plant and synthetic cannabinoids have been attributed anti-inflammatory, antitumorigenic, analgesic and psychoactive effects. Over recent years increasing interest in the EC system as a target for therapeutic treatment of joint diseases has emerged. Cannabidiol (CBD) is the most abundant non psychoactive compound of Cannabis sativa extracts and has been shown to have anti-arthritic potency in animal models. In the present study we investigated the effects of CBD on the cell viability and Ca^(2+) homeostasis in human articular chondrocytes.

Methods: Cell viability, discrimination of intact, apoptotic and necrotic cells and caspase 3/7 activity were determined by Resazurin assays, Annexin-V/7-AAD staining followed by flow cytometry and caspase-Glo 3/7 assay respectively. Intracellular Ca^(2+) was monitored by time-lapse fluorescence imaging. The perforated whole-cell patch clamp technique was used for measuring the cell membrane potential. Western blot analysis was performed for the quantification of Erk1/2 phosphorylation.
Results: C28/i2 and human primary chondrocytes showed a significantly reduced viability with an apoptosis maximum at 10 µM CBD after treatment with rising amounts of CBD. This apoptotic effect was accompanied by an increase of caspase 3/7 activity. Flow cytometry analysis of Annexin-V/7-AAD stained cells revealed a decline of intact cells and a significant dose dependent increase of the early apoptotic cell population after treatment with CBD. CBD significantly elevated intracellular Ca_i^(2+) accompanied by a depolarization of the cell membrane. This increase of Ca_i^(2+)was abrogated, when Ca^(2+)was omitted from the bath solution indicating an influx of extracellular Ca^(2+)rather than depletion of internal stores. Several blocking substances were tested to identify the channel/receptor responsible for this Ca^(2+) influx. Cannabinoid receptor1 (CB1) antagonist AM251 significantly inhibited the Ca^(2+) influx triggered by CBD. Moreover, preincubation of chondrocytes with AM251 significantly reduced the toxic effects of CBD. Looking for mediators of the apoptotic CBD effect downstream of the CB1 receptor enhanced Erk1/2 phosphorylation could be detected. However this Erk1/2 activation proved to be unaffected by CB1 receptor blockage.
Conclusion: Micromolar concentrations CBD induce apoptosis in human articular chondrocytes. CBD also triggers an influx of extracellular Ca^(2+) and potentiates Erk1/2 phosphorylation. The apoptotic effects are at least partially mediated by the CB1 receptor indicated by an increased cell viability and reduction of caspase activity after combined treatment with CBD and CB1 antagonist AM251. Since CBD induced Erk1/2 phosphorylation seems to be independent of CB1 signalling, the involvement of other signalling pathways and/or a crosstalk with other Ca^(2+) channels or receptors seems likely and will be the focus of further investigations.

5.3
Therapeutic nuclear magnetic resonance therapy (NMRT) influences the miRNA profile and the hypoxic behavior of human chondrocytes stimulated by IL-1beta

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Aim: Osteoarthritis (OA) is the most common joint disease characterized by progressive degradation of articular cartilage, synovial hyperplasia, bone remodeling and angiogenesis. As the main consequences, patients suffer from loss of function and joint pain, followed by psychological distress and significant restrictions in daily living. While OA induced pain represents the most frequent cause of chronic pain, its mechanisms are poorly understood and treatments are not satisfactory. The development of more effective and in particular non-invasive methods to gain pain reduction of OA patients therefore is of exceptional interest. Clinical trials based on therapeutically applied nuclear magnetic resonance (NMRT) embedded within the treatment of patients with degenerative rheumatic diseases revealed pain reduction as the main clinical outcome. Improvements in pain of patients with low back pain or knee OA have been documented, the latter being explained by chondroprotective effects on the articular cartilage induced by NMRT. It is in addition noteworthy to mention that the observed reduction in pain sustained for up to one year. While NMRT is discussed to participate in repair processes regarding cartilage and may influence pain signaling, the mechanisms of action of NMRT at the cellular level remain to be illuminated. To substantiate the application of NMRT this work aims to explore effects and mechanisms at the cellular level. We investigated NMRT induced changes of the
Methods: Human primary chondrocytes and the chondrocyte cell line Tc28/2a were used for the experiments while NMRT treatment was applied for 5 × 1 h within a time-span of two days. RNA was extracted using RNeasy Mini Kit and was used as input for the Thermo Fisher Ion Total RNA-Seq Kit v2. Sequencing was performed on Ion Proton sequencer using the Ion PI Hi-Q™ Sequencing 200 system. Signal processing and base calling was performed using Torrent Suite version 5.6. Hypoxic conditions were established and enabled cell growth in presence of 1–5 % O2. Expression of miRNAs and target proteins was studied by a standard PCR procedure as well as protein detection by western blot. Histon-Deacetylasen (HDAC) activity was measured by HDAC-Glo I/II assay.
Results: Characterization of the miRNA profile showed a slight up regulation of miR-24-1-5p and miR-502-5p while miR-25-5p and miR-365a-5p was down regulated after NMR treatment. For miR-365a-5p known to directly targeting HDAC and NFkB a decrease of HDAC activity by NMRT was detected. The miR-25-5p targeting COX2 was changed in expression by NMRT whereas no influence on CDK4 was detected known to be controlled by miR-24-1-5p. NMRT treatment of chondrocytes under hypoxic conditions (1–5 % O2) changed the expression profile with respect to NOS, IGF2, PDGF and IGFBP and a change in the expression of Hif1/2 under the influence of IL1beta was observed. Concerning the hypoxic conditions modifying apoptotic behavior of the cells, NMRT showed no influence.
Conclusion: Our investigations concerning the influence of the NMRT at the cellular level revealed a modulatory effect on miRNA, their regulatory units and chondrocytes under hypoxic conditions. The results underline our former findings indicating that NMRT counteracts IL-1b induced changes. Therefore we deduce that pain reduction by NMRT might be due to NMRT holding against inflammatory mechanisms under OA.

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6 Fallstudien

6.1
Über 6 Millionen Ferritin …

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Fallbeschreibung: Ein 67-jähriger männlicher Patient wurde im Juni 2018 wegen einer akut aufgetretenen Oligoarthritis nach St.p. 2 × iger Urethritis und Pharyngitis mit einem Stamm betonten Exanthem zugewiesen. Im Zuge der erhobenen Befunde wurde bei neg. RF, neg. ACPA, pos. HLA B27-Wert, neg. Procalcitonin und erhöhtem Ferritin schließlich die Diagnose eines adulten Mb. Still (AOSD) gestellt. Eine systemische Steroidtherapie und in der Folge MTX wurden nach Erhebung der relevanten Vorbefunde eingeleitet – darunter trat zunächst eine Remission ein. 01/2019 wurde der Pat. aufgrund der klinischen Verdachtsdiagnose eines Erysipels der linken unteren Extremität wieder hoch fiebernd vorstellig. Er wurde antibiotisch behandelt. Das Leitsymptom der folgenden Wochen war Therapie-resistentes Fieber bis 39 °C mit anhaltend 4 SJ (beide Hand- und Kniegelenke), ein Exanthem am Stamm und ein therapieresistentes, teils bullöses Exanthem am rechten Unterschenkel. Der bis dato mobile Pat. entwickelte eine ausgeprägte Malaise mit massiven Myalgien und eine zunehmende Bein-betonte Muskelschwäche mit distaler Paraspastik und konnte schlussendlich nicht mehr gehen. In der Nervenleitgeschwindigkeit wurde eine beinbetonte hochgradige, vorwiegend axonale Polyneuropathie, in der Elektromyographie mäßiggradig neurogene Veränderungen

festgestellt. In einer MRT des ZNS zeigte sich eine Leukenzephalopathie, eine Mikroangiopathie und ventrikelnahe Läsionen, vermutlich entzündlichen Ursprungs, die Paraspastik erklärend. Die neurologische Expertise attestierte eine Begleitneuropathie und Begleitencephalopathie. Zur Focussuche wurden serielle Blut- und Harnkulturen abgenommen. Die CMV-Serologie war negativ, EBV ergab pos. IgG- aber keine IgM-Ak. Die Immunglobuline ergaben nur erniedrigte IgM-Werte, die IgG-Subklassen waren normal. Ein positiver Naproxentest führte zum Verdacht auf ein Tumor-assoziiertes Fieber. Die umfassende Bildgebung (Herzlungen-Röntgen, Sonographien des Abdomens und der LK-Stationen, CT-Abdomen und Thorax, MRT der BWS) blieb ohne pathologischen Befund. Im Labor zeigte sich eine Leukozytose mit Linksverschiebung, ein erhöhtes CRP bis zu 13,2 mg/dl und am Krankheitshöhepunkt ein Ferritinwert mit einem Zenit von >6 Millionen yg>/l.

Schlussfolgerung: Die initiale Antibiose des Erysipels mit Sulbactam und Ampicillin wurde aufgrund der Therapieresistenz auf Piperacillin und Tazobactam eskaliert, die systemische Steroidtherapie auf 100 mg PÄ (ca. 1,2 mg/kg KG) tgl. gesteigert und das interkurrent pausierte MTX s.c. wieder begonnen – darunter kam es auch zu einer Besserung der Lokalsituation am rechten Unterschenkel. Nach negativer Focussuche wurde – unter Annahme eines Schubes des AOSD trotz Steroiden und MTX – eine IL-1-Blockade mit Anakinra eingeleitet, was ohne Erfolg blieb. Bei anhaltend hohem Fieber wurde in weiterer Folge – bei Verdacht auf ein Makrophagenaktivierungs-Syndrom – die Steroiddosis auf 1 g täglich gesteigert und mit einer IL 6-Blockade mit Tocilizumab in einer Dosis von 8 mg/kg KG begonnen. Darunter wurde der Pat. nach einem Tag fieberfrei und umfassend Symptom gebessert mit guter Wirkung auf Allgemeinzustand, Exanthem, Gelenke und Entzündungswerte.

Weiterer Verlauf: Der Pat. ist nach der mittlerweile 5. Tocilizumab-Infusion (14.06.2019) anhaltend fieberfrei, ohne TJ oder SJ, und konnte wieder zum Status quo ante mobilisiert werden. Die Leukozytenwerte sind normal, die Akutphase unter IL-6-Blockade (erwartungsgemäß) negativ, das Exanthem am rechten Unterschenkel ist deutlich rückläufig. 06/2019 ist der Ferritinwert erstmals im Normbereich. Die nun klinisch im Vordergrund stehende Polyneuropathie ist unter einer Tagesdosis von 75 mg Pregabalin deutlich gebessert. Tocilizumab wird weiter alle 4–6 Wochen i.v. gegeben; die Umstellung auf die s.c. Gabe wird für die nächste Zukunft geplant. Hier wird der Fall eines 67-jährigen männlichen Patienten mit AOSD vorgestellt, der im Verlauf ein MAS entwickelte und im Anschluss an Hochdosis-Kortikosteroide und eine IL-1-Blockade schlussendlich mit dem IL-6-Blocker Tocilizumab anhaltend gebessert werden konnte.

6.2 MORBUS BEHCET: eine therapeutische Herausforderung …

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Einleitung: Fallbericht über einen Mb. Behcet bei einem 21jährigen türkischen Patienten mit jahrelanger Erkrankung, therapierefraktärer Augenbeteiligung und rezentem Auftreten von neurologisch-psychiatrischen Symptomen.

Fallbeschreibung: Es handelt sich um einen 21jährigen türkischen Patienten, der seit 2013 in unserer Ambulanz in Betreuung ist. Initial stellt sich der Patient mit Erythema nodosum, Ulzera im Bereich der Mundschleimhaut sowie einer Panuveitis vor. Wegen fehlender Besserung der Panuveitis unter Kortison wurde bald von der betreuenden Augenärztin die Indikation für ein Biologikum gestellt und ab 10/2013 eine Therapie mit Adalimumab begonnen. Im weiteren Verlauf konnte die Kortisondosis jedoch immer nur kurzfristig reduziert werden. Im Rahmen von rezidivierenden Panuveitis-Schüben war die wiederholte Gabe hoher Kortisondosen von bis zu 100 mg tgl. notwendig, sodass ab 6/2015 die Therapie auf Infliximab umgestellt wurde. Auch unter Infliximab konnte die Kortisondosis immer nur kurzfristig reduziert werden. Trotz Erhöhung der Infliximab-Dosis auf bis zu 7,5 mg/kgKG und Verkürzung der Verabreichungsintervalle auf alle 4 Wochen kam es weiterhin zum Auftreten rezidivierender Panuveitiden. Ab 1/2019 wurde die Therapie erneut auf Adalimumab – diesmal in kürzerem Verab-

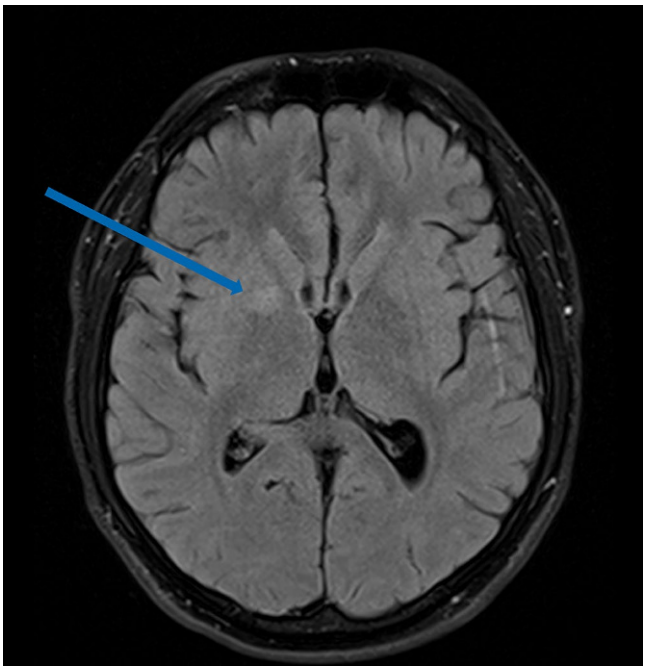

Abb. 1 ▲ MRT

reichungsintervall mit wöchentlicher Verabreichung und in Kombination mit MTX – gewechselt. Auch diese Therapie führte nicht zum gewünschten Erfolg, sodass ab 7/2019 nach Rücksprache mit der behandelnden Ophthalmologin eine Behandlung mit Cyclosporin in Kombination mit MTX begonnen wurde. Nur wenige Wochen nach Therapiebeginn mit Cyclosporin zeigte sich eine deutliche Verschlechterung des Allgemeinzustandes mit Kopfschmerzen, Schwindel und Apathie, sodass der Patient stationär aufgenommen werden musste. In der MRT des Schädels zeigte sich ein (zum Vorbefund aus 5/2015 neu aufgetretenes) etwa 1 cm messendes rundliches T2-gewichtet hyperintenses Areal am ventralen Rand des rechten Putamens/Globus pallidus (siehe **Abb. 1**). Dieser Befund ist vereinbar mit einer zerebralen Mitbeteiligung im Rahmen der Grunderkrankung. Auch die Panuveitis ist zu diesem Zeitpunkt wieder hochaktiv. Eine Hochdosis-Kortisontherapie mit 1g tgl. über insgesamt 5 Tage wurde eingeleitet, Cyclosporin wurde entsprechend der Therapieempfehlungen bei Neuro-Behcet sofort abgesetzt. Der Allgemeinzustand des Patienten besserte sich umgehend. Nach der Reduktion der Kortisondosis auf 1 mg/kgKG kam es jedoch erneut zu einer rapiden Verschlechterung mit massiven Kopfschmerzen sowie einem soporösen, später deliranten Zustandsbild, was in der Literatur als Leitsymptom des Neuro-Behcets beschrieben wird. Der Patient musste sediert werden, die Kortisontherapie wurde erneut auf 1g tgl. erhöht. Aufgrund der Dramatik des klinischen Zustandsbilds und dem sehr hohen Kortisonbedarf wurde bei bereits mehrmals erfolgloser Therapie mit TNF-Blockern eine Kombinationstherapie bestehend aus Rituximab und Cyclophosphamid begonnen. Unter dieser Behandlung kam es zu einem raschen und völligen Sistieren der neurologischen Symptomatik und auch zu einer Besserung der Panuveitis.

Schlussfolgerung: Personen mit Migrationshintergrund stellen einen zunehmenden Anteil jener Patienten/-innen dar, die rheumatologisch betreut werden. Genaue Kenntnisse und Erfahrungen bezüglich Mb. Behcet sind deshalb von großer Bedeutung, da eine therapierefraktäre Uveitis oder ein ZNS-Befall eine therapeutische Herausforderung darstellen können. Derzeit wurde die Therapie bei unserem Patienten um eine Kombinationstherapie mit Rituximab und Cyclophosphamid intensiviert.

6.3
2 Varianten des Antisynthetase-Syndrom oder: Der Weg zur Therapie über die Immunhistochemie

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Fallbeschreibung: Im Juli 2019 wurden innerhalb einer Woche 2 Patientinnen zur Abklärung von Myalgien auf unserer Station aufgenommen. Bei der ersten Patientin handelte es sich um eine 76-Jährige Frau, bei welcher im Jahr 1986 die Erstdiagnose eines systemischen Lupus erythematodes gestellt wurde. Diese konnte sich durch die weitere Betreuung durch einen niedergelassenen Rheumatologen nicht bestätigen. Bis zum Jahr 2019 wurde sie unter der Diagnose einer seropositiven rheumatoiden Arthritis mit TNFa-Blocker behandelt. Aufgrund eines Wirkungsverlustes erfolgte eine Therapieumstellung. Zusätzlich bestanden Myalgien und eine CK-Erhöhung von 4700 U/L. Es erfolgte eine umfassende internistische Durchuntersuchung einschließlich EMG, MRT und CT. Als auffallendste Befunde fanden sich erhöhte Anti-Jo1-AK (>200 u/ml), Milchglastrübungen der Lunge und hyperdense Areale der Oberarmmuskulatur. Die Biopsie des Musculus biceps brachii ergab ein endomysiales Infiltrat bestehend aus CD8+ T-Lymphozyten und Histiozyten ohne Nachweis von CD20+ B-Zellen. Aufgrund dieser Befunde wurde begleitend zur oralen Cortisontherapie (1 mg kg/KG) eine Behandlung mit Tacrolimus eingeleitet, wodurch eine deutliche klinische Besserung und schlussendlich eine Normalisierung der CK-Werte erzielt werden konnte. Bei der zweiten Patientin handelte es sich um eine 61-jährige Frau, die bis zum Zeitpunkt der Aufnahme seit ca. 1 Jahr aufgrund einer Polymyalgia rheumatica, mit Cortison therapiert wurde. Die Reduktion der Dosis führte zu einem erneuten Auftreten von Myalgien und Cephalea. Eine Arteriitis temporalis wurde mittels Sonographie und Biopsie ausgeschlossen. Auch hier erfolgte eine internistische Durchuntersuchung. Die Serologie ergab erhöhte Anti-Jo1-AK (>200u/ml) bei leicht erhöhter CK (600 U/L). Aufgrund der im MRT und EMG erhobenen Befunde wurde eine Biopsie des M. vastus lateralis durchgeführt. Diese zeigte ausgeprägte CD20+ lymphozytäre endomysiale Infiltrate. Auch bei dieser Patientin bestand eine interstitielle Lungenbeteiligung. Aufgrund des histologischen Befunds erfolgte eine Therapieeinleitung mit Cortison (1 mg kg/KG) und Rituximab. Unter dieser konnte eine klinische Remission mit Normalisierung der CK-Werte erreicht werden.
Schlussfolgerung: Anti-JO-1 assoziierte Myositiden werden unter der Gruppe der Antisynthetase-Syndrome (ASS) subsumiert. Diese sind idiopathische Autoimmunerkrankungen, welche allesamt Antikörper gegen den Aminoacyl-RNAt (anti-ARS)-Komplex und klinisch die klassische Trias Arthritis, Myositis und interstitielle Lungenerkrankung (ILD) aufweisen. Weitere relevante aber weniger häufig anzutreffende Symptome sind Hyperkeratosen mit sogenannten Mechanikerhänden, Fieber und Raynaud-Symptomatik. Das Antisynthetase-Syndrom ist eine seltene Erkrankung mit ca. 0,6 Neuerkrankungen auf 100.000 Einwohner. Frauen sind in etwa doppelt so häufig betroffen wie Männer. Das mittlere Alter bei Diagnosestellung beträgt ungefähr 50 Jahre. Bei Auftreten der ersten Symptome sind bei den meisten Patienten sogenannte inkomplette Syndrome anzutreffen, bei denen die klassische Trias nicht erfüllt ist. Erst im weiteren Krankheitsverlauf treten bei ca. der Hälfte der Patienten alle drei Hauptkriterien auf. Die Antisynthetase-Syndrome haben im Vergleich zu isolierten Polymyositiden eine schlechtere Prognose, was vor allem auf die pulmonalen Beteiligung zurückzuführen ist. Die geschilderten Verläufe zeigen exemplarisch die Spannungsfelder bei der Betreuung von Patienten mit Myositiden: Zum einen der wichtige Aspekt des zeitlichen Verlaufs in der rheumatologischen Diagnostik. Beide Patientinnen wurden initial, gut begründet, unter einer anderen Diagnose betreut und erst im klinischen Verlauf, ergänzend durch die neu aufgetretenen Befunde und klinischen Symptome, konnte die endgültige Diagnose gestellt werden. Zum anderen wird die große Bedeutung der immunhistochemischen Diagnostik zu differenzierten Therapieentscheidungen betont. Erst die Analyse der vorherrschenden Zellpopulationen ermöglichte die optimale Medikation.

6.4
Rezidivierende Fieberschübe bei Aortitis

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Fallbeschreibung: Frau P. wurde uns Mitte Juni 2019 zugewiesen mit Verdacht auf rheumatische Systemerkrankung bei generalisierten schulterbetonten Gelenksschmerzen und rezidivierenden Fieberschüben bis 38 °C. Laborchemisch fand sich eine geringgradige Anämie (Hb 11g/dl), eine unauffällige Leukozytenzahl und ein CRP von 10 mg/dl bei einer BSG von 105 mm/1h. In der Vorgeschichte litt die Patientin im März 2019 an einem fieberhaften Infekt. Damals wurde eine in den Blutkulturen nachgewiesene Pasteurella multocida Infektion nach Katzenbiss antibiotisch über 7 Tage behandelt. In den darauffolgenden 2 Monaten war die Patientin fieberfrei. Für eine maligne Erkrankung fand man in den auswärtigen Untersuchungen (Computertomographien, Gastro- und Koloskopie) keinen Hinweis. Anfang Juni 2019 traten erneut Fieberschüben bis 38 °C auf. Die Blutkulturen waren negativ. Zum Ausschluss einer Riesenzellarteriitis und weiteren Focussuche wurde ein PET-CT veranlasst, welches wider Erwarten einen länglichen bis saumförmigen gesteigerten pathologischen Tracer-Uptake an der thoraken Aorta ergab. Das CRP stieg auf 16 mg/dl an, die Leukozyten waren nach wie vor im Normbereich. Die 2 Tage später durchgeführte CT-Angiographie der thoraken Gefäße zeigte ein penetrierendes, gedeckt perforiertes Aortenulkus (1,8 × 2,3 × 1,7 cm -sagittal x transversal x craniocaudal) mit begleitender Aortitis. Die Patientin wurde auf die Gefäßchirurgie transferiert und ein Aortenstent eingesetzt. Am Tag darauf einlangende Blutkulturen waren erneut positiv auf Pasteurella multocida. Unter Antibiose mit Piperacillin/Tazobactam laut Antibiogramm war die Patientin rasch fieberfrei. Amoxicillin wurde für insgesamt 5 Wochen fortgeführt.
Schlussfolgerung: Bei entsprechender Klinik und Laborkonstellation muss eine infektiöse Aortitis erwogen und von einer autoimmunen Aortitis abgegrenzt werden.

6.5
Fallbericht: Osteoporose bei Morbus Bruton

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Einleitung: Osteoporose gilt auch heute noch als Erkrankung des höheren Lebensalters. Seltene Erkrankungen und Komorbiditäten können jedoch bereits in jungen Lebensjahren zu einer manifesten Osteoporose führen. Beim Mb. Bruton handelt es sich um eine totale Agammaglobulinämie mit X-chromosomal rezessivem Erbgang. Die Inzidenz liegt bei 1:200.000. 1) Ursächlich ist ein Gendefekt im BTK-Gen (Bruton Tyrosinkinase), welcher zu einer gestörten Reifung der B-Zellen führt. Hieraus resultiert eine fehlende Produktion sämtlicher Immunglobuline (Ig) und damit einhergehend eine fehlende humorale Abwehr.
Fallbeschreibung: Wir berichten über einen 1984 geborenen Patienten mit Morbus Bruton. Seit 2004 erfolgt eine Ig-Substitution über eine rheumatologische Ambulanz. Während relevante systemische Infektionen durch adäquate Substitution von IgG weitgehend vermieden werden konnten, kam es jedoch aufgrund des nicht therapierbaren IgA-Mangels zu rezidivierenden Infekten der Augen, des oberen Respirationstraktes und des uro-genital Traktes. Zusätzlich kam es wiederholt zu bakterieller Fehlbesiedelung des Dünndarmes mit Malabsorbtionssyndrom, bedingt durch eine Zottenatrophie bei gestörter Schleimhautbarriere. Diese Problematik wurde in den ersten Lebensjahren nicht erkannt und daher nicht therapiert. Weiters besteht bei unserem Patienten ein sekundärer Hypogonadismus, bedingt durch frühkindliche Infektionen der Gonaden. Rezidivierend auftretende schwere Augeninfektionen wurden nebst multiplen Antibiotikatherapien mit oralen Glukokortikoiden behandelt. Bis zum Alter von 20 Jahren traten bereits mehrere osteoporotische Frakturen (Deckplattenimpression LWK 2, 2xig Fraktur MTP, sowie Keilwirbelbildung BWK 12 und LWK 1) auf. Seit 2004 wird der Patient regelmäßig auf bakterielle Fehlbesiedelung

gescreent und bei Notwendigkeit auch leitliniengerecht therapiert. Ebenso erfolgt eine Testosteronsubstitution, sowie diätologische Interventionen und Krafttraining. Antiresorptive Therapien mit Alendronsäure, Pamidronsäure und Ibandronsäure erfolgten seit 2001. Unter genannten Therapien, kam es zur Verbesserung der Knochendichte (letzte DXA Messung 2013: L1–L4: T-Score −0,9, Neck: −1,5, Hüfte ges. −1,9; im Vergleich zu 2011 Verbesserung um 6 %). Da keine neuen osteoporotischen Frakturen auftraten, wurde im November 2018 die antiresorptive Therapie abgesetzt.

6.6
Fallbericht: Manifeste Osteoporose einer 40-jährigen Patientin mit Risikofaktoren

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Fallbeschreibung: Osteoporose gilt weitläufig als Erkrankung des höheren Lebensalters. In diesem Fallbericht wird gezeigt, dass auch junge Patienten mit entsprechenden Risikofaktoren an manifester Osteoporose erkranken können. Die Erstvorstellung der damals 31-jährigen Patientin erfolgte mit der Diagnose systemischer Lupus erythematodes und sekundäres Raynaud-Syndrom, durch einen niedergelassenen Rheumatologen, zur Verabreichung von Ilomedininfusionen. Als Therapie ihrer Grunderkrankung erhielt die Patientin intermittierend unterschiedlich hohe Dosen von Glukokortikoiden und Methotrexat. Als Osteoporoseprohylaxe wurde primär Vitamin D3 und Calcium gegeben. Im Verlauf wurde eine zusätzliche Therapie mit Alendronsäure 70 mg 1x/Woche für insgesamt 3 Jahre etabliert. Nachdem die Patientin mit 39 Lebensjahren zusätzlich an einem invasiv ductalen Mammakarzinom rechts (pT1b, N0(sn), M0, L0, V0–G2, ER und PR +++ pos., Ki 67 15 %, HER2/neu 0 neg) erkrankte, erfolgte neben einer Operation und einer Hormontherapie mit Nolvadex und Zoladex auch eine Umstellung der antiresorptiven Therapie auf Zolendronsäure durch die behandelnden Onkologen. Trotz dieser Medikation kam es, bei der zu diesem Zeitpunkt 40-jährigen Patientin, durch ein Bagatelltrauma (Husten) zu einer Fraktur der 9. und 10. Rippe. Nach eingehender Evaluierung der Befunde, erfolgte eine Umstellung der antiresorptiven Therapie auf Denosumab 60 mg 6-monatlich. Dies dient neben einer Osteoporosetherapie auch einer Metastasenhemmung.
Schlussfolgerung: Bei der geschilderten Patientin liegen als Risikofaktoren für eine prämature Osteoporose, neben der rheumatologischen Grunderkrankung mit rezidivierenden Gaben von Glukokortikoiden, auch ein Mammakarzinom mit entsprechender antihormoneller Therapie vor. Die sicher indizierte antiresorptive Therapie ist bei genannten Grunderkrankungen eine Herausforderung und muss zur Vermeidung weiterer Komplikationen konsequent reevaluiert werden.

6.7
Panarteriitis nodosa – ein Fallbericht

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Fallbeschreibung: Eine 53-jährige Patientin wird erstmals mit heftigen Bauchschmerzen, Diarrhoe und Fieber bis 38,8 °C seit 14 Tagen an der allgemeinchirurgischen Ambulanz vorstellig. In den durchgeführten Untersuchungen kann eine Pankolitis mit multiplen Dickdarmperforationen und 4-quadranten Peritonitis diagnostiziert werden. Nach durchgeführter subtotaler Kolektomie mit Anlage eines Ileostomas wird eine stationäre Remobilisation angeschlossen. In der histologischen Untersuchung des OP-Präparats zeigten sich ischämische Schleimhautnekrosen sowie granulomatös-vaskulitische Veränderungen größerer und mittelgroßer arterieller und venöser Blutgefäße. Bei suspizierter Vaskulitis erfolgte eine weitere Abklärung. Laborchemisch finden sich normale Entzündungsparameter, eine mäßiggradige normochrome Anämie, eine unauffällige Hepatitisserologie, negative Kryoglobuline, negative immunologische Parameter (ANA, ANCA) und normale Komplementfaktoren. Computertomographien des Thorax und Abdomens zeigen keine Läsionen, welche für Malignome oder eine Vaskulitis typisch wären. Bei der digitalen Subtraktionsangiographie (DAS) der Viszeralgefäße kamen eine umschriebene ektatische Ausweitung der A. lienalis sowie multiple kleinste Ausweitungen der peripheren Gefäße im Verlauf des Truncus coeliacus zur Darstellung. In Zusammenschau der Befunde konnte somit die Diagnose einer idiopathischen PAN gestellt werden. Eine Therapie mit Azathioprin (AZA; 2 mg pro kg Körpergewicht) und Aprednislon (1 mg pro kg Körpergewicht und Dosisreduktion auf 7,5 mg innerhalb von 3 Monaten) wurde eingeleitet. Nach zehn Monaten erfolgte eine Stoma-Rückoperation. Aufgrund von abdominellen Beschwerden, die nicht sicher durch die Operation erklärt wurden, erfolgte die Umstellung der immunmodulatorischen Therapie auf Mycophenolat mofetil (MM; 3 g täglich). Im weiteren Verlauf aggravierten sich die abdominellen Beschwerden der Patientin jedoch weiter und es kam zusätzlich zu Durchfällen. Differentialdiagnostisch wurde ein Relaps der PAN sowie eine MM-Unverträglichkeit erwogen. Eine durchgeführte Computertomographie konnte portoperative Komplikationen wie eine Anastomoseninsuffizienz oder eine Abszessbildung ausschließen. Eine Koloskopie, in welcher sich kleine aphtöse Schleimhautläsionen, eine ödematöse Schwellung und Vulnerabilität der Darmschleimhaut mit punctum maximum im Rektumrest und im Bereich der Anastomose zeigten, wurde durchgeführt. Die Histologie der entnommenen Biopsien erbrachte den Befund einer unspezifischen, am ehesten infektiösen, Colitis. Aus unserer Sicht lag somit eine Diversionskolitis vor. Entsprechend wurde eine Therapie mit Metronidazol (500 mg 3 × täglich über 14 Tage), Mesalazin-Klysmen und einer diätologischen Intervention initiiert. Hierunter kam es zu einer signifikanten Besserung der Beschwerden.
Schlussfolgerung: Bei gastrointestinalen Beschwerden nach kompliziert verlaufender PAN muss neben einem Relaps der Grunderkrankungen auch an Nebenwirkungen der Therapie, postoperative Komplikationen und lokal infektiöse Probleme, wie die beschriebene Diversionskolitis gedacht werden.

6.8
Phospho interleukin-1 receptor-associated kinase 4 (IRAK-4) signalling on B cells as a potential biomarker for Schnitzler's syndrome

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Case record: Schnitzler syndrome (SchS) is a rare autoinflammatory disease characterized by chronic urticarial rash, monoclonal gammopathy and signs of systemic inflammation, triggered by IL-1β hyperactivation. Phosphorylation of interleukin-1 receptor-associated kinase 4 (IRAK-4) can give insight in the level of activation of the IL-1 inflammatory cascade. Here we present a case vignette of a patient with SchS and his cellular phosphorylation profile. A 62-year old male patient, diagnosed with Castleman's disease, was referred to the immunology department due to recurrent fever episodes with accompanying urticarial rash, lymphadenopathy and malaise for the last 17 years. A longstanding treatment with steroids and multiple immunosuppressive drugs had shown no improvement of his condition. Detailed history, laboratory-, cytokine- and phospho-flow analysis were performed. Laboratory examinations revealed leucocytosis (19.5 × 109cells/L), lymphopenia (9% of leucocytes) with a low percentage of B-cells (1% of lymphocytes), elevated CRP (87.5 mg/L) and IL-1 receptor antagonist levels (755 pg/ml), as well as a monoclonal gammopathy of the IgM class. Phospho-flow revealed a high percentage of phosphorylated IRAK-4 in B-cells (86.3%) compared to a patient with rheumatoid arthritis (43.6%) and a healthy control (0.05%). SchS was diagnosed according to Strasbourg-criteria and treatment initiation with anakinra lead to clinical remission and a distinct decrease in the percentage of phosphorylated IRAK-4 B-cells (0.33% after 6 months).
Conclusion: Our results suggest that IL-1 signalling in SchS directly acts on B-cells, giving further insight in the pathophysiology of the disease,

but also highlighting phosphorylated IRAK-4 in B-cells as potential diagnostic biomarker.

6.9
Rheumatologische Abklärung von Myalgien: es muss nicht immer eine Myositis sein

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Fallbeschreibung: Einleitung: Myositiden sind eine heterogene Gruppe entzündlicher Muskelerkrankungen. Das klinische Bild besteht primär in einer Muskelschwäche. Die Abklärung bezüglich Myositis erfolgt mittels klinischer Untersuchung, Erfassen von Laborparametern inklusive CK-Werten und immunologischen Parametern, MRT und EMG der betroffenen Muskulatur sowie schlussendlich einer Muskelbiopsie. Patient 1: Ein 31-jähriger Patient klagte seit einigen Monaten über ausgeprägte Muskelschwäche vorwiegend der Oberarme und Oberschenkel. Zusätzlich bestanden Gewichtsverlust, Nachtschweiß, Beinödeme und Schluckbeschwerden. Laborchemisch auffällig waren ein CRP 74,3 mg/L (NW 0,5–5,0 mg/L), eine CK-Auslenkung von 337 U/L (NW 20–200 U/L), ein erhöhtes proBNP von 718 ng/L (NW 0,0–63,0 ng/L), eine ausgeprägte Hypoalbuminämie von 24,8 g/L (NW 35–52 g/L) und ein deutlicher Gammapeak in der Elektrophorese. Sämtliche rheumatologisch-immunologischen Laborparameter waren unauffällig. Eine internistische Abklärung zum Ausschluss eines Malignoms ergab keine Raumforderungen. Im MRT der Oberschenkeln fanden sich Ödeme im Bereich des Musculus rectus femoris und die Nervenleitgeschwindigkeit dieser Region zeigte verkürzte MUPs (motor unit potentials), sodass bei Muskelschwäche und erhöhten CK-Werten, unter Verdacht auf das Vorliegen einer Myositis, eine Muskelbiopsie durchgeführt wurde. Diese ergab unauffälliges Skelettmuskelgewebe mit minimalen perivaskulären, entzündlichen Infiltraten um die Gefäße der Bindgewebssepten, jedoch keine Myositis. Bei pathologischer Elektrophorese erfolgte eine Knochenmarksbiopsie. Das histologische Ergebnis zeigte das Vorliegen eines Plasmozytoms, sodass der Patient zur weiteren Behandlung auf die Abteilung für Hämatoonkologie transferiert wurde. Patient 2: Ein 71-jähriger Mann wurde von seinem Hausarzt zur Abklärung massiv erhöhter CK-Werte von 18.900 U/L (NW 20–200 U/L) zugewiesen. Der Patient klagte über Muskelschmerzen sowie Muskelschwäche seit etwa 3 Wochen, wobei vorwiegend die proximale Muskulatur betroffen war. Bei bekannter KHK war einige Monate zuvor eine Statin-Therapie begonnen und die Statindosis zuletzt erhöht worden. Laborchemisch waren sämtliche rheumatologisch-immunologischen Parameter unauffällig. Die internistische Durchuntersuchung ergab keinen Hinweis auf eine Neoplasie. Da sich im MRT der Oberschenkel das Bild einer Myositis zeigte und sich in der EMG-Untersuchung ebenfalls ein pathologisches Ergebnis fand, wurde eine Muskelbiopsie durchgeführt. Die histologische Untersuchung ergab Skelettmuskel mit disseminierten Einzelfasernekrosen im Sinne einer nekrotisierenden Myopathie. Die HMG-CO-A-Reduktase-Antikörper waren negativ. Die Statintherapie wurde unverzüglich beendet, und im Verlauf des stationären Aufenthalts kam es zu einem schrittweisen Rückgang der CK-Werte, welche schlussendlich im Normbereich lagen. Bei diesem Patienten lag somit keine Myositis, sondern eine Statin- induzierte toxische Myopathie vor. Patient 3: Die stationäre Aufnahme des 18-jährigen Patienten erfolgte zur Abklärung massiv erhöhter CK-Werte von >20.000 U/l (NW 20–200 U/L). Der Patient war weitgehend beschwerdefrei, es bestand lediglich eine gering eingeschränkte sportliche Belastbarkeit. Extern durchgeführte EMG- und MRT-Untersuchungen der Oberschenkel ergaben den Verdacht auf Vorliegen einer Myositis. Sämtliche rheumatologisch-immunologische Laborparameter waren unauffällig. Eine Muskelbiopsie wurde durchgeführt. Die histologische/elektronenmikroskopische Untersuchung ergab keinen Hinweis auf eine Myositis, allerdings zeigten sich ausgeprägte myopathische Veränderungen mit zahlreichen Muskelfasernekrosen/Kaliberunregelmäßigkeiten/Aufregulierung von N-terminalen Utrophin sowie komplettem Fehlen der Dysferlinexpression, entsprechend dem Befund einer Dysferlinopathie (sog. Gliedergürtelmuskeldystrophie).
Ergebnis: Die Abklärung von Patienten/Patientinnen mit Myopathie und erhöhten CK-Werten ist eine Domäne rheumatologischer Spezialabteilungen. Vorliegende Patientenberichte belegen, dass trotz Hinweisen auf Vorliegen einer Myositis in MRT- und EMG-Untersuchungen eine Muskelbiopsie zur endgültigen Diagnosesicherung unumgänglich ist, da erst durch die histologische/elektronenmikroskopische Aufarbeitung die Diagnose Myositis bestätigt bzw. widerlegt werden kann.

Autorenverzeichnis

Ausschreibung

Projektpreise

der Österreichischen Gesellschaft für Knochen- und Mineralstoffwechsel

Durch die ÖGKM-Projektpreise soll die wissenschaftliche Arbeit auf dem Gebiet des Knochen- und Mineralstoffwechsels gefördert werden.

Die ÖGKM schreibt für 2019/2020 drei mit jeweils maximal Euro 5.000,00 dotierte Projektpreise aus. Dadurch soll die wissenschaftliche Arbeit auf dem Gebiet des Knochen- und Mineralstoffwechsels gefördert werden. Gestiftet werden diese Projektpreise von den fördernden Mitgliedern der ÖGKM.

Zur Einreichung berechtigt sind alle WissenschafterInnen, die Mitglieder der ÖGKM sind, wobei pro Institution nur ein Antrag gestellt werden kann. Die Arbeit muss überwiegend in Österreich durchgeführt werden. Nach elektronischer Einreichung an Bettina Pugl (oegkm@medacad.org) wird eine Jury die Bewertung vornehmen. Der Antrag kann in deutscher oder englischer Sprache abgefasst sein. Eine Kurzfassung mit maximal 250 Wörtern sowie eine genaue Auflistung der anfallenden Kosten und ein zeitlicher Ablauf des geplanten Projektes sind beizulegen.
Sollte kein förderungswürdiges Projekt eingereicht werden, wird kein ÖGKM-Projektpreis vergeben.

Bei Projektabschluss ist der Projekteinreicher/ die Projekteinreicherin verpflichtet, dem Vorstand der ÖGKM einen Abschlussbericht und einen Nachweis über die Verwendung der Fördermittel vorzulegen. Bei Publikationen ist auf die Projektförderung durch die ÖGKM hinzuweisen.

Einreichfrist:
Donnerstag, 31. Jänner 2020

Die Projektpreise werden im Rahmen des Osteoporoseforums 2020 verliehen werden.

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