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The role of cholinergic anti-inflammatory pathways during arthritis

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Purpose: Recent studies demonstrate that the central nervous system (CNS) can regulate peripheral inflammation. In the rat adjuvant arthritis model, inhibition of the p38 inhibitor SB203580 (SB) induces inflammation studied was in the rat carrageenan paw edema (CPE) model. The expression of the alpha7 cholinergic receptor (alpha7R) was determined in human synovium and cultured synoviocytes (FLS) using immunohistochemistry (IHC). Western blot and quantitative PCR. The role of the alpha7R on cytokine and chemokine production by FLS was tested with acetylcholine, the selective alpha7R antagonist methyllycaconitine (MLA), the selective agonist PNU-282987 and sirtaxen. Knockdowns of regulation pathways were repressed by reporter and gel retardation assays and mRNA half-life determination.

Results: IT SB and systemic administration of the cholinesterase inhibitor Galanthamine decreased inflammation in the CPE model (p < 0.001). IHC demonstrated abundant alpha7R in RA and OA synovium, especially in the inlining lining. Expression was also demonstrated in FLS lines by Western blot and q-PCR. ACh and PNU-282987 inhibited IL-6 and chemokine release by in IL-1 stimulated RA and OA FLS in a dose dependent manner (p < 0.001). The alpha7R specific antagonist methyllycaconitine (MLA) blocked the anti-inflammatory action of ACh in FLS. alpha7R knockdown with specific siRNA blocked the effect of ACh on IL-6 production. Steady state mRNA levels of IL-6 in IL-1 stimulated FLS were decreased by ACh (7 ± 2% inhibition, n = 14, p < 0.001). The alpha7R specific antagonist methyllycaconitine (MLA) blocked the anti-inflammatory action of ACh in FLS. alpha7R knockdown with specific siRNA blocked the effect of ACh on IL-6 production. Steady state mRNA levels of IL-6 in IL-1 stimulated FLS were decreased by ACh (7 ± 2% inhibition, n = 14, p < 0.001). ACh had no effect on gene transcription in immortalized or NF-kappaB binding activity. Instead, ACh significantly decreased the half life of IL-6 mRNA in IL-1 stimulated FLS from 13.8 to 6.5 hours.

Conclusion: Inhibition of alpha7R in the CNS increases vagal outflow and cholinergic mechanisms can potentially account for the anti-inflammatory action of spinal p38 blockade. alpha7R agonists could represent new therapeutic agents in RA.

Inhibition of IL-33 signaling attenuates the severity of experimental arthritis

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Introduction: IL-33 (IL-1F11) was recently identified as the ligand of the IL-1R2. IL-33 production in human and mouse joints and to investigate the role of IL-33 and T1/T2 in experimental arthritis.

Methods: IL-33 mRNA and protein expression was examined in cultured human rheumatoid arthritis synovial fibroblasts (SF) and arthritic mouse joints. Mice with collagen-induced arthritis (CIA) were treated with blocking anti-IL-33 or control antibodies from the onset of disease. Disease activity was assessed by clinical and histological scoring. Draining lymph node cell (DLN) responses were examined ex vivo and joint mRNA was used for expression profiling. Results: IL-33 SF and its expression strongly increased in response to IL-1 and/or TNF-alpha. Moreover, IL-33 mRNA was detected in the joints of mice with CIA and increased during the early phase of the disease. The administration of a blocking anti-IL-33 antibody at the onset of disease attenuated the severity of CIA and reduced joint destruction. Anti-IL-33 antibody treatment was associated with a marked decrease in TNF-alpha production, as well as more limited reduction in IL-17 production by ex vivo-stimulated DLN cells. Finally, RANKL mRNA levels in the joint were reduced by treatment with the ST2 antibody.

Conclusion: IL-33 is produced locally in inflamed joints and neutralization of IL-33 signaling has a therapeutic effect on the course of arthritis. These observations suggest that locally produced IL-33 may contribute to the pathogenesis of joint inflammation and destruction.

Malnutrition in a rehabilitation center

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Introduction: In 2004, we found that 28.6% of our patients had a high risk for malnutrition. (Nutrition Risk Score ≥3) [1, 2]. Our objective in this follow up study is to determine how many of our at risk patients are effectively suffering from malnutrition.

Methods: From July 1st 2007 to March 31st 2008, all patients were screened with the NRS within the first two days of admission. Subsequently the patients were assessed by the nutritionist using standardized assessments with Nutritional parameters: BMI, ability of eating, upper arm circumference, triceps skinfold thickness [3], cover of caloric needs [4] and laboratory data.

Results: From the 195 patients screened with the NRS, 110 (56.4%) had a NRS score ≥3 (58.7%) from these 110 at risk patients were classified as undernourished. “Vascular brain injury” (stroke, trauma) was the most common diagnosis (65%) among the remaining 46 patients, who received subsequently either one cycle of RTX or an alternative aTNF. The primary outcome is the evolution of the DAS28 over the first year, which is analyzed using multivariate regression models for longitudinal data.

Results: 300 RA patients are included, 101 with a first RTX cycle and 199 with alternative aTNFs (adalimumab 56%, etanercept 25%, infliximab 19%). Overall 65% of patients had experienced a prior aTNF failure due to ineffectiveness (28% primary, 72% secondary) and 35% due to an AE. At baseline, there was no significant difference between the two therapeutic groups in age, disease duration, function, RF positivity, concurrent glucocorticoid or OMDR use, but groups differed in baseline DAS28 levels and in number of previous aTNF failures. After adjustment for potential confounders, and in particular for baseline DAS28, the evolution of DAS28 was overall more favourable in the RTX group compared to the aTNF group (p < 0.01). However, the relative benefit of RTX varied with the type of prior aTNF failure (effect modification). When the motive for switching was ineffectiveness aTNF failure, than to a 2nd or 3rd alternative aTNF agent. However, patients who received subsequently either one cycle of RTX or an alternative aTNF had no effect on gene transcription in promoter assays or NF-kappaB production. Steady state mRNA levels of IL-6 in IL-1 stimulated FLS were decreased by ACh (7 ± 2% inhibition, n = 14, p < 0.001). ACh had no effect on gene transcription in immortalized or NF-kappaB binding activity. Instead, ACh significantly decreased the half life of IL-6 mRNA in IL-1 stimulated FLS from 13.8 to 6.5 hours.

Conclusion: Inhibition of p38 in the CNS increases vagal outflow and cholinergic mechanisms can potentially account for the anti-inflammatory action of spinal p38 blockade. alpha7R agonists could represent new therapeutic agents in RA.

Which subgroup of RA patients benefit most from switching to Rituximab versus alternative Anti-TNF agents after previous failure to Anti-TNF agent?

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Background: Rheumatoid arthritis (RA) patients who experience a failure on anti-TNF agents (aTNF failure) may respond more favourably to a different class of biologic therapy, such as rituximab (RTX), than to a 2nd or 3rd alternative aTNF agent. However, patients may interrupt aTNF therapy for various reasons (i.e. ineffectiveness, adverse events (AE), preferences) and it remains unclear in which clinical setting each therapeutic strategy offers most benefit.

Objective: To analyze the effectiveness of RTX versus alternative aTNFs on disease activity (DAS28) in RA patients with aTNF failure and examine potential effect modification by the type of prior aTNF failure or the type of aTNF switch.

Methods: This is a prospective cohort study nested within SCQM-RA (cohort including all aTNF patients) and an alternative aTNF, who received subsequently either one cycle of RTX or an alternative aTNF. The primary outcome is the evolution of the DAS28 over the first year, which is analyzed using multivariate regression models for longitudinal data.

Results: 300 RA patients are included, 101 with a first RTX cycle and 199 with alternative aTNFs (adalimumab 56%, etanercept 25%, infliximab 19%). Overall 65% of patients had experienced a prior aTNF failure due to ineffectiveness (28% primary, 72% secondary) and 35% due to an AE. At baseline, there was no significant difference between the two therapeutic groups in age, disease duration, function, RF positivity, concurrent glucocorticoid or OMDR use, but groups differed in baseline DAS28 levels and in number of previous aTNF failures. After adjustment for potential confounders, and in particular for baseline DAS28, the evolution of DAS28 was overall more favourable in the RTX group compared to the aTNF group (p < 0.01). However, the relative benefit of RTX varied with the type of prior aTNF failure (effect modification). When the motive for switching was ineffectiveness aTNF failure, than to a 2nd or 3rd alternative aTNF agent. However, patients who received subsequently either one cycle of RTX or an alternative aTNF had no effect on gene transcription in promoter assays or NF-kappaB production. Steady state mRNA levels of IL-6 in IL-1 stimulated FLS were decreased by ACh (7 ± 2% inhibition, n = 14, p < 0.001). ACh had no effect on gene transcription in immortalized or NF-kappaB binding activity. Instead, ACh significantly decreased the half life of IL-6 mRNA in IL-1 stimulated FLS from 13.8 to 6.5 hours.

Conclusion: Inhibition of p38 in the CNS increases vagal outflow and cholinergic mechanisms can potentially account for the anti-inflammatory action of spinal p38 blockade. alpha7R agonists could represent new therapeutic agents in RA.

Conclusion: This observational study suggests that RTX is more effective than switching to an alternative aTNF in RA patients who have persistent active disease despite of aTNF. However, when the motive for interrupting aTNF was other than ineffectiveness, both RTX and alternative aTNF agents appear to offer similar levels of effectiveness.
Refined insights into the pain-depression association in chronic pain patients

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Background: The relationship between chronic pain and depression is controversial and the data on association show large variation in current literature, especially when using diagnostic thresholds. This study aimed to provide refined correlation and regression data on the basis of continuous measures.

Methods: Cross-sectional assessment was performed with standardized instruments that measure on quasi-continuous scales, the Multidimensional Pain Inventory (MPI) and the Hospital Anxiety and Depression Scale (HADS). Correlations between the depression and pain scales were determined controlling for 13 potentially disease-modifying confounders, and within chronic pain subgroups as defined by the MPI cluster patterns using multivariate regression analysis.

Results: In 273 chronic pain patients on admission to an inpatient pain rehabilitation program, the MPI pain severity scale and the HADS depression scale showed overall partial correlation of 0.30 (1.00 means perfect association). Distinguishing three subtypes of pain patients, the partial pain-depression correlation was moderate (0.57) in the “interpersonally distressed” subgroup (characterized by relatively low social support), weak (0.26) in the “dysfunctional” subgroup (characterized by relatively high levels of symptoms), and absent (0.01) in the “adaptive copers / minimizers” subgroup (characterized by relatively low levels of symptoms).

Conclusions: The strengths of the pain-depression association and the “dose-response” relationship were both weak – weaker than to be expected if the hypothesis of a causal relationship were true. In the “interpersonally distressed” subgroup, the moderate association may have an impact on pain management, i.e. pain could be treated by treatment of depression and vice versa.

Systematic tutoring, education and aftercare of family members from stroke-patients in the process of rehabilitation

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Introduction: 76% of our stroke patients return home after discharge. Follow up care in the home setting is provided mainly by family members. Caregiver training, education and counselling interventions play a decisive role, to make the optimal adjustment for living with a stroke [1, 2]. In order to optimise the long-term support of family caregivers, we wanted to recognise their most relevant needs.

Methods: From 2006 to 2007, 143 family members from a total of 199 hospitalised stroke patients were systematically tutored. The different interventions were coordinated using a flowchart. Instruments for the preparation of discharge included: Information packages to the disease, a guide book, an invitation to a lecture on Stroke, interdisciplinary tutoring, domicile inspection and assessment of home weekend-visits. 2 Weeks after discharge, family caregivers were assessed for stress situations using the self-rated burden (SRB) and the Caregiver Strain Index (CSI) [3]. An interview also disclosed possible burdens and suggestions were made to reduce strain.

Results: We found a linear correlation between the SRB and the CSI. 9 out of the 46 respondents had a total score of 0.7/13 which verifies a high level of stress. The most frequently experienced problems were less flexibility and adaptation of planning as well as emotional adjustment. Physical strain was seldom mentioned. Surprisingly we found no correlation between the SRB and CSI neither with the Functional Impairment Index (FIM) nor with the nursing capacity performance (LEP minutes) of patients.

Discussion: This study showed that Family Caregivers felt relatively secure with their handling techniques, regardless of the level of nursing care of the patients. We conclude that this could be due to the offered systematic and educational concept in our clinic. Given these conclusions we are challenged to further develop this approach, in order to find ways to reduce the stress factors specified above. This therefore implicates a further development of the present tutoring program into the long term setting with counselling, education and other specific interventions, as well as possibilities for screening in order to maintain an acceptable stress level over time.

Diagnosis of complex regional pain syndrome type I – a delphi survey

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Objective: To define the complex regional pain syndrome type I (CRPS I) by a process of consensus and to identify its diagnostic criteria.

Method: Delphi survey with 13 experts. A first round to list relevant criteria. In the second round, experts were asked to rate and prioritize the criteria.

Results: Forty-eight criteria were identified in the first round. The experts agreed that a minimum of six diagnostic criteria were necessary for a diagnosis of CRPS I. The experts also agreed on a minimum of four diagnostic criteria as a threshold for intervention.

Conclusion: The Delphi survey was successful in defining the diagnostic criteria for CRPS I. Further studies are needed to validate these criteria and to determine their reliability and validity.

Long-term study of three dosages of epicutanenously applied Diractin® (Ketoprofen in Transfersome®) in patients with Osteoarthritis (OA) of the knee

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Background: The risk of oral NSAIDs to cause gastrointestinal, renal or cardiovascular adverse events related to systemic drug exposure could be reduced by local application. Conventional topical formulations face skepticism about their efficacy for use in OA, given that very few long-term studies have been published. Diractin® is a new, carrier based NSAID formulation for local application that showed efficacy comparable to oral celecoxib in a 6-week study of knee OA [1]. Results of a 12-week study were reported recently [2]. Here we report data for a 3-month extension of that 12-week study, being the first trial providing 24-week safety and efficacy data for a locally applied NSAID.

Methods and objective: The multicentre, multinational, randomised, double-blind, parallel-group, dose-controlled study enrolled 510 patients with knee OA, and investigated doses of 25, 50 and 100 mg ketoprofen in Diractin® per knee b.i.d. Study objective was to check, whether long-term treatment effects are maintained, as defined by comparison of the OMERACT-OARSI Responder Index between weeks 12 and 24, and evaluation of treatment induced changes of the WOMAC.

Results: The responder rates for all three treatment groups (n = 390) remained high (82.8%, 83.5% and 84.4%, respectively) at week 24 (P = 0.02). In the intention to treat analysis mean change scores were not statistically different between ADA and PL: 2.4 (9.4–4.5), ODI (31 (17–38) versus 31 (17–50)).

Conclusions: At short term follow-up, systemically delivered adalimumab may decrease the need for surgery in acute severe sciatica. However, in the intention to treat analysis, adalimumab was devoid of significant effect on either pain or function.

Calcium und Vitamin D-levels in in-patients of our clinic, in both summer and winter

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Introduction: A sufficient supply of Calcium (1000–1500 mg/d) and Vitamin D (25-OH-Vitamin-D-level 80–120 nmol/l) is the essential foundation for a healthy skeleton and the basis of Osteoporosis treatment (1) – although far from self-evident (2). We present the preliminary results of an observation study designed to evaluate the supply levels of our patients on entry, and to show the influence of age, gender, and season.

Methods: We collected the data from 238 patients on admission, of these in summer (April 2007 to 27 August 2007) and in winter (mid-January to mid-February 2008), in each case over a 4 week period. We used a standard Calcium questionaire to establish the daily elementary Calcium intake (mg) and determined with blood tests on admission the 25-OH-Vitamin-D-level (nmol/l). We investigated the relationship between these values and factors of age, gender and the season of the year.

Results: From our patients on entry – 69.5% women and 31.2% men, with an average age of 67.5 years (22–91 years) – the average daily elementary Calcium intake was 791 mg (10 mg to 414.5 mg) in summer and 907 mg (40 mg to 3308 mg) in winter. In the case of 21.8% of the patients the Calcium intake was insufficient (<500 mg/d). The average Vitamin-D-level in summer was 63.3 nmol/l (<30 nmol/l to 143 nmol/l), and in winter was 38.8 nmol/l (<30 nmol/l to 145 nmol/l). A Vitamin-D deficiency (<30 nmol/l) was found in 23.9% of the patients (summer 8.1%, winter 37.8%). The difference between summer and winter for Vitamin D was significant (chi-squared test p <0.0001). No significant correlation was determined between Vitamin D level and age or gender; or between elementary Calcium intake and age, gender or season.

Conclusion: In a large number of our patients the elementary Calcium intake and the Vitamin D serum levels were below the recommended norm values. The deficiency of Vitamin D was significantly more pronounced in winter than in summer. For patients in rehabilitation the supply of Calcium and Vitamin D deserves additional attention.

References:

Adalimumab in the treatment of acute severe sciatica, a randomized double blind placebo controlled study

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Purpose: Inflammation in tissues surrounding the herniated disc seem to play an important role in sciatica. Animal studies have shown that tumor necrosis factor (TNF)-alpha plays an important in this inflammatory process. In addition, we have recently shown that TNF-alpha levels are increased in the peridiscal fat of patients with sciatica. The objective was to determine the role of TNF-alpha in the pathogenesis of sciatica and whether adalimumab (ADA), a human anti-TNF-alpha agent administered subcutaneously, could fasten the evolution of severe acute sciatica.

Methods: Patients with acute (less than 3 months of leg pain) and severe sciatica (Oswestry score (ODI) >50 despite adequate pain treatment) were randomized into two groups. In addition to standard analgesic therapy, the treatment group (ADA) received two subcutaneous injections of 40 mg of adalimumab at 1 week interval, while the control group received two injections of placebo (PL).

Results: 61 patients were included (31 ADA, 30 PL). Baseline data were balanced between both groups for age (48 v. 45 y.o), duration of leg pain (13 v 16 days), mean ODI, ODI score (86 v. 70), VASb (7.55 v. 8.45) and VASsp (4.85 v. 2.85). VASbp, VASlp, and ODI levels decreased significantly in both groups at day 10 and at week 6. At day 10 no significant difference were found for leg pain but ODI decreased significantly more in the ADA group (P = 0.05). At week 6, 5 patients were lost to follow up (1 ADA and 4 PL). Five patients in the PL group, but none in the ADA group were excluded for intractable leg pain (p = 0.02). In the intention to treat analysis mean change scores were not statistically different between ADA and PL: Median VASb (1.2 (0.4–2.4) versus 1.1 (0.3–4.8), VASlp (2.4 (1.0–4.2) versus 2.4 (0.9–4.5), ODI (31 (17–38) versus 31 (17–50)).

Conclusions: Adalimumab in the first 12 weeks had significant further improvements of the WOMAC. The responder rates for all three treatment groups (n = 390) remained high (82.8%, 83.5% and 84.4%, respectively) at week 24 (P = 0.02). In the intention to treat analysis mean change scores were not statistically different between ADA and PL: 2.4 (9.4–4.5), ODI (31 (17–38) versus 31 (17–50)).

Method: We included 280 subjects: 160 men and 120 women. Mean age 43.6 by the women and 44 years by the men. We studied the caring foot-hip, hip-shoulder, 5 meter carrying, push-up and lifting and the global weight carried during the test. We found this global value to be 696 kg by men and 422 kg by women suffering from chronic lumbal pain. The increase in this value had a clear incidence on a greater work ability, as had a decrease.

Conclusions: We were able to develop a lifting capacity program that is easy to reproduce and not expensive, giving us the possibility to have an idea on how to reorient the patients according to their work place and their capacities. We could also have an information of work performance and power consumption. It should be more tested and compared to standard capacity in the healthy population.

An easy functional capacity evaluation in chronic low back pain

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Lifting is said to be on of the major risk factors for the onset of low back pain, several different measures has been developed to study this. Several programs are available in order to measure these components, or to determine the ability of an individual to perform a certain job or to discover if the job creates dangerous positions for the worker. In these different fields reliable and valid instruments exist but they are costly and time spending. We present a simplified functional capacity measuring that we use daily in practise.

Method: 280 patients have been evaluated on base of this protocol. The majority was referred to multidisciplinary rehabilitation treatment. The patients had recurrent back problems for months or years. Inclusion criteria were between 18 and 64 years, current of work and no work compensation. Exclusion criteria were chronic low back pain with a specific cause. They followed a one-hour evaluation test as a functional capacity evaluation at the end of the multidisciplinary treatment period, it was compared to the PILE-test done at the beginning and at the end.

Results: We included 280 subjects: 160 men and 120 women. Mean age 43.6 by the women and 44 years by the men. We studied the caring foot-hip, hip-shoulder, 5 meter carrying, push-up and lifting and the global weight carried during the test. We found this global value to be 696 kg by men and 422 kg by women suffering from chronic lumbar pain. The increase in this value had a clear incidence on a greater work ability, as had a decrease.

Conclusions: We were able to develop a lifting capacity program that is easy to reproduce and not expensive, giving us the possibility to have an idea on how to reorient the patients according to their work place and their capacities. We could also have an information of work performance and power consumption.
Correlation between Nutrition Risk Score (NRS) and clinical parameters for malnutrition in a rehabilitation center

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Introduction: The significance of malnutrition is underestimated and no “golden standard” exists for determining nutritional status [1]. Our objectives were to improve the method for screening malnutrition in our clinic. We therefore compared the Nutrition Risk Score (NRS) [2] with other recommended screening tools.

Methods: Between July 1st 2007 and March 31st 2008, all patients within the first 2 days of admission, were screened using the NRS. In addition, the following clinical parameters were performed: Laboratory values, BMI, the total caloric content using the plate diagram [3], capability to eat, measurement of upper arm circumference and triceps skinfold thickness [4].

Results: 21 (28.6%) of the 85 patients screened with the NRS <3 had an insufficient intake of calories. As expected we found a statistical correlation between NRS and albumin as well as hemoglobin, but the NRS did not correlate with creatinine, urea, and lymphocytes. NRS was correlating with upper arm circumference but only weakly with triceps skinfold thickness. Further we did not observe any correlation between the NRS and the Functional Independence Index (FIM) total score.

Conclusion: The findings of this study showed that almost a quarter of the patients who were not identified to be at risk for malnutrition by NRS, had an insufficient intake of calories. Because these patients may develop relevant malnutrition during rehabilitation we will continue to screen all patients for correct intake. Further, routine laboratory screening of biochemical makers will be limited to albumin. References: 1) Mangelernährung im Spital, SÄZ 2006;87:19. 2) Kondrup J. et al. Clin Nutr. 2003;22:415–21. 3) Rüfenacht U. et al. Aktuel Med. 2006;31:66–72. 4) Ballmer P.E. et al. Schweiz Med Forum. 2001;887–91.

New treatment option for osteoarthritis using Transfersome® carriers – preclinical results

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Objective: Topical application of NSAIDs is frequently used but faces skepticism regarding efficacy and true local nature of drug delivery as shown by comparable synovial drug concentrations in the treated and untreated joint after topical application [1]. This implies a systemic rather than a local drug distribution explained by rapid drug absorption via cutaneous blood capillaries. Innovative Transfersome® carriers actively pass the skin driven by the transcutaneous moisture gradient, transport drug across the skin, prevent their systemic absorption and allow high local drug concentrations deep below the application site. We therefore provide experimental data obtained in pigs supporting the innovative transport mechanism of Transfersome® carriers and their contribution to a new treatment option for osteoarthritis (OA).

Methods: Diractin® was applied on joints of pigs. Treated and untreated joints were taped at different timepoints post application to compare ketoprofen levels in the synovial fluid. In separate studies, Diractin® was applied dermally on pigs in different area and total doses. Tissue biopsies below the application site were taken at different timepoints post application to compare ketoprofen levels in different subdermal tissue layers.

Results: The mean ketoprofen concentration in synovial fluid on the treated side was 3 to 5 times higher than on the untreated, side. Ketoprofen concentration in the synovial fluid of the untreated side was in the range of the drug concentration in plasma in pigs. Diractin® showed superior targeted drug delivery into different structures of subdermal pig tissue as compared to conventional oral and topical products.

Conclusions: The findings prove the feasibility of the Transfersome® mediated targeted delivery of ketoprofen and indicate a highly efficient concept for the treatment of OA. They also indicate that Transfersome® carriers deliver a substantial portion of the drug directly into the joint below application site, supporting their truly local mode of action.


Adalimumab is effective and well-tolerated in treating Ankylosing Spondylitis (AS) in real-life clinical practice: subanalysis of results for Swiss patients in the RHAPSODY trial

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Introduction: We evaluated the effectiveness and safety of adalimumab in a large cohort of patients (pts) with active ankylosing spondylitis (AS) eligible for anti-TNF therapy in daily rheumatologic practice.

Methods: Pts with active AS and insufficient responses to >1 prior NSAID received adalimumab 40 mg every other week for 12 weeks in an open-label European study, “Review of safety and effectiveness with Adalimumab in Patients with active ankylosing Spondylitis (RHAPSODY).” Evaluations of treatment effects on spine and peripheral joints and routine safety evaluations were conducted at Weeks 2, 6, and 12. Adverse event (AE) reports were collected during therapy plus a 70-day follow-up period.

Results: In RHAPSODY, 1,250 pts enrolled at 211 centers in 15 countries. A total of 1,159 (92.7%) patients completed 12 weeks of adalimumab treatment, including all 16 patients from Switzerland. Baseline characteristics for all Swiss pts were (mean) age 44/40 years; AS duration, 11/8 years; male, 71/88%; HLA-27+, 82/81; BASDAI (0–10), 6.3/5.8; BASS (0–10), 5.4/3.3; ASAS 40/30, 75/83; enthesis, 55/63; comodication with NSAID, 74/81; and history of anti-TNF therapy, 26/31. Treatment response is summarized in the table. Adalimumab was well-tolerated, with serious AEs occurring in 3.4% of all pts and in none of the Swiss pts, respectively. No cases of TB or malignancy were observed.

Adalimumab was effective in this large cohort of patients with AS, with more than half of patients achieving a BASDAI 50 or ASAS40 response and more than a quarter reaching partial remission at Week 12. Despite slightly lower disease activity at study entry, Swiss patients exhibited a trend toward better response.

Effectiveness of Adalimumab Therapy at Week 12 in RHAPSODY

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<tr>
<th>ASAS20</th>
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Lower trabecular bone mineral density and thinner cortices at peripheral bones in patients with RA
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Introduction: It is well established that peripheral areal bone mineral density (aBMD) measured by dual x-ray absorptiometry (DXA) and the juxta-articular BMD metacarpal index (ratio of cortical area/total bone area) assessed by plain radiographs are reduced in patients with RA compared to the general population. Using peripheral quantitative computed tomography (pQCT), the aim of the present study was to compose a more detailed assessment of trabecular and cortical bone involvement in RA.

Methods: Consecutive RA patients seen at the Department of Rheumatology of the Inselspital Bern were recruited. PQCT measurements were performed at the distal epiphyses and mid-shafts of the radius,ibia and 3rd metacarpal (additional measurement was placed at one third of bone length from the distal end of the 3rd metacarpal). At the epiphyses bone mineral content (BMC), total BMD and trabecular BMD of the central 45% of the bone cross sectional area (CSA) were determined. At the shafts, total bone CSA (including medullary CSA), cortical bone CSA (excluding medullary CSA), cortical wall thickness, and cortical BMD were determined. Bone parameters were compared to those recently measured in a healthy reference population in our department by means of independent t-tests.

Results: Twenty-six RA patients and 133 reference participants were analysed for this abstract. Both patients and reference populations were comparable with regard to age, sex and weight. Trabecular and total BMD were significantly lower and shaft cortical wall thickness thinner (all p < 0.01, 95% confidence intervals not overlapping) in RA patients than controls at the radius (14-22%), tibia (8-10%) and metacarpal bone (8-16%). In addition, trabecular BMD at the 3rd metacarpal tended to be lower in patients with erosive RA than in patients without erosive changes.

Conclusions: Bone involvement in RA was found at all measured peripheral skeletal sites in the form of lower total and trabecular BMD as well as thinner shaft cortices. P QCT measurement is shown to be a sensitive and discriminative method to detect bone involvement in RA.

Peripheral bone mineral density and bone geometry in patients with diffuse idiopathic skeletal hyperostosis (DISH): preliminary results
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Introduction: Recent studies in patients with DISH have suggested that peripheral areal bone mineral density (aBMD) measured by dual x-ray absorptiometry (DXA) and the metacarpal index assessed by plain radiographs are elevated in these patients. Using peripheral quantitative computed tomography (pQCT), the aim of the present study was to assess whether a potential bone mass increase in DISH patients is of densitometric or geometric nature.

Methods: Consecutive patients with radiographically established DISH seen at the Department of Rheumatology of the Inselspital Bern were recruited. An age, sex and height matched control group were recruited from hospital staff and by locally distributed flyers, was also measured using the same protocol. P QCT measurements were performed at the distal epiphyses and mid-shafts of the radius, tibia and 3rd metacarpal. At the epiphyses total BMD and trabecular BMD of the central 45% of the bone CSA were determined. At the shafts, total cross sectional area (CSA) (including medullary CSA), cortical CSA (excluding medullary CSA), cortical wall thickness, and cortical BMD were determined. Muscle and fat CSA were also determined at the lower arm and lower leg by means of pQCT. Bone parameters were compared between the two groups using independent t-tests with alpha set at 0.05.

Results: 17 DISH patients and 30 reference participants were analysed for this abstract. DISH patients were age, sex and height matched to controls, but they were 21.2 kg (95% confidence interval 12.7-29.8 kg, p < 0.0001) heavier than controls. Muscle CSA at the lower arm and leg were comparable between the two groups, but DISH patients had a 65% (95% CI 17-113%, p < 0.0001) greater fat CSA at the lower arm. None of the measured bone parameters at the radius tibia or 3rd metacarpal bone differed between the two groups.

Conclusions: Measured with pQCT, we found no generalised bone apposition at peripheral skeletal sites in DISH patients. Lower DISH patients were significantly heavier and had greater fat mass at the lower arm, which would lead to overestimation of BMC and aBMD measured by DXA.
Relationship between lower arm muscle cross-section and bone densitometric and geometric parameters of the 3rd metacarpal bone

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Introduction: Metacarpal index (ratio between cortical bone area and total bone area) assessment by plain radiographs has been widely used to classify the severity of RA disease activity and progression. Using peripheral quantitative computed tomography (pQCT), the aim of the present study was to determine the contribution of muscle forces (via surrogate measurement of muscle cross-sectional area (CSA)) of the lower arm to densitometric and bone geometric parameters of the 3rd metacarpal bone.

Methods: Consecutive RA patients seen at the Department of Rheumatology of the Inselspital Bern were recruited. Additionally, a reference population of healthy controls was recruited from hospital staff and by locally distributed flyers. PQCT measurements were performed at 4%, 30% and 50% of total bone length measured from the distal bone end. At the epiphysis (4%) bone mineral content (BMC), total BMD and trabecular BMD of the central 45% of the bone (CSA) were determined. At the shaft (30% and 50%), BMC, total bone CSA (including medullary CSA), cortical CSA (excluding medullary CSA), cortical wall thickness, and cortical BMD were determined. Muscle CSA of the lower arm was measured at 66% of ulnar bone length measured from the distal end of the radius. A Pearson linear correlation coefficient matrix was formed with independent parameters group (RA and control), age and muscle CSA and dependent bone parameters of the 3rd metacarpal.

Results: 26 RA patients and 133 controls were included in the analysis. Lower arm muscle CSA showed the highest correlation coefficients with all measured bone parameters of the 3rd metacarpal except trabecular BMD of the distal epiphysis. Correlation coefficients between lower arm muscle CSA and shaft cortical CSA and shaft BMC were between 0.75 and 0.86. Group showed the highest correlation coefficient with trabecular BMD (r = -0.35).

Conclusions: There is a strong underlying positive relationship between lower arm muscle volume and cortical shaft bone parameters which can not be neglected when assessing bone involvement in RA patients. Thin cortices at the metacarpal bones of RA patients are likely to be the result of muscle disuse. Trabecular BMD of the distal 3rd metacarpal bone is less dependent on muscle volume but instead more strongly associated with RA induced inflammation driven bone change.

Mycobacterium marinum infection in undifferentiated spondyloarthritis: Role of TNF blocking strategies?

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Patient history: This 44 year old farmer suffered from a dactylitis of the first toe. After injection with corticosteroid he developed a chronic fistula, which was finally surgically removed. Several months thereafter a carpal tenosynovitis and arthritis of the left hand developed and the patient reported inflammatory back pain.

Laboratory results at admission were: CRP 6 mg/l; Lc 6.3 G/L; Tc: 218; rheumatoid factor, ANA, HLA B27 negative. Quantiferon Test 10.7 IU/ml (<0.4); Serology for Rubella, Parvovirus B19, Bartonella, Borrelia Burgdorferi, Chlamydia trachomatis, Salmonella, Campylobacter, Yersinia, Brucella, Streptococcae were negative.

Treatment and evolution: NSAR and corticosteroids, later co-medicated with methotrexate proved insufficient. Additional etanercept combined with INH for treatment of latent tuberculosis ameliorated peripheral synovitis and also improved back pain. Unexpectedly, however, tenosynovitis secondarily deteriorated. This prompted a synovectomy. Histological examination revealed granuloma formation with giant cells (Fig. 1). Bacterial cultures remained negative for mycobacteriae and eubacteriae. Due to an increase of liver enzymes methotrexate was temporarily stopped. As a consequence synovitis flared and the prior fistula of the first toe became active.

A second synovectomy led to the detection of Mycobacterium marinum. Etanercept and methotrexate were stopped and an antibacterial therapy with ethambutole, clarithromycine, and rifampicine was initiated. Despite improvement of general health and resumption of work as a farmer, sterile synovitis of the carpal joint flared after 6 months. MRI showed synoval proliferation with concomitant osseous activity (Fig. 2).

After a thorough discussion we decided to destroy granulomatous inflammation with the use of infliximab. 2 infusions at a dose of 5 mg/kg were sufficient to induce a remarkable regression of swelling and pain.

Conclusions: Unexpected inflammatory signs under successful treatment with TNF blocking agents should always prompt a thorough search for complicating infections. While TNF blocking strategies are known to promote latent tuberculosis, they can also be helpful to destroy granulomatous inflammatory reaction and help to achieve complete remission in cases of mycobacterium marinum.
Erhebung der Fitness und Einfluss des Body Mass Index und Alter bei Jugendlichen von 13–15 Jahren in den Kantonen SG und AR

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Hintergrund: Die Zunahme überwiegender Jugendlicher (BMI) und einer Abnahme der physischen Fitness (pF) ist ein breites Thema in der Presse. Es wird angenommen, dass ein Zusammenhang zwischen der pF und dem BMI besteht. Es gibt jedoch keine epidemiologischen Studien, die 

Relevanz: Die Bevölkerung wird immer überwiegender und die allgemeine Fitness nimmt ab. Für Präventionsprogramme ist es wichtig, den BMI und der pF in Relation zum BMI zu überprüfen. Es ist wichtig, in Zukunft präventive Maßnahmen aufzunehmen, die den BMI und der pF verbessern können.


Untersuchung der Intra- und Intertester Reliabilität der Evaluation der funktionellen Leistungsfähigkeit für stationäre Arbeitshaltungen

Barbara Aschbacher, Peter Oesch, Otto Knüsel
Rehabilitationsschwerpunkt Valens


Ziel: Die Darstellung der Intra- und Intertester Reliabilität der EFL Tests für stationäre Arbeitshaltungen

Schmerzgrenze durchgeführt. Ein dritter Therapeut mass mit einer asymptomatischen Personen, einen standardisierten Upper Limb Neural Tension Test 2a, sowie die normalen Symptome an den oberen Extremitäten bei sonst asymptomatischen Personen zu ermitteln. Methode: Uns hat nicht die Anzahl von Patienten, der die Testen absolvierte, und die Methoden die Ergebnisse, die die Bewegungsausmaße auf den Schultergürteln, dem Ellenbogen und dem Handgelenk wurden. Die Reliabilität kann als moderat bis gut bezeichnet werden. Die Variabilität des Bewegungsausmasses war auch bei diesen gesunden Probanden gering, was die Durchführung dieser Reliabilitätsstudie an gesunden Personen rechtfertigt. Die Lokalisation der Symptome am Ende der Bewegung entsprach der in der Literatur beschriebenen.


Könklusion: Die Reliabilität kann als moderat bis gut bezeichnet werden. Die Variabilität des Bewegungsausmasses war auch bei diesen gesunden Probanden gering, was die Durchführung dieser Reliabilitätsstudie an gesunden Personen rechtfertigt. Die Lokalisation der Symptome am Ende der Bewegung entspricht der in der Literatur beschriebenen.
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