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Antibodies against periodontal pathogens are not associated with joint swelling or autoimmunity associated with RA in a cohort of healthy individuals at increased risk of rheumatoid arthritis. A. Finckh1, R. B. Mueller2, J. Dudler1, B. Moeller2, D. Kyburz3, U. Walker4, I. Von Muehlenen1, S. Bas1, C. Gabay1, N. Bostanci2
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Introduction: Evidence suggests an association between periodontitis and rheumatoid arthritis (RA). If the association between the two diseases is causal, an immune response against common pathogenic bacteria involved in periodontitis should precede the development of the disease. The objectives of this work is to examine if serum antibodies against pathogenic bacteria involved in periodontitis are associated with early symptoms of the disease in healthy individuals at increased risk of developing RA.

Methods: This is a nested case-control study of a prospective cohort of first degree relatives of patients with RA (FDRs). FDRs had no established rheumatologic condition at inclusion. All FDRs provided serum at inclusion and are followed prospectively until development of RA. We selected 4 groups of patients, corresponding to different phases of RA disease development: (1) Group 1 – FDRs at risk of RA without signs and symptoms of arthritis includes the autoimmunity (control group); Group 2 – FDRs with systemic autoimmunity associated with RA (anti-CCP+ or rheumatoid factor+); Group 3 – FDRs with inflammatory arthritis without clinical arthritis; Group 4 – FDRs who have presented at least one swollen joint (“Unclassified arthritis”). The four groups were matched for tobacco smoking, age, sex and shared epitope status using propensity scores. The primary outcome was the levels of serum immunoglobulin (Ig) G against five selected periodontal Pathogens: Porphyromonas gingivalis, Treponema denticola, Tannerella forsythia, Aggregatibacter actinomycetemcomitans and Prevotella intermedia and one non-pathogenic oral species (Streptococcus oralis) assessed using validated enzyme-linked immunosorbent assays. We also normalized the absolute levels of IgG against the pathogens using the IgG level against the non-pathogenic S. oralis (ratio). Non-linear ANCOVA models were fit to test the association between levels of IgGs against pathogenic oral bacteria and specific phases of RA development.

Results: The four groups each included 51 FDRs balanced for potential confounding factors of periodontitis. Median age was 51 years (IQR: 39–60). 70% were women, 27% smokers. Although quantitative differences existed between the four groups of probands, none of the IgG against the periodontal pathogens differed significantly between the groups. Furthermore, IgG levels against P gingivalis were not associated with seropositivity (ACPA or RF) (p = 0.90), age (P = 0.15), shared epitope status (p = 0.63) or sex (P = 0.26).

Conclusion: Longitudinal studies are still needed to establish the causal involvement of periodontitis, or its associated bacteria, on RA development. However, the results from this case-control study do not suggest that circulating antibody levels against common periodontal pathogens are associated with specific phases of RA development and useful as a prognostic tool.

Figure 1
Baseline mRSS in patients with and without skin regression: patients with skin regression (shown in black bars) have higher baseline mRSS relative to patients without skin regression (shown in grey bars).

Cortisol Circadian Rhythm Changes are associated with low trabecular bone score and increased fracture risk, without any influence on bone mineral density: the OsteoLaus Cohort
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Aim: In glucocorticoid (GC)-induced osteoporosis, fracture risk is poorly correlated with BMD. TBS is a bone texture analysis which correlates with micro-architecture parameters. It independently correlates to fracture risk. Lower TBS but normal BMD are found in patients with high GC levels, even in subclinical hyper-cortisolism. Cortisol production and bone turnover exhibit a circadian cycle. Cortisol circadian rhythm changes with age, with globally a greater area under the curve mainly due to an increase of the nadir levels during the 1st half of the night. Bone turnover circadian pattern is inversely correlated to cortisol one with a time lag of 4h. Changes in therapy and medical resources. Moreover, it could improve cohort selection in CT with skin fibrosis as a major outcome. In this study, we aim to identify predictors for improvement of skin fibrosis over a 1 year follow-up in dCSSc patients.

Methods: We performed a longitudinal analysis on the EUSTAR registry. The inclusion criteria were: dCSSc, fulfillment of ACR criteria, baseline mRSS ≤ 7, available data for mRSS at 12 ± 2 months. The primary outcome was skin improvement, defined as decrease in mRSS of >5 points AND ≥25% within 1 year. Variables with p < 0.2 in univariate analysis were selected for multivariable analysis using ordinal group technique. Multiple imputation for missing data was used. Multiple logistic regression was applied to each of the imputed datasets. Variables included in >50% of the models were re-tested in the available dataset. The final model was validated in a second temporal cohort from the EUSTAR database.

Results: Out of 11228 EUSTAR patients, 704 fulfilled the inclusion criteria and 155/704 (22%) patients had skin improvement. In univariate analysis, high baseline mRSS (fig. 1), a high modified skin fibrosis progression rate at baseline, cardiac involvement (defined as presence of at least one conduction blocks, diastolic dysfunction or left ventricular ejection fraction <45%), immunosuppression and ESR<25 mm/h were associated with skin improvement after 1 year. In multivariable logistic regression, the variables present in >50% of the models from the imputed datasets were baseline mRSS (100%), Anti-SCl-70 positive (97%), ESR <25 mm/h (98%), DLCO ≥70% (91%). These were tested again in the available dataset. The final model revealed high mRSS at 1st visit and ESR <25 mm/h as independent predictors of skin improvement after 1 year. The model was confirmed in the validation cohort.

Conclusions: These results show that patients with already advanced skin fibrosis are more likely to regress under standard of care in the next 12 months than patients with milder skin fibrosis. Thus, focus for treatment intervention and recruitment in CT aiming at skin fibrosis should shift from these patients with high baseline mRSS to at risk patients characterized by lower moderate skin fibrosis.

Background and objectives: Improvement of skin fibrosis over time is part of the ‘natural history’ of diffuse cutaneous systemic sclerosis (dcSSc). However, in individual patients, the pattern of change in skin fibrosis varies widely. The extent of skin fibrosis measured by the modified Rodnan skin score (mRSS) is the major outcome measure in clinical trials (CT) in dcSSc. Understanding the factors behind the improvement of skin fibrosis in dcSSc could avoid unnecessary use of
Secukinumab, a Monoclonal Antibody to Interleukin-17A, Significantly Improves Signs and Symptoms of Active Ankylosing Spondylitis: Results of a Phase 3, Randomized, Placebo-controlled Trial with Subcutaneous Loading and Maintenance Dosing

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Background/Purpose: Previous data indicate that interleukin (IL)-17, a key pro-inflammatory cytokine, might play a role in the pathogenesis of ankylosing spondylitis (AS). We assessed the efficacy and safety of two different doses of secukinumab, a fully human anti–IL-17A monoclonal antibody, in a randomized, multicenter, double-blind, placebo (PBO)-controlled, phase 3 trial in patients with AS (MEASURE 2; NCT01649375).

Methods: Adults with active AS fulfilling modified New York Criteria and a BASDAI ≥4, despite adequate NSAID therapy, were randomized to receive weekly subcutaneous (s.c.) secukinumab 75 mg, 150 mg, or PBO for 4 weeks followed by dosing every 4 weeks. Subjects naïve to anti-TNF agents (61.2%) and subjects with prior intolerance or inadequate response to anti-TNF agents (anti–TNF-IR, 38.8%) were included. The primary endpoint was the proportion of subjects achieving an ASAS20 response at Week 16. Secondary endpoints included ASAS40, hsCRP, BASDAI, ASAS 5/6, SF-36 PCS, ASQoL, and ASAS partial remission. Statistical analyses used non-responder imputation and followed a pre-defined hierarchical hypothesis testing strategy to adjust for multiplicity.

Results: 219 subjects were randomized. Demographics and baseline disease characteristics were comparable between study arms; mean age 43.3 years, mean time since diagnosis 6.2 years and mean BASDAI 6.65. The primary endpoint was met with secukinumab 150 mg at Week 16: ASAS20 response rate was 61.1% vs 28.4% with PBO (P <0.001; fig.), with significant improvements seen as early as Week 2. Secukinumab 150 mg also significantly improved hsCRP, ASAS40, ASAS 5/6, BASDAI, SF-36 PCS and ASQoL compared with PBO. Efficacy of secukinumab 150 mg vs. PBO was observed in both anti–TNF-naïve and anti–TNF-IR subjects for ASAS20 (68.2% vs. 31.1% and 50.0% vs 24.1%, respectively; both P <0.05) and ASAS40 (43.2% vs 17.8% and 25.0% vs 0%, respectively; both P <0.05). Secukinumab 75 mg provided numerically greater responses than PBO at Week 16, but these did not reach statistical significance for any of the pre-specified primary or secondary endpoints based on hierarchical testing. Similar adverse event (AE) rates were reported up to Week 16 for secukinumab 75 mg (57.5%), 150 mg (65.3%), and PBO (63.5%). Serious AEs were reported in 5.5% of subjects in the secukinumab 75 mg group, compared with 5.6% in the secukinumab 150 mg group and 4.1% in the PBO group.

Conclusion: Secukinumab 150 mg s.c. was effective at rapidly reducing the signs and symptoms of disease and improving health-related quality of life in subjects with active AS, regardless of prior anti-TNF exposure. Secukinumab was well tolerated, with no unexpected safety findings.

Patients with non-radiographic axial spondyloarthritis classified by the clinical or the imaging arm of the ASAS classification are comparable regarding disease characteristics, response to TNF inhibition and radiographic progression to ankylosing spondylitis

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Background: The concept of non-radiographic axial spondyloarthritis (nr-axSpA) is still controversial and treatment with tumor necrosis factor inhibitors (TNFi) for this condition has not been approved by all
national health authorities. Concerns have been raised with regard to the natural history of the disease and to the issue that patients with non-inflammatory musculoskeletal conditions on the background of HLA-B27 positivity might be misclassified as having nr-axSpA. The aim of this study was to compare patients with nonradiographic axial spondyloarthritides (nr-axSpA) classified by the clinical arm versus the imaging arm of the Assessment of Spondyloarthritis international Society (ASAS) classification criteria in a real-life observational cohort.

Methods: In an analysis of 376 nr-axSpA patients within the Swiss Clinical Quality Management cohort, we compared 227 patients in the imaging arm and 149 patients in the clinical arm with respect to disease characteristics, response to TNF inhibitors (TNFi) at 1 year and progression to ankylosing spondylitis (AS) during follow-up. Pelvic X-rays were scored according to the modified New York criteria by two calibrated readers, blinded to patient and disease characteristics, in chronological order.

Results: Patient and disease characteristics were similar in the 2 groups, except for minor differences, partly imposed by disparities inherent to classification (inflammation on MRI versus HLA-B27 positivity) and to the fact that in this arm ≥2 clinical and laboratory features are needed for classification as opposed to only ≥1 for the imaging arm. A positive family history of SpA, peripheral arthritis and uveitis were found more frequently in the clinical arm vs the imaging arm (39% vs 24%, 47% vs 35% 25% vs 7%, respectively). The longer disease duration in the clinical vs the imaging arm (11.6 vs 7.1 years, p <0.001) might be due to changing clinical practice over time and the increasing role of MRI over HLA-B27 in the diagnosis of the disease. After initiation of TNFi in 40% of nr-axSpA patients, ASAS40 response at 1 year was reached by 33% in the imaging arm versus 44% in the clinical arm (odds ratio 0.6, 95% confidence interval 0.1–2.9, p = 0.4) (Table). A similar proportion of patients developed AS during a comparable median observation period of 3.4 years in the imaging arm and of 3.2 years in the clinical arm (24% vs 20%, respectively, p = 0.7).

Conclusion: nr-axSpA patients meeting the ASAS imaging or clinical arm were comparable regarding disease characteristics, response to treatment with TNFi and radiographic progression to AS.
Estrogen exposure and the development of anticitrullinated protein antibodies in women at risk of rheumatoid arthritis (RA)

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Introduction: The etiopathogenesis of rheumatoid arthritis (RA) is viewed as a multi-step process whereby environmental factors induce pathologic activation of the immune system, the development of autoimmunity and finally the clinical onset of RA in susceptible individuals. The role of female hormones is controversial and their characteristics such as heavy tobacco smoking (>10 pack-years), alcohol consumption, obesity, shared epitope or rheumatoid factor positivity were balanced between ACPA positive and negative FDRs. Safety data collected during the OLE were consistent with previous baricitinib findings.

Results: A total of 668 women FDRs were analyzed, of which 32 (5%) were ACPA-positive. We found an older mean age in ACPA-positive (54 years) compared with ACPA-negative (45.1) FDRs. Other characteristics such as heavy tobacco smoking (>10 pack-years), alcohol consumption, obesity, shared epitope or rheumatoid factor positivity were balanced between ACPA-positive and negative FDRs. Moderate and high estrogen exposure categories by CLE score were associated to ACPA positivity, but without statistical significance. We found associated, OR 2.7 (95% CI: 1.1–6.5). Other female hormonal exposure and the development of systemic autoimmunity associated to the development of ACPAs, OR 3.3 (95% CI: 1.1–10.4). The exposure of interest was concomitant statin use reported by the treating rheumatologist and/or the patient and categorized as ever or never. To minimize exposure misclassification or false negatives, we excluded patients with hypercholesterolemia, but no information on lipid lowering therapy. The primary end point was radiographic disease progression as measured by the rate of change from baseline in radiographic damage scores. The damage score (ERO) was assessed on 38 joints of hands and feet with a validated scoring method (Ratinogen score) by a single experienced reader, blinded to clinical history. We analyzed the rate of ERO progression in pts treated with statins or not using a mixed regression model for longitudinal data, adjusting for potential confounding factors.

Methods: This is a prospective observational cohort study nested within the Swiss RA registry (SCQM-RA). The SCQM monitors disease activity, radiographic damage, patient characteristics and treatments at regular intervals. All patients in the SCQM-RA database with sequential X-rays and information on statin use were included. The exposure of interest was concomitant statin use as reported by the treating rheumatologist and/or the patient and categorized as ever or never. To minimize exposure misclassification or false negatives, we excluded patients with hypercholesterolemia, but no information on lipid lowering therapy. The primary end point was radiographic disease progression as measured by the rate of change from baseline in radiographic damage scores. The damage score (ERO) was assessed on 38 joints of hands and feet with a validated scoring method (Ratinogen score) by a single experienced reader, blinded to clinical history. We analyzed the rate of ERO progression in pts treated with statins or not using a mixed regression model for longitudinal data, adjusting for potential confounding factors.

Results: 4213 RA patients with a median of 4 [2–6] sequential X-rays/pt and 3.9 [2.0–6.4] years of follow-up/pt were included. 493 (11%) of pts were taking statins during follow-up. Statin users were significantly more often males (34% versus 23%, p < 0.001), older (mean age 58 versus 54 years, p < 0.001) and overweight (mean BMI 27.0 versus 24.9, p < 0.001). RA treatment and disease characteristics were balanced between statin-users and non-users. After adjusting for differences in baseline prognostic factors, we found no significant difference in ERO progression in statin-users compared to non-users (ERO progression in statin-users 0.98 % of the maximum score per year (95% CI: 0.46–1.49), compared to 0.95% (95% CI: 0.70–1.20); p = 0.36). Disease characteristics associated with higher ERO were male sex, longer disease durations, rheumatoid factor positivity, higher disease activity and treatment types.

Conclusion: The results of this study do not support the hypothesis that statins are protecting against progression of structural joint damage and bone erosions.

Can ultrasound (US) predict an evolution towards rheumatoid Arthritis (ra) in patients with inflammatory polyarthralgia without anti-citrullinated antibodies (ACPA)?

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Background: Subclinical synovitis elicited by US in pre RA patients with anti-citrullinated antibodies (ACPA) have been shown to be predictive of future development for RA [1]. No such study has been conducted in ACPA negative patients.

Objectives: The primary aim of the study was to assess the value of the US as a screening tool to detect early joint involvement in patient complaining of polyarthralgia and to predict the future development of an inflammatory disease in particular RA in absence of ACPA. The secondary aims were to look for clinical and biologic additional predictors of RA development in these patients.

Methods: This is a retrospective real life study of 101 consecutive patients seen in investigation in our ambulatory unit between 2009 and 2013 for poly-arthritis with or without clinical synovitis who did not meet before US examination ACR / EULAR 2010 criteria for RA or for another inflammatory rheumatology disease. To detect significant
US synovitis, we applied the criteria validated in the SONAR score. The follow-up data were extracted from the flow charts of the service or information taken from regular doctors.

Results: At baseline (30/%) had significant synovitis according to the SONAR criteria. After including US synovitis for the calculation of the number of synovitis, 2 patients fulfilled already the ACR EULAR criteria for RA. The mean (SD) follow-up time was 19 (7). 17 patients developed a clear inflammatory arthritis (11 RA, 6 another inflammatory arthritis). Significant US synovitis at baseline was a better independent predictor of an evolution to RA than CRP and clinical synovitis (see table).

Conclusions: Our study suggests that US can be a good predictor of an evolution to RA in patients presenting inflammatory poly-arthritis without ACPA.

Methods: Investigator-driven phase I/II, dose-finding, placebo-controlled study to describe rheumatic adverse events following rVSV-ZEBOV vaccination. The aim of this work is to establish the safety of various doses of rVSV-ZEBOV. We described the clinical presentation of arthritis following rVSV-ZEBOV vaccination.

Results: 59 subjects received either rVSV-ZEBOV (n = 51) or placebo (n = 8). Baseline characteristics did not differ among the groups. Mild to moderate early-onset reactogenicity was frequent (50/51 vaccinees, 98%), with early low grade fevers, headaches and myalgias in 84%, but no replication of the virus could be demonstrated in the peripheral blood or skin lesions. rVSV RNA was detected in the synovial fluid (11) and in skin vesicles (3), but no replication of the virus could be demonstrated in the synovial fluid. Occurrence of arthritis was associated with decreased drop in lymphocyte count at day 1 (ρ = 0.033). All patients responded well to a limited course of NSAIDs or a single infiltration with glucocorticoids.

Conclusion: The occurrence of arthritis following a symptom-free interval was unexpected and lead to a temporary suspension of the trial. Detection of rVSV RNA in the synovial fluid suggests the presence of rVSV-ZEBOV in affected joints, as reported following rubella infection or vaccination. However, no replication of rVSV-ZEBOV could be demonstrated. The most likely hypothesis is thus that rVSV-ZEBOV-induced arthritis is associated with immune-complex deposition.

Anti-TNF treatment in patients with chronic low back pain associated with Modic I changes

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Introduction: There are elements from the scientific literature supporting the concept that chronic low back pain (CLBP) patients with Modic I endplate changes have a peculiar clinical and biological presentation. They have more often an inflammatory pain pattern that may resemble to axial spondyloarthritides [1] and TNF-α-alpha has been shown to be expressed in the endplate [2]. We hypothesized that anti-TNF treatment could be a possible new treatment for these patients.

Methods: Patients suffering from CLBP, who had an inflammatory pain pattern according to adapted Calin criteria, Modic I changes on lumbar MRI and who failed previous NSAIDs treatments received 3 months of adalimumab (40 mg subcutaneous injection, 1 every other week, i.e., 7 injections) in addition to their usual pain medication. Patients with sign or symptoms of specific LBP including patients who fulfilled the criteria for spondyloarthopathies were excluded. Primary endpoint was defined as at least 20% of the patients achieving low disease activity defined as pain ≤2/10 and Roland-Morris questionnaire (RMDQ) ≤4/24. Secondary outcomes were the Bath Ankylosing Spondylitis Disease Activity Index (BASDAI), intensity and duration of morning stiffness, modification of pain medication and quality of sleep.

Results: Ten consecutive patients (4 male) with mean age 42.4 ± 3.9 years were included. They were suffering from CLBP for an average of 6.5 ± 1.6 years. At inclusion the level of pain was 6.5 ± 1.6, RMDQ 14.9 ± 4.2, BASDAI 4.9 ± 1.8. At 3 months, 2 patients had VAS for back pain ≤2 and only 1 of them had RMDQ ≤4 thus the primary outcome was not achieved. Median (interquartile range) back pain decreased from 6.50 [6.00–7.75] to 6.00 [5.125–7.00], RMDQ 16.0 [11.0–18.0] to 12.0 [8.75–13.75] and BASDAI from 5.095 [4.380–5.270] to 4.075 [3.280–4.725], all p >0.05. No significant difference was observed on coexisting pain medication, morning stiffness or quality of sleep.

Conclusion: This proof of concept study failed to achieve the predefined primary outcome. In addition no significant global effect was observed in secondary outcomes. In conclusion TNF-α-alpha does not appear to be a key molecule in patients with chronic inflammatory low back pain associated with Modic I endplate modification and anti-TNF-α-alpha treatment should not be used in these patients.

Disclosure: This study received an unconditional research grant from Abbvie.


New patients consulting the CHUV rheumatology outpatient clinic, a 6 months evaluation

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Objectives: The objectives were to assess, in a quality control process, the management and the characteristics of new patients referred to the general rheumatology outpatient clinic in the Lausanne University Hospital.

Methods: All new patients seen at the general rheumatology outpatient clinic between 01.06.2014 and 30.11.2014 were included. New patients were defined as patients consulting for the first time or patients who have not been seen for 2 years or more. Patients seen in the back pain unit, musculoskeletal ultrasound consultation, bone disease center consultation, paediatriac transition consultation, multi-disciplinary consultations and patients participating in clinical studies were excluded.

Results: 543 new patients were seen within 6 months: 59% of patients at the standard consultation (27% by a resident, 11% by a fellow, 21% by a senior rheumatologist) and 41% at the rheumatology emergency consultation.
Patients were coming from the canton of Vaud (90%), the canton of Valais (4%) and the canton of Fribourg (3%). Patients were mainly women (80%). Mean age was 53.

Patients were referred for emergency consultations mainly by the emergency department (35%), by hospital wards (31%) and by general practitioners (10%). For these patients, 17% were finally hospitalized in the rheumatology ward within 2 weeks.

Patients were referred for general rheumatology consultations mainly by general practitioners (33%), other outpatient clinics in the hospital (32%), by themselves (10%) and rheumatologists in private practice (7%).

A follow-up visit was planned for 55% of patients (patients seen by a resident/fellow: 75%, by a senior rheumatologist: 42%).

The waiting time to get an appointment was <1 day for the emergency rheumatology consultation, 25-37 days to see a resident or fellow and 35 days to see a senior rheumatologist.

For patients seen by a resident or fellow, there was a consultation report available in 67%. Reports were sent within 3 months of the first consultation for 58% of patients seen by a resident and 74% by a fellow.

Patients seen at the general rheumatology consultation were suffering mainly from non-inflammatory arthropathies (21%), abarticular diseases (16%), back pain (15%), spondyloarthritis (8%) and rheumatoid arthropathy (6%). Patients seen at the emergency rheumatology consultation were suffering mainly from crystal arthropathies (27%), back pain (18%) and abarticular diseases (10%). 32 and 27 new patients suffering of spondyloarthritis and rheumatoid arthritis respectively were identified in 6 months.

Conclusion: Patients seen in the rheumatology outpatient clinic were mainly local, middle aged women. Main pathologies seen in the rheumatology consultation were non-inflammatory arthropathies and abarticular diseases and, for the emergency consultation, crystal arthropathies. Waiting time for an appointment was generally less than 6 weeks. A consultation report was available for most of patients.

3D vs 2D musculoskeletal ultrasound of supraspinate tendon tears

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Background: 3D (three-dimensional) US (ultrasound) of the shoulder seems to be as accurate as 2D (two-dimensional) US when compared with MRI and surgical findings for the diagnosis of full- and partial-thickness rotator cuff tears. However, 3D ultrasound transducer acquired images have poorer inter- and intra-rater reliability for the assessment of supraspinate tendon partial tears compared to 2D images.

Objectives: The aim of this study was to determine the intra- and inter-rater reliability in the analysis of conventional 2D and of 3D acquired ultrasound images in the detection of different tear types of the supraspinate tendon performed by rheumatologists with different experience level in musculoskeletal ultrasound.

Methods: Non-interventional prospective observational pilot study of 2309 images (210 3D image sets) of 127 adult patients suffering from unilateral shoulder pain. 2D and 3D images were scored by three readers (one fellow sonographer EULAR Teacher/EFUMB Level 2 = reader A, one advanced sonographer EULAR Teacher/EFUMB Level 2 = reader B, and one advanced sonographer EULAR Teacher/EFUMB Level 3 = reader C) independently as partial-thickness tears (bursal sided partial-thickness tear, intrasubstance partial-thickness tear, articular sided partial-thickness tear, full-thickness tear and no tear. The intra-and inter-rater reliability were calculated.

Results: There was an excellent intra-rater agreement of reader A in the overall classification of supraspinate tendon tears (2D vs 3D images k = 0.892, pairwise agreement 93.81%, 3D scoring round 1 vs 3D scoring round 2 k = 0.875, pairwise agreement 92.857%). The inter-rater agreement was only moderate compared to reader C on 3D images (k = 0.497, pairwise agreement 70.95%) and fair compared to reader B (k = 0.236, pairwise agreement 42.38%). There was however excellent overall agreement in the classification of full thickness tears between the 2D and 3D images (k = 0.810) and overall good agreement in the classification of partial thickness tears (k = 0.667).

Conclusions: The use of 3D ultrasound in the assessment of supraspinate tendon tears has an excellent intra-rater agreement for an advanced sonographer and an excellent inter-rater agreement in the detection of full thickness tears. We found a good inter-rater agreement for an advanced sonographer and a fair to moderate inter-rater agreement for a less experienced sonographer. The main reason for discordant results were articular sided partial thickness tears at the footprint where anisotropy makes interpretation difficult.

Therefore we emphasise to consider the anisotropy at this special anatomical level and special care in probe positioning while taking the 3D scans. Nevertheless 2D evaluation has the advantage of additional information (e.g. sonopellogen, dynamic examination) and the differentiation of articular sided partial thickness tears versus tendinosis or anisotropy.


Anti-fractureary effect of combined teriparatide and denosumab treatment in a patient with systemic mastocytosis and successive vertebral fractures

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Introduction: Systemic mastocytosis (SM) is a rare cause of secondary osteoporosis. Up to 51% of patients with SM have bone involvement, with 37% presenting osteoporotic fractures. Standard treatment of osteoporosis secondary to SM consists of bisphosphonates, although treatment of SM with interferon 2balpha has shown an effect on bone density and fracture risk. However, the most efficacious osteoporosis treatment as measured by evolution of Bone Mineral Density consists in combination of teriparatide and denosumab. One unique report has described teriparatide use in 2 patients with osteoporotic fractures resistant to bisphosphonates in the context of SM, with good anti-fractureary effect. No case report on denosumab has been published to our knowledge.

Case description: We present a case of severe osteoporosis in an 85 years old man addressed because of multiple successive spontaneous vertebral fractures (9 in 3 months). Bone densitometry at the time of first fractures showed vertebral and hip osteopenia (minimal T-score –1.9 DS in lumbar spine and left femoral neck).

Because of the severity of the osteoporosis in the absence of risk factors excepted for age, extended research of secondary causes was performed and showed persistent high tryptase values (48.5 µg/l) and 49.1 µg/l; N <13.5 µg/l), suggesting the SM diagnosis. The patient developed skin pruritic lesions which are being investigated. Bone biopsies effectuated on the same time as vertebroplasties showed CD25+ mast cells aggregates of up to 10 cells. Because of the recurrence of vertebral fractures, we considered it as a case of severe osteoporosis and a combined treatment of teriparatide 20 µg s.c. q.d. and denosumab 60 mg twice a year was started. Since the introduction of the treatment 8 weeks after the occurrence of last vertebral fracture, till now, 9 months later, our patient did not present any more vertebral fracture. A follow up bone densitometry will be effectuated one year after the beginning of the treatment. Surveillance of tryptase values under treatment did not show any evidence of progression of mastocytosis.

Conclusion: We first describe here the use of the combined teriparatide-denosumab treatment in a patient with systemic mastocytosis probably due to systemic mastocytosis. Although our patient developed 9 spontaneous vertebral fractures in 3 months, he did not present any more fracture since the introduction of the treatment 9 months ago. A combined treatment is to be considered in the presence of severe osteoporosis with multiple fractures.

Discontinuation of denosumab is associated with a severe increase risk of spontaneous vertebral fractures: 3 case reports

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Introduction: The discontinuation of bisphosphonates is associated with a prolonged reduction in bone turnover markers (BMMs), a slow decrease of bone mineral density (BMD) and no increase of fracture risk (FxR). In contrast, the discontinuation of other antiresorptive agents, is associated with a BTMs rebound and a rapid decrease of BMD to above pretreatment values. FxR is increased after the discontinuation of oestrogens. The discontinuation of Denosumab (Dmb) is associated with a severe rebound effect on BTMs and BMD. It is not known whether this rebound effect is associated with an increase of FxR.

Method: We report the cases of 3 women with postmenopausal osteoporosis without any prior fracture. They received Dmb 60 mg
Endothelin-1 receptor antagonists do not improve skin fibrosis of systemic sclerosis patients from EUSTAR cohort

Suzanna Jordan1, Jing H. W. Distler2, Britta Maurer3, Ulrich Walker3, Dörte Huscher1, Yannick Allamand1, Gabriela Riemekasten4 and Oliver Distler4 on behalf of EUSTAR
1Department of Rheumatology, University Hospital Zurich, Switzerland; 2Department for Internal Medicine 3, Friedrich-Alexander-University Erlangen-Nuremberg, Germany; 4University Hospital Basel, Basel, Switzerland; 5Châtel University Hospital and German Rheumatism Research Centre, Berlin, Germany; 6Paris Descartes University, Sorbonne Paris Cité, Rheumatology A department, Cochin Hospital, Paris, France; 7Department of Rheumatology, University of Lübeck, Germany

Background: Major feature and obstacle of systemic sclerosis (SSc) is fibrosis of skin and internal organs. Preclinical studies showed that endothelin plays important role in perpetuating fibrotic responses in SSc. Positive effects of endothelin-1 receptor antagonists (ETRA) are shown in pulmonary arterial hypertension, in the prevention of digital ulcers, but not in SSC-associated intestinal lung disease. One small, open-labeled, uncontrolled trial showed that ETRA might improve skin fibrosis. Due to promising preclinical, but inconsistent clinical data, studies with a larger number of patients are needed.

Objectives: Aim of our observational, controlled, real-life study was to evaluate the effect of ETRA on skin fibrosis in SSc patients from the large EUSTAR cohort.

Methods: SSc patients from the EUSTAR cohort who fulfilled ACR classification criteria and had at least 3 follow-up visits (pre-study visit without ETRA treatment, baseline and follow-up visit with ETRA treatment) were included. The control group consisted of SSc patients with the same inclusion criteria, but without ETRA treatment. The change of the modified Rodnan skin Score (mRSS) between baseline and follow up was the primary endpoint of the study. Nonparametric data are shown as median and interquartile range and data were analyzed by Mann-Whitney test or the Wilcoxon signed rank test for paired samples.

Results: Data on 75 ETRA treated and 969 control patients were collected from the EUSTAR database. Baseline characteristics of all available patients were as following:
(a) in ETRA group: 69 female/6 male, 41 diffuse/34 limited, age 56 (47–66) years, disease duration 10 (5–18) years, median follow-up (between baseline and follow up) 12 (11–14) months, 30 received DMARDs. 
(b) in control group: 832 female/137 male, 349 diffuse/620 limited, age 56 (47–66) years, disease duration 8 (4–14) years, median follow up 12 (11–14) months, 359 received DMARDs.

Change of the mRSS between baseline and follow up didn’t show any significant difference between the control and the ETRA group (n = 969) 0 (0–2) vs n = 75, (0–2) p = 0.5).

Conclusion: Despite the limitation of our study which includes its observational nature, this controlled study in a real-life setting with a large sample size does not support the use of ETRA as an anti-fibrotic agent.

Myopathy associated with SSc – a joint EUSTAR-SCTC sub-cohort initiative

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Background: Clinical registries and biopositories are indispensable tools for studies in orphan diseases providing unique insights into disease characteristics, outcomes, and pathogenesis. In systemic sclerosis (SSc), muscle disease is common and results in significant disability. The reported prevalence (5–96%) reflects the lack of diagnostic consensus criteria and established diagnostic tools.

Objectives: The purpose of this initiative is to foster collaboration between the EUSTAR and SCTC registries, to promote the inclusion of myopathy in SSc patients into the clinical studies. This joint effort aims at creating a large sample size of patients with myopathy associated with SSc in order to perform meaningful data analyses.

Methods: To address this unmet need, EUSTAR (European Scleroderma Trial and Research) and SCTC (Scleroderma Clinical Trials Consortium) experts launched the joint EUSTAR-SCTC initiative on SSc-associated myopathy. To generate meaningful data, the steering committee decided to create a myopathy sub-cohort within the EUSTAR registry, which currently comprises >12 000 annually followed patients from >200 centres worldwide.

Results: Based on extensive literature review and expert opinion, the Minimal Essential Data Set online was extended for myositis-related items in different categories (table 1). Patients fulfilling one of the inclusion criteria, i.e. elevated levels of the serum muscle enzymes or proximal muscle weakness on physical examination or muscle atrophy on physical examination or positive myositis-associated autoantibodies, became eligible for the study. In parallel, in centers with established biobanking, biosamples are collected in parallel, yet independently from the observational study.

In 05/14, EUSTAR and SCTC centers were invited to participate by e-mail. An interim-analysis in 02/15 showed that 94 patients from 14 SSc expert centers with a total of 417 visits had been included. After a recent reminder, 20 more centres expressed interest and are in the process of getting ethic committee approval.

Table 1: EUSTAR-SCTC myositis sub-cohort

<table>
<thead>
<tr>
<th>Type of registry</th>
<th>Key objectives</th>
<th>Captured features</th>
<th>Biosamples</th>
</tr>
</thead>
<tbody>
<tr>
<td>Multicenter, international, observational</td>
<td>Clinical characterization, consensus criteria, risk-stratified therapies</td>
<td>Demographics, clinical data, function tests, lab tests incl. myositis-associated auto-antibodies, MRI, EMG, biopsies, treatment outcome</td>
<td>Serum, DNA, muscle/ skin biopsies</td>
</tr>
</tbody>
</table>

Conclusions: The joint EUSTAR-SCTC initiative led to the successful establishment of a myopathy sub-cohort with longitudinal data collection, which will provide unique insights in a common, disabling, yet neglected complication of SSc. Furthermore, when linked to biosamples, the registry will become a powerful tool to explore and define pathophysiology mechanisms and biomarkers. Since this is an ongoing study, we encourage all centers with regular follow-up of SSc patients to participate.
Pulmonary Function Tests: High Rate of False Negatives in the Early Detection and Screening of Scleroderma Interstitial Lung Disease

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*contributed equally; 1Division of Rheumatology, University Hospital Zurich, Zurich, Switzerland; 2Department of Internal Medicine and Rheumatology, Drt.Cantacuzino Hospital, Bucharest, Romania; 3German Rheumatism Research Centre, Berlin; Rheumatology and Clinical Immunology, Charité University Hospital, Berlin, Germany; 4Institute of Diagnostic and Interventional Radiology, University Hospital Zurich, Zurich, Switzerland

**Pulmonary Division, Department of Internal Medicine, University Hospital Zurich, Zurich, Switzerland**

**Background and Objective:** Validated methods for screening and early diagnosis of scleroderma-associated interstitial lung disease (SSc-ILD) are needed. In this study, we evaluated the performance of pulmonary function tests (PFT) compared to high resolution computer tomography of the chest (HRCT) for the detection of SSc-ILD in clinical practice and aimed to identify predictors of functionally-occult, but HRCT-significant lung involvement.

**Methods:** Prospectively enrolled patients suffering from SSc were assessed following the EUSTAR standards, including PFT and HRCT. The images were blindly evaluated by two experienced radiologists. The performance parameters of PFT for the diagnosis of SSc-ILD were calculated. Predictors of significant ILD in HRCT in patients with normal FVC were identified through logistic regression.

**Results:** 84/102 (63.0%) patients showed significant ILD on HRCT, while only 27/102 (26.0%) had an FVC <80% and 54/102 (53.0%) had an FVC <80%. Sixty-one (60.2%) patients had a decrease in at least one PFT. 40/64 (62.5%) patients with significant ILD on HRCT had a normal FVC, translating into a high false negative rate. Notably, 5/40 (6.0%) of patients with normal FVC had severe, functionally-occult lung fibrosis, 2 of these having all PFT in normal limits. Applying more comprehensive combinations of PFT to define lung restriction did not result in a significantly improved test performance. The false negative cases had more frequently anti-Scl-70 antibodies and diffuse skin involvement and less frequently anti-centromere antibodies compared to ILD-free patients.

**Conclusion:** The derived evidence-based data reveal a high risk of missing the detection of significant SSc-ILD when relying solely on PFT. More comprehensive screening algorithms for the early detection are warranted. Particularly, additional imaging investigations should be considered in anti-centromere antibodies negative patients with normal FVC for the early detection of SSc-ILD.

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Quadriceps performance under activation of foot dorsal extension in healthy volunteers

Felix Angst, Martina Kaufmann, Susanne Lehnann, André Aeschlimann, Thomas Benz
RehaClinic, Research Department, Bad Zurzach

**Background and aims:** The m. quadriceps femoris is the strongest muscle in the body and plays an important role for mobility in sports, activities of daily living and independence. Two older studies showed increased electromyographic (EMG) activity of the quadriceps if the dorsal extendors of the foot were pre-activated. The aim was to physiologically replicate this finding by EMG and to verify it functionally by single leg hop.

**Methods:** EMG activity (root mean square, RMS) was tested on the leg press at an isometric load of 12-repetition-maximum (12RM) individually specified weight (on average 79.7 kg) at 45° and 90° knee flexion.

**Results:** 45° knee flexion

<table>
<thead>
<tr>
<th>Muscle</th>
<th>without dorsal foot ext.</th>
<th>with dorsal foot ext.</th>
<th>SRM</th>
<th>p</th>
</tr>
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<tr>
<td></td>
<td>mean stddev</td>
<td>mean stddev</td>
<td></td>
<td></td>
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<td><strong>45° knee flexion</strong></td>
<td></td>
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<tr>
<td>m. biceps femoris</td>
<td>14.2 1.4</td>
<td>12.4 0.6</td>
<td>-0.20</td>
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<td>m. tibialis anterior</td>
<td>7.9 1.0</td>
<td>80.3 0.3</td>
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<td>&lt;0.001</td>
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<tr>
<td>m. vastus medialis</td>
<td>32.4 2.4</td>
<td>32.4 1.3</td>
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<tr>
<td>m. rectus femoris</td>
<td>9.4 1.2</td>
<td>15.3 0.7</td>
<td>0.71</td>
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**90° knee flexion**

<table>
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<tr>
<td></td>
<td>mean stddev</td>
<td>mean stddev</td>
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<tr>
<td>m. biceps femoris</td>
<td>23.6 13.4</td>
<td>28.9 16.3</td>
<td>0.97</td>
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<tr>
<td>m. tibialis anterior</td>
<td>26.5 30.1</td>
<td>92.2 2.18</td>
<td>2.18</td>
<td>&lt;0.001</td>
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<tr>
<td>m. vastus medialis</td>
<td>124.9 71.6</td>
<td>78.7 1.08</td>
<td>1.08</td>
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<tr>
<td>m. rectus femoris</td>
<td>77.8 56.4</td>
<td>107.7 0.89</td>
<td>0.89</td>
<td>&lt;0.001</td>
</tr>
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Pilates, Yoga and Tai Chi: evidence-based methods in the active treatment of chronic low back pain?

Thomä Benz, André Aeschlimann, Felix Angst
RehaClinic, Research Department, Bad Zurzach

**Background and aims:** For the conservative treatment of non-specific chronic low back pain (CLBP) exercise therapy, cognitive behavioral therapy, educational interventions, and multidisciplinary (bio-psycho-social) treatment can each be recommended based on the scientific evidence. Complementary, exercise based therapies are rarely used because of less known efficacy. The aim was to evaluate the scientific evidence of Pilates, Yoga and Tai Chi as methods used in exercise therapy for the treatment of CLBP.

**Methods:** Review and discussion of the scientific literature about Pilates, Yoga and Tai Chi as methods of treatment of CLBP with focus on effectiveness.

**Results:** Pilates: The large body of studies about Pilates and eight reviews were summarized by two reviews of 2014 and 2015. Heterogeneity of the single studies was high due to different methodology and quality. In 1/4 to 1/2 studies, Pilates showed significant superior effects when compared to control interventions within groups with the same control intervention. Yoga: Based on two reviews of 2013, there is strong evidence for short-term effectiveness of Yoga. The pooled effect sizes were 0.33 to 0.62 for reduction of pain and 0.35 to 0.65 for improvement of function (short- to mid-term). However, some studies were uncontrolled. Therefore, the effects of Yoga may not be superior to other exercise therapies. Tai Chi: Scientific evidence on Tai Chi is limited to one randomized controlled trial (RCT) of good quality. It concluded that Tai Chi is a safe and effective method for the treatment of CLBP improving pain and disability after a program of 10-weeks duration.

**Conclusions:** Available scientific data of Yoga and Tai Chi showed moderate to strong evidence for short term effectiveness in the treatment of CLBP. In contrast, evidence for Pilates is inconclusive. Mid-term effects were smaller and therefore, the evidence is weaker.

Schweiz Med Form 2015; in review.
Intra-individual changes between with and without dorsal foot extension were quantified and compared by standardized response means (SRM).

Results: Included were 35 healthy subjects between 21 and 57 years.

Conclusions: Pre-activation of dorsal foot extensors significantly increased EMG activity in the quadriceps femoris and single leg hop distance. It can therefore be used to improve functional muscle performance and knee joint stability in training and musculoskeletal rehabilitation.

BMC Musculoskeletal Dis 2015; in review

Discussion: We conclude that there is a strong relation between fear of movement and self perception of functional capacities. This point is important to catch in order to restore this lost of confidence. The importance of a multidimensional rehabilitation programs that address kinesiophobia is hereby reinforced.


Clear relation between kinesiophobia and personal evaluation of activity: important for treatment

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Introduction: Fear of movement, has been proven to be a central element in the understanding of chronic pain. Kinesiophobia is the important variable of the fear-avoidance model. The assessment of perceived functional ability for work-related activities is important in the management of patients with chronic low back pain (CLBP). We investigated the relationship between kinesiophobia and perceived functional ability comparing the Tampa Scale of Kinesiophobia (TSK), the Fear-Avoidance Beliefs Questionnaire (FABQ), and the Performance Assessment and Capacity Testing (PACT).

Methods: 179 patients integrating an intensive 3 week functional Performance Assessment and Capacity Testing (PACT) program were recruited. The PACT program was based on musculoskeletal training and capacity in whiplash associated disorders (WAD) cause high burden for the individual and costs for healthcare. The aim was to determine state and change of health and working-capacity five years after a standardized inpatient pain program of 4 weeks.

Methods: Prospective cohort study. Health and quality-of-life were quantified by the generic Short Form 36 (SF-36; 100 = best) comparing to age-, sex-, and comorbidity-specific German population norms, the neck-specific Northern American Spine Society (NASS) form, and the Coping Strategies Questionnaire (CSQ). Changes of health were determined using effect sizes (ES) at the 6 month and the 60 month follow-up.

Results: The 59 participants had mean age of 40.3 years (sd = 12.3), 83% were women, and 37% had one or more comorbidities. At 5 years, clinical and radiological (RX) evolution was not successful and a new treatment was indicated. As far as fracture healing was concerned the results were spectacular.

Conclusions: Large to moderate long-term effects were observed. Substantial improvements still occurred between 6 and 60 months after start of the rehabilitation program. Improvements observed after having completed rehabilitation could be maintained and expanded in the long-term at home.

Effect sizes (ES) to 6 months follow-up

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<th>SF-36 Physical functioning</th>
<th>Entry to 60 months</th>
<th>6 months to 60 months</th>
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<tr>
<td>0.99</td>
<td>0.16</td>
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<td>SF-36 Role physical</td>
<td>2.22</td>
<td>0.83</td>
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<tr>
<td>SF-36 Bodily pain</td>
<td>1.61</td>
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<td>SF-36 Vitality</td>
<td>0.89</td>
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<td>SF-36 Social functioning</td>
<td>0.71</td>
<td>0.47</td>
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<tr>
<td>SF-36 Mental health</td>
<td>0.61</td>
<td>0.30</td>
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<td>NASS Pain</td>
<td>1.12</td>
<td>0.56</td>
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<tr>
<td>NASS Function</td>
<td>0.78</td>
<td>0.26</td>
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<td>CSQ Catastrophizing</td>
<td>1.03</td>
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