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Abstracts
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In conclusion we diagnosed a first onset of secondary generalized chondrocalcinosis. Her young age made us consider a metabolic condition promoting her joint disease and laboratory examination revealed a chronic hypomagnesemia due to renal wasting. Genetic testing demonstrated a heterozygous 17q12 microdeletion (including the Hepatocyte Nuclear Factor 1-beta (HNF1B) and LHX1 genes) in this family.

Case report: A woman of 43 years was seen in rheumatology for recurrent inflammatory joint complaints. At time of referral, she had a tarsitis and an achilles tendinitis with sub-cutaneous tissue inflammation. Conventional radiography revealed severe chondrocalcinosis and tendon calcification at the feet, knees and wrists. She was known with maturity onset diabetes of the young (MODY), metabolic syndrome, stade 3 chronic kidney disease, a renal agenesis and a pancreatic head atrophy. Her familial history was also noteworthy with a son requiring an abdominal surgical procedure during the neonatal period and a left lobe hepatic atrophy. The radiologic and clinical symptoms prompted us to consider a calcium pyrophosphate deposition disease. She was treated with anakinra (Kineret®) for 5 days with a complete response.

Her young age made us consider a metabolic condition promoting her joint disease and laboratory examination revealed a chronic hypomagnesemia due to renal wasting. Genetic testing demonstrated a heterozygous 17q12 microdeletion (including the Hepatocyte Nuclear Factor 1-beta (HNF1B) and LHX1 genes) in this family.

The radiologic and clinical symptoms prompted us to consider a calcium pyrophosphate deposition disease. She was treated with anakinra (Kineret®) for 5 days with a complete response.

Discussion: In times of specialization and sub-specialization, it is of increasing importance to approach a medical symptom with a holistic view. On rare occasion, seldom, but potentially life-threatening disease might hide behind presentations that could suggest trivial musculoskeletal disorders at first glance. These include well-known severe conditions like acute cardiac ischemia, aortic dissection, lung embolism or pneumothorax but can also encompass rarer causes like undiagnosed epilepsy. As an astute clinician it is therefore of utmost importance to always challenge one’s primary and subsequent assessment when piecing together symptoms, clinical signs and findings.

Case 3

Dermatomyositis after treatment with antitumor immune checkpoint inhibitor: improvement with rituximab after TNF blocker failure

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Case report: A 65 years-old woman with metastatic non-small cells lung carcinoma was addressed to our department for evaluation of muscle weakness, myalgia and biological rhabdomyolysis, that appeared 2 weeks after the introduction of the anti-PD1 pembrolizumab. In the initial hypothesis of a non-specific, immunotherapy-related myositis, she had unsuccessfully been treated by her oncologists first with high doses of prednisone and then by an TNF-alpha-blocking agent. Complementary medical history revealed rapid progressive proximal weakness of upper and lower extremities. She also presented typical skin findings (heliotrope rash, Gottron’s sign) and slight swelling and dysphagia. Immunological workup revealed high titers of antinuclear and anti-TIF1-gamma antibodies, confirming the diagnosis of dermatomyositis. Transient partial symptoms relief was achieved first with high dose (2g/kg) of intravenous immunoglobulins. In front of severe worsening with inability to walk and severe skin manifestations, she was further treated with 2 g rituximab, with significant improvement of skin and muscle function and the ability to walk again.

Discussion and conclusion: This case illustrates the great difficulties faced by clinicians with the occurrence, diagnosis and management of autoimmune paraneoplastic syndrome in the context of immune checkpoint inhibitor (ICI) treatments. Patients may be at particular risk given the conjunction of the risk conferred by the tumor itself, and the additional risk imparted by the ICI. In this case, the presence of anti-TIF1-gamma antibodies, well known to be associated with paraneoplastic forms of dermatomyositis, suggest that autoimmune processes were already evolving before ICI treatment. However, the fact that the disease manifested clinically soon after ICI introduction, together with the wide diversity of autoimmune manifestation that can be provoked by these treatments, indicates that the form that takes an auto-immune manifestation in this context depends on a sum of parameters associated to each patient, including genetics, comorbidities and treatments. Last, treatments such as IVg and possibly B-cell directed therapies, that have the potential to spare the immune boost desired to fight the tumor are probably preferable to the sequence of high doses glucocorticoids eventually followed by TNF blockers that are frequently recommended indiscriminately in these situations.

Case 4

Vertebral tuberculosis in a patient treated with rituximab

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Introduction: W4h describe the case of a patient treated with rituximab (RTX) for a SJögren syndrome

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Case report: A 78-year-old woman with a Sjögren syndrome had been treated for 5 years with RTX i.v. perfusions (2g in 2013, followed the next year by 1g every 6 months). 18 months ago, she developed progressive low back pain in a context of degenerative changes with scoliosis and mild osteoporosis, and in May 2017 an osteoporotic fracture of the L1 superior endplate was diagnosed. The lumbar pain were again severe in autumn 2017, but stabilised with a brace, physiotherapy and antalgic medications (Ibuprofen, Paracetamol). However, 4 months later very severe back pain progressively recurred, especially during the night, with poor relief under opioid medications. An MRI showed abnormal modifications of L3 and L4 intervertebral space and vertebral bodies suggestive of Modic I changes. Given the severity of the symptoms, a biopsy L3 under CT scan control was performed and revealed mycobacterium tuberculosis by PCR. Cultures grew positive for mycobacterium tuberculosis. A retrospective investigation stated that she was screened for TB before (2013) and during rituximab therapy (2016), and experienced no risk of exposure to Tb, nor travels in regions hazardous for this disease; On the other hand she had worked in at risk developing countries before 2013. Of note, CRP and sedimentation rate always remained within the normal range. Expectorations were negative for tuberculosis. She was treated with an anti-tuberculous quadritherapy (Rifampicin, Isoniazid, Pyrazinamid, Ethambutol) for 2 months, followed with Rifampicin and Isoniazid for 10 months. The lumbar pain decreased progressively and eventually completely resolved.

Discussion: The initial clinical presentation lead to investigate for supporting one of the following diagnosis: vertebral fracture, degenerative modification and non-Tb infection. The final diagnosis of vertebral tuberculosis came as a surprise and is to be considered between an acquired TB and an activated latent TB.

Conclusion: Rheumatologists should be aware that tuberculosis under immunosuppressive therapy can appear despite a negative screening for TB and the absence of fever and CRP elevation.

Case 5

A spontaneously resolving aortic stenosis
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The stenosis of the abdominal aorta and its branches is a pathological entity that can have different causes. The aorta is an elastic artery and a transient spasm at its level is unlikely. In contrast, Arterial spasms in the distal and muscular arteries such as the femoral, splenic and renal arteries have been described. We describe the case of a 56-year-old woman with spontaneously resolving aortic stenosis of the abdominal aorta.

A 56-year-old woman with cardiovascular risk factors with high blood pressure, diabetes and dyslipidemia. She has as antecedents, a multi-operated abdomen (inguinal hernia, ovarian cyst, abdominal flanges, hysterectomy). She complains of recurrent abdominal pain like cramps, not aggravated by the diet. An abdominal scan was performed, revealing the presence of a tight stenosis of the abdominal aorta measured at 5 mm at the height of the diaphragm and 5 mm in the anteroposterior axis upstream of the iliac bifurcation with parietal circumferential thickening of the aortic wall extending to the iliac and visceral arteries. The exhaustive clinical and paraclinical etiological assessment was negative. A PET scan was performed which unexpectedly revealed the disappearance of the narrowed aspect of the aorta and no sign of vasculitis. 6 months later, a control CT-Scan demonstrates a normal and regular caliber of the aorta.

This case illustrates an exceptional phenomenon of spontaneously resolving aortic stenosis evoking the hypothesis of aortic spasm. An extensive bibliographic search has found a single publication on a case of mesenteric ischemia on aortic spasm treated medically by vasodilators with a very good evolution. To our knowledge, this is the second case described in the literature.
Human lumbar spine facet joint osteoarthritis displays predominant NGF expression and signaling in synovial and subchondral bone marrow tissues

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Background: Treatment regimens for chronic low back pain (CLBP) are often not efficacious. Nerve growth factor (NGF) and its major receptor TrkA link tissue inflammation to pain. They regulate pro-inflammatory further downstream neurotransmitters such as substance P (SP). Inhibition of NGF has shown significant efficacy in osteoarthritis (OA) and in CLBP, but OA clinical trials have revealed rare cases of rapidly progressive OA (RPOA) of peripheral joints.

Objective: To describe the intensity and the tissue distribution of NGF, TrkA, SP and CD68+ macrophages in facet joint osteoarthritis (FJOA) of the lumbar spine.

Methods: FJOA specimens (n=10) were obtained by facetectomy from patients (average age 69 years, 5 males) undergoing intervertebral fusion. FJOA severity and synovitis was graded using preoperative MRI. Relative abundance of NGF, CD68 (macrophages), TrkA and SP in synovium (SY), cartilage (CL), subchondral bone (SB) and subchondral bone marrow (BM). Immunohistochemical tissue distribution was evaluated using a semi-quantitative scale ranging from 0-3. Association between imaging parameters and tissue expression was determined using Pearson correlation analysis.

Results: Synovitis was present in 6 cases and median Weishaupt grade of FJOA was 2 (1.5 – 3) corresponding with moderate to severe OA. Immunostain intensities (median [range]) were as follows: NGF: SY (3 [0-3]) and BM (1 [0-3]), TrkA: SY (0 [0-1]) and BM (3 [2-3]), CD68: SY (0.5 [0-1]) and BM (3 [2-3]), SP: SY (3 [1-3]), CL (2 [1-3]) and BM (3 [2-3]). NGF in SY and BM were strongly correlated (r=0.94), but not to synovitis or FJOA severity. The relative abundance of macrophages and NGF was strongly correlated exclusively in SY (r = 0.78).

Conclusion: NGF expression and signalling is present in FJOA, but not strongly associated with synovitis or osteoarthritis severity. These results are in agreement with recent studies of human knee OA, which have shown osteochondral NGF expression as a hallmark of symptomatic OA independently of chondropathy or synovitis. Targeting NGF in CLBP and FJOA might affect pathomechanisms in SY and BM tissues.

The predictive value of rheumatoid factor, anti-citrullinated protein antibodies, anti-cardiolipin antibody and anti-epitope arginine deiminase type-3 antibodies alone or in combination, on radiographic damage in rheumatoid arthritis

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Background: Autoantibodies such as anti-citrullinated protein antibodies (ACPA), anti-cardiolipin antibody and anti-epitope arginine deiminase type-3 antibodies were absent (p=0.03).

Conclusions: The presence of anti-PAD3 antibodies was associated with significantly higher scores of radiographic damage at baseline, in both the overall population and in the subgroup of ACPA-negative patients. Combinations of autoantibodies (including anti-CarP and anti-PAD3) predicted both higher baseline radiographic damage and greater radiographic progression over time.

Disturbed PD-L1 upregulation is characteristic of B cells in SLE

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Background: Prior studies on systemic lupus erythematosus (SLE) B cells reported an altered responsiveness to TLR9 stimulation, such as proliferation, cytokine production as well as indications for impaired T and B cell interaction [1]. The role of co-inhibitory and co-stimulatory (check-point) molecules in this setting has not been delineated in detail so far.

Objective: To assess the expression of co-inhibitory (PD-1, PD-L1 and PD-L2) and co-stimulatory molecules (CD86 and CD40) by SLE B cells after in vitro stimulation and their potential contribution for B cell hyperresponsiveness in SLE.

Methods: PBMCs from 10 SLE patients and 10 healthy donors (HD) were stimulated with IL-2/IL-10, anti (α) - B cell receptor (BCR), CpG and CD40L alone or in combination. Expression of PD-1, PD-L1, PD-L2 as well as CD86, CD40 on CD19+CD20+ B cell subsets after 48h stimulation was analyzed by FACS. CD71 was employed to measure proliferation of CD19+CD20+ B cells after 48h stimulation.

Results: SLE B cells exhibited a substantially decreased upregulation of PD-L1 (p = 0.0006) and CD 86 (p = 0.0186, Fig. 1) associated with significantly reduced B cell proliferation (p = 0.0039) after 48h stimulation with CpG alone and in combination compared with HD. While TLR9 engagement in SLE B cells appeared to be abnormal, activation of CD40 resulted into a consistent upregulation of both, inhibitory and stimulatory molecules. PD-L1 was positively correlated with B cell proliferation (p = 0.003). Notably, the expression of PD-L1 and CD 86 correlated inversely with SLEDAI, as surrogate marker for Type I interferon signature (IFN-I, p < 0.0001 and p = 0.0021 respectively).

Conclusions: Hyperresponsive lupus B cells are characterized by a functionally diminished PD-L1 and CD86 upregulation associated with IFN-I signature. Reduced upregulation capacity of PD-L1 correlated also with clinical activity and reduced proliferation. The data mandate evaluations of innovative therapeutic interventions in SLE.

The impact of pregnancy on structural progression in premenopausal women with rheumatoid arthritis

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Background: Disease activity often improves during pregnancy and worsens at the postpartum period. The long-term effect of pregnancy on radiographic joint damage progression among premenopausal women with RA has been barely studied.

Objectives: The aim of this study was to analyse the impact of pregnancy on radiographic progression in premenopausal women with RA.

Methods: This is an observational cohort study of RA patients included in the SCQM-RA. Patients enrolled are followed-up and have radiographic assessments at regular intervals. Information about female reproductive factors, such as pregnancies, breastfeeding and hormonal treatment were retrospectively retrieved using a questionnaire. For this analysis we included premenopausal women with at least two radiographic assessment and full information on reproductive factors. The primary outcome was the rate of radiographic progression. We analysed the radiographic progression between premenopausal women with at least one pregnancy and those with no pregnancies. Baseline time was the first radiographic assessment. We used a multilevel regression model for longitudinal data, adjusted for potential confounders, such as baseline age, disease duration, DAS-28 and treatment.

Results: A total of 430 premenopausal women were analysed, half of which had at least one pregnancy. Women with at least one pregnancy were older than nulliparous (median of 41 vs 36 years, p<0.001) and had longer disease duration (median of 3.4 vs 2.6 years, p = 0.04). During follow-up, the rate of radiographic progression was lower in women with pregnancies than in nulliparous women ([0.9% (95% CI: 0.0 to 1.9) vs 2.1% (95% CI: 0.9 to 3.1) over 10 years, respectively, p = 0.04]). In a sub-analysis, the rate of radiographic progression appeared to be lower during the 13-year period after first pregnancy than after this period ([0.2% (95% CI: -0.8 to 1.3) vs 2.6% (95% CI: 1.3 to 3.9) over 13 years, respectively, p = 0.003). We found no difference in the rate of radiographic progression between women with a single pregnancy and multiparous women.

Conclusion: In premenopausal women with RA, joint damage progressed more rapidly in nulliparous women than in women with at least one pregnancy. However, we cannot make any definitive causal inference, since it is well possible that women renouncing getting pregnant might be patients with more severe disease. Radiographic progression appeared to increase the longer the time since pregnancy.

Concurrent calcium pyrophosphate deposition arthritis and rheumatoid arthritis successfully treated by tocilizumab

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Background: Calcium pyrophosphate deposition (CPPD) arthritis and rheumatoid arthritis (RA) can be potential mimickers and concurrent diseases. Indeed, recent studies suggest a positive association between the two diseases, with a prevalence of CPP crystals in RA patients up to 25%. Although an etiological connection between CPPD and RA is still lacking, CPPD is thought to be a late complication of longstanding RA. Nevertheless, simultaneous diagnosis of both CPPD and RA is possible.

CPP crystals induce inflammatory response involving IL-6 mainly through the NALF3 inflammasome and IL-1 pathway. Anti-IL-1-mediated therapy is therefore used effectively in some cases of CPPD arthritis resistant to classical medications. Tocilizumab, an anti-IL-6 used for the treatment of moderate to severe and resistant RA, has recently shown exciting results in the management of two cases of CPPD arthritis resistant to anti-IL-1.

Here, we report a case of a 66-years-old man with concurrent CPPD arthritis and seropositive RA successfully treated by tocilizumab.

Case presentation: The patient suffered from chronic peripheral polyarthralgia and polyarthritis on a rather asymmetrical and migratory pattern, affecting predominantly the medium-large joints but also the small ones in a lesser extend. Laboratory findings demonstrated an inflammatory syndrome, rheumatoid factor and anti-cyclic citrullinated peptide positivity. No RA typical lesion, but chondrocalcinosis (CC) of the right knee, pubic symphysis and left hip was seen on plain radiographs. Ultrasound confirmed the CC in knee and hip and CPP crystals were isolated in inflammatory synovial fluid samples from these two joints. Pulmonary exams demonstrated an interstitial pneumopathy. The diagnosis of seropositive RA and CPPD arthritis were retained, according to the ACR/EULAR classification criteria and recommendations. The diseases were still clinically and biologically active despite the successive use of NSAIDs, glucocorticoids, leflunomide and colchicine. Tocilizumab (8mg/kg IV) was started at this point, with major improvements of symptoms and clinical status, and normalization of the inflammatory markers.

Conclusion: In CPPD arthritis pathomechanisms, IL-6 is one of the major pro-inflammatory cytokine involved, mainly stimulated via the NALF3 inflammasome/IL-1 pathway. IL-6 blockade, currently used in RA, could be an interesting treatment option next to anti-IL-1 and classical treatments for CPPD, especially in patients with concurrent RA.
Tocilizumab in a patient with rheumatoid arthritis secondary to checkpoint inhibitor therapy - a case report

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Background: The emerging use of immune checkpoint inhibitors in oncology for a variety of malignancies has led to an increase of immune related adverse events (irAE). IrAE often require interdisciplinary consideration and management. We present a case of steroid refractory rheumatoid arthritis (RA) secondary to immune checkpoint inhibitor therapy in malignant melanoma, successfully treated with an IL-6-receptor inhibitor, tocilizumab, and achieving remission according to the Disease Activity Index (DAS) 28.

Case presentation: A 57-year-old female patient with a history of non-pigmented melanoma was treated with pembrolizumab, a programmed death receptor ligand 1 (PD-L1) antibody (200 mg/Q3W, intravenous) from November 2017 to July 2018. 4 months after the first administration of pembrolizumab, she developed morning stiffness and polyarthritis with joint swelling (mainly knee and finger joints). The patient was evaluated in our rheumatology department, which revealed active polyarthritis with joint swelling. The patient was treated with prednisone orally (initial dose 100 mg/d in a tapering dose, 30 mg/kg body weight, administered every 4 weeks, intravenous) was started 2 months later. After 3 cycles (12 weeks) of tocilizumab, symptoms improved significantly and prednisone was successfully tapered and stopped after 5 months. DAS 28 score improved from 6.28 to 2.08 after 5 months of therapy with tocilizumab. No tumor progression was noted (clinically and by imaging). We continued tocilizumab as a remission maintenance therapy for RA.

Conclusion: Tocilizumab may be a safe and efficient treatment option in steroid refractory arthritis secondary to checkpoint inhibitor therapy. Further randomised studies are needed to evaluate safety, efficacy and long-term effects of tocilizumab in rheumatoid arthritis secondary to PD-L1 inhibition.

Upadacitinib in Patients with Rheumatoid Arthritis and Inadequate Response or Intolerance to Biological DMARDs: Results at 60 weeks from the SELECT-BEYOND Study

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Methods: In patients (pts) with active rheumatoid arthritis (RA) and inadequate response or intolerance to biological DMARDs (UPA), a JAK1-selective inhibitor, resulted in significant improvements over 24 weeks (wks).

Purpose: We assessed UPA safety & efficacy through Wk60 in an open-label extension of the phase 3 SELECT-BEYOND study.

Methods: A population of pts with active RA who had failed at least one prior biologic therapy was enrolled.1 Pts received UPA 15mg or 30mg once daily (QD) or placebo (PBO) on csDMARD background for 12 wks. From Wk12, pts randomized to UPA at baseline (BL) continued the extension on study drug. By the safety data cut-off date, 19% pts discontinued treatment. By the safety data cut-off date, 19% pts discontinued treatment. By the safety data cut-off date, 19% pts discontinued treatment. Results: 418/498 pts were randomized, completed 24wks & entered the extension on study drug. The safety data cut-off date, 19% pts discontinued study drug: 5/43/25% due to AE/efficacy/died

Summary of indirect comparisons to evaluate efficacy of biologic DMARDs in patients with rheumatoid arthritis

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Objective: We summarize findings from matching-adjusted indirect comparison (MAIC) and network meta-analysis (NMA), conducted in conventional synthetic/biologic disease-modifying anti-rheumatic drug (cs/b DMARD)-naive and methotrexate inadequate responder (MTX-IR) populations, respectively.

Methods: Systematic literature reviews were performed for MAIC and NMA. For MAIC, pain (visual analog scale [VAS], 0-100 mm) and HAQ-DI at Week (Wk) 24 for BARI 4mg arm, ORAL-START tofacitinib (TOFA) 5mg arm and tocilizumab (TCZ) 8mg/kg arm from NMA. For NMA, pain (visual analog scale [VAS], 0-100 mm) and HAQ-DI at Week (Wk) 24 for BARI 4mg arm, ORAL-START tofacitinib (TOFA) 5mg arm and tocilizumab (TCZ) 8mg/kg arm from NMA. For NMA, pain (visual analog scale [VAS], 0-100 mm) and HAQ-DI at Week (Wk) 24 for BARI 4mg arm, ORAL-START tofacitinib (TOFA) 5mg arm and tocilizumab (TCZ) 8mg/kg arm from AMBITION+FUNCTION, respectively; MTX arms were also matched between trials. After adjustment, mean changes in radiographic progression were observed for Wk 24 TCZ and TOFA and Wk 26 ADA data. NMA as randomized controlled trials reporting American College of Rheumatology (ACR) response. The summary of indirect comparisons for MTX-IR populations, respectively.
Association between baseline hemoglobin levels and radiographic joint damage progression in patients with rheumatoid arthritis treated with baricitinib or standard of care

Disclosure: This abstract was originally submitted to British Society for Rheumatology-2019 Annual Meeting; Birmingham, UK; Apr 30-May 2, 2019 and published by Rheumatology.

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Association between baseline hemoglobin levels and radiographic joint damage progression in patients with rheumatoid arthritis treated with baricitinib or standard of care

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Objectives: To assess the association between baseline Hb levels and structural joint damage progression and study the effect of BARI 4-mg once daily on structural damage progression at 52 weeks (wks) based on baseline Hb levels.

Methods: Data from the modified intention-to-treat populations of RA-BEGIN (MTX = 210/BARI 4-mg = 159/BARI 4-mg+MTX = 215 patients) and RA-BEAM (placebo [PBO] = 488/adalimumab [ADA] = 328/BARI 4-mg = 487 patients) were analyzed. Structural damage progression is the change from baseline (CFB) greater than the smallest detectable change (SDC) in modified total Sharp score (mTSS) at wk52; RA-BEGIN SDC: 1.1; RA-Beam SDC: 1.5. mTSS data at wk52 were imputed using linear extrapolation based on baseline data and most recent radiographic data prior to missed radiograph. The number of patients with CFB in mTSS>SDC at wk52 were calculated for low (males/females: <13/12g/dl) or normal baseline Hb for each treatment arm from both studies. Multivariate logistic regression (MLR) was used to study the association of baseline Hb with structural joint damage at 52 wks. MLR included treatment; baseline values of Hb, hsCRP, CDAI, HAQ-DI, and joint erosion status; BMI; smoking status; and geographical area. Patients with missing baseline/post-radiographic data (RA-BEGIN: 39/RA-BEAM: 68) were excluded from MLR analyses; as were patients with missing data for covariates of MLR (RA-BEGIN: 7/RA-BEAM: 19). All analyses were post-hoc.

Results: Overall, patients with higher baseline Hb were less likely to show CFB in mTSS>SDC (RA-BEGIN: adjusted odds ratio [OR] = 0.72, p = 0.001; RA-BEAM: adjusted OR = 0.76, p<0.001) at 52 wks, independent of other factors of the MLR model. In RA-BEGIN, CFB in mTSS>SDC was less frequent in patients with low baseline Hb receiving BARI alone or BARI+MTX vs those on MTX alone; in patients with normal baseline Hb, difference between treatments was less pronounced. In RA-BEAM, CFB in mTSS>SDC was less frequent in patients with low or normal baseline Hb receiving BARI or ADA vs PBO. Conclusions: In RA patients, lower baseline Hb levels were associated with increased structural damage progression. Treatment with BARI 4-mg reduced structural progression irrespective of baseline Hb status; structural progression at 52 wks was more pronounced in patients with low baseline Hb receiving MTX alone (RA-BEGIN) or PBO and background MTX (RA-BEAM).

Background: Upadacitinib (UPA), a selective JAK1 inhibitor, has demonstrated efficacy & safety in patients (pts) with rheumatoid arthritis (RA) as monotherapy (mono) and in combination (combo) with conventional synthetic disease-modifying anti-rheumatic drugs (csDMARDs) such as methotrexate (MTX). 1,2 However, UPA mono has not been compared directly with UPA combo in the Phase 3 program.

Objectives: To compare the efficacy of UPA mono & UPA combo with MTX using data from two Phase 3 trials of RA pts with an inadequate response (IR) to prior MTX therapy.

Methods: In SELECT-MONOTHERAPY, 648 MTX-IR pts were randomly assigned to receive UPA 15mg or 30mg mono once daily (QD), or continue with MTX mono (cMTX; blinded study drug), for 14 weeks. In SELECT-NEXT, 661 csDMARD-IR pts were randomized to receive UPA 15mg or 30mg QD or placebo (PBO) for 12 weeks on csDMARD background. Primary endpoints were the proportion of pts achieving ACR20 & DAS28(CRP) ≤3.2. Additional endpoints included ACR50/70, DAS28(CRP) ≤2.6, CDAI remission ≤28, CDAI low disease activity (LDA; ≤10), and change from baseline in HAQ-DI. Logistic regression or ordinary least squares analyses were used to compare outcomes with mono vs combo, adjusting for demographics & baseline disease characteristics.

Results: A total of 1114 pts were included, of whom 648 received monotherapy in SELECT-MONOTHERAPY & 466 received combo in SELECT-NEXT. Of the pts receiving combo, 338 (72.5%) were receiving MTX background therapy only and 128 (27.5%) were receiving MTX + other csDMARDs. Baseline characteristics were similar between study cohorts; the majority of pts were female and of white ethnicity, with a mean age of approx. 70 yrs & a mean MTX dose of approx. 17mg/week. Both UPA mono & UPA combo led to significant improvements in efficacy outcomes versus cMTX/PBO+MTX. No significant differences were observed between UPA mono & UPA combo across a range of clinical endpoints, including ACR20/50/70 responses & measures of LDA & remission. Improvements in quality of life were similar with UPA mono & combo. Efficacy was comparable between the two UPA doses in the combo group, whereas in the mono group numerically higher responses were observed with UPA 30mg vs UPA 15mg.

Conclusions: In MTX-IR pts with RA, the efficacy of UPA appears comparable when administered as mono or when given in combo with MTX.

References

A comparative analysis of upadacitinib monotherapy and upadacitinib combination therapy for the treatment of rheumatoid arthritis from two Phase 3 trials

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Background: Upadacitinib (UPA), a selective JAK1 inhibitor, has shown efficacy in patients (pts) with rheumatoid arthritis (RA) when combined with methotrexate (MTX) or other conventional synthetic disease-modifying anti-rheumatic drugs (csDMARDs). 1,2 However, the efficacy of UPA plus MTX has not been directly compared with UPA plus other csDMARDs.

Objectives: To compare the efficacy of UPA in combination with MTX versus UPA in combination with other csDMARDs in pts with an inadequate response (IR) to csDMARDs (SELECT-NEXT1) or biologic DMARDs (bDMARDs; SELECT-BEYOND2).

Methods: 661 pts in SELECT-NEXT and 498 pts in SELECT-BEYOND received UPA15mg or 30mg once daily (QD) or placebo (PBO) for 12 weeks; all pts received concomitant csDMARDs. The primary endpoints for both studies were rates of ACR20 response and DAS28(CRP) ≤3.2. Additional endpoints included DAS28(CRP) ≤2.6, CDAI low disease activity ≤10, and CDAI remission ≤28. Pts were grouped according to concomitant csDMARD use (MTX vs non-MTX csDMARDs); pts receiving both MTX and a non-MTX csDMARD were included in the MTX group.

A comparison of upadacitinib plus methotrexate and upadacitinib plus other csDMARDs in patients with rheumatoid arthritis: An analysis of two phase 3 studies

References
Results: In SELECT-NEXT and SELECT-BEYOND, 535 and 410 pts, respectively (~80%), were receiving concomitant MTX (mean dose 17mg/week), and 124 and 82 pts were receiving non-MTX csDMARDs. Demographics and disease characteristics were broadly similar between treatment groups; the majority of pts were female and of white ethnicity, and around half were using oral corticosteroids at baseline. Across all subgroups, the proportion of pts achieving efficacy outcomes was higher with both UPA doses compared with PBO. There were no significant differences between efficacy outcomes with UPA in combination with MTX versus UPA in combination with non-MTX csDMARDs in either pt population. This included ACR20 response as well as low disease activity and remission defined by DAS28(ESR) and CDAI.

Conclusions: In this post hoc analysis, the efficacy of UPA in pts with RA appeared comparable whether administered in combination with MTX or non-MTX csDMARDs.

Reference

P 10

Safety of baricitinib: update from up to 6 years of treatment in rheumatoid arthritis clinical trials

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Background/purpose: Baricitinib (BARI), an oral, selective inhibitor of Janus kinase (JAK1 and JAK2), is approved for the treatment of moderately to severely active rheumatoid arthritis (RA) in adults in over 50 countries. This analysis provides an update on the safety profile of BARI up to 6 years of treatment in RA clinical trials.

Methods: Data were pooled from 8 randomised trials (4 Phase 3, 3 Phase 2, 1 Phase 1b) and 1 long-term extension (LTE) study (data up to 01-April-2017). The safety data were analysed in 3 integrated data-sets: placebo (PBO)-controlled (6 studies comparing BARI 4-mg QD to PBO 0-24 weeks), extended BARI (4 studies with BARI 2- and 4-mg QD, including LTE data) and ALL-BARI-RA (all patients exposed to ≥1 dose of BARI from 8 randomised trials and LTE). Incidence rates (IRs, per 100 patient-years [PY]) for safety events with 95% CIs are reported.

Results: In total, 3492 patients were exposed to BARI for up to 6 years (7860 PY of total exposure; median: 2.5 years). The IRs for serious infections, malignancies, major adverse cardiovascular events, arterial thrombotic events, and venous thromboembolism did not increase with prolonged exposure. During the 24-week PBO-controlled period, deep vein thrombosis (DVT)/pulmonary embolism (PE) was reported with BARI 4-mg (n = 6N = 997) but not with PBO. However, this was not observed during the first 24 weeks after switch to BARI 4-mg from PBO (n = 1/1N = 2) or active comparator (adalimumab/methotrexate; n = 0/N = 451). At longer exposures, DVT/PE IRs were comparable between BARI 2- and 4-mg doses and the overall IR was 0.53. The IRs for gastrointestinal perforation and tuberculosis were 0.04 and 0.14, respectively in All-BARI-RA dataset.

Conclusion: The safety profile of BARI up to 6 years of treatment in RA clinical trials remained consistent with the profile previously reported and remains acceptable in the context of demonstrated efficacy.

P 11

Reduction of vertebral fractures and rapid loss of bone after discontinuation of Denosumab: A cohort study of 97 postmenopausal women treated with denosumab 2 years, followed by a single infusion of zoledronate

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Background: Discontinuation of denosumab is associated with rapid loss of bone mineral density (BMD) back to baseline and may be associated with an increased risk of vertebral fractures. No sequential treatment has been established yet on how to prevent either the loss of BMD or to prevent rebound fractures after discontinuation of denosumab. The aim of this 8-year cohort study in a resident rheumatology practice was to investigate the effect of a single zoledronate infusion, administered 6 months after the last denosumab injection on the occurrence of fractures and on rapid loss of BMD.

Methods: 97 women with postmenopausal osteoporosis were treated with denosumab 60 mg every 6 months for 2 years and one single infusion of 5 mg zoledronate 6 months after the last denosumab injection. Patients were controlled clinically, by DXA and by vertebral fracture assessment before the first denosumab injection, after 2 years and after 4 years. Subgroup analyses were made for patients with or without prevalent fractures, prior bisphosphate treatment and lumbar spine BMD gain of >9% versus <9%.

Results: 1%-2% years after the last denosumab injection 2 vertebral fractures (1.1% per 100 patient years), and 3 non-vertebral fractures (1.7% per 100 patient years) had occurred. Multiple vertebral fractures were not observed. 64% (CI: 52-81%) of BMD gain was retained at lumbar spine, 52% (CI: 26-72%) at total hip. There was no significant difference in decrease of BMD in patients with BMD gain of >9% vs <9% while treated with denosumab. Previous antiresorptive treatment or prevalent fractures had no impact on decrease of BMD. Patients controlled 1.5 versus 2.5 years after the last denosumab injection had comparable decrease of lumbar spine BMD, suggesting that the entire loss of BMD occurs between 6-18 months after the last denosumab injection.

Conclusions: A single infusion of zoledronate reduces the risk of rebound vertebral fractures after discontinuation of denosumab patients treated for postmenopausal osteoporosis. Some patients, especially those with a high risk for osteoporotic fractures may need to be treated with bisphosphonates longer than one year.

P 12

Can we avoid the loss of bone mineral density one year after denosumab discontinuation? The ReoLaus Bone Project

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Objectives: Denosumab discontinuation (DD) induces bone turnover markers (BTMs) increase, bone mineral density (BMD) decrease, and increased risk of spontaneous vertebral fractures. Prescribing a bisphosphonate after DD could avoid this rebound effect. The objective of the ReoLaus (Rebound Effect Observatory in Lausanne) Bone Project is to follow bone parameters after DD. We report the determinants associated to BMD loss 1 year after DD.

Methods: 170 patients are followed in ReoLaus. Patients with a BMD follow-up >1 year after DD and a standardized management were included. We defined as significant a lumbar spine BMD loss (Loosers group) over 3.96% at one year after DD as compared with values at the end of the denosumab treatment 18 months after last injection.

Results: 71 post-menopausal women stopped denosumab after 7.7±2.2 injections; age 63.8±8.1 years, BMI 23.8±4.5, 0.96 prevalent fractures/patient, 8.45% previously exposed to corticoids, 22.54% to anti- aromatases. 17.25 months after last denosumab injection 30 patients were classified as Loosers and 41 as Stable. At denosumab interruption Loosers were younger (61.4±7.3 vs 65.5±8.2 years, p = 0.034) with higher sCTX level (644.7 vs. 474.1 ng/ml, p = 0.055). The rate of BP given less than 2 years before denosumab was not different, but none of the Loosers had received zoledronate vs. 12% of the Stable (p = 0.047). Other pre-denosumab characteristics were not different. Number of denosumab injections, BTMs and BMD values were comparable in both groups during denosumab treatment. First BTMs values measured 7.5 months (median) after last denosumab injection and before bisphosphonates were not different (sCTX: Loosers, 592 ng/ml; Stable, 379 ng/ml, p = 0.06). At DD 99% received zoledronate, 24% alendronate, 3% others, and 14% nothing (p = 0.39 between groups). BTMs 12 months post-DD were higher in Loosers as compared to Stable (sCTX S373 vs. 336 ng/ml, p = 0.009). Incidence of new fractures was low (0.18/patient) without between group’s difference.

Conclusion: In our sub-cohort, being younger, having high BTMs and not having received zoledronate before denosumab discontinuation increase the risk of a BMD loss, even if a bisphosphonate is prescribed at DD. Our results support the use of denosumab after a bisphosphonate to maintain BTMs as lowest as possible after DD.

EMMMedia
P 13
Bone health in patients with psoriatic arthritis in a Swiss cohort
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Introduction: The effect of psoriatic arthritis (PsA) on bone mineral density (BMD) is not well understood and there is much controversy regarding loss of bone mass in patients with PsA. We analyzed data from the Swiss Clinical Quality Management (SCQM) cohort, which is a large national cohort database of patients with inflammatory arthritis.

Patients and methods: We analyzed 2443 consecutive patients included in the cohort between September 1997 and April 2010. We evaluated demographic and clinical characteristics assessed in the SCQM cohort, such as age, gender, body mass index (BMI), disease duration, smoking and alcohol habits, patient’s and physician’s global assessment, American College of Rheumatology (ACR) joint count, inflammatory activity measured by erythrocyte sedimentation rate (ESR), C-reactive protein (CRP), disease activity score (DAS 28), quality of life assessed by health assessment questionnaire (HAQ), rheumatoid factor, anti-CCP, HLA B27 status and medication use. First, we compared the patient group with bone density measurement (DXA) with the group with no DXA. In a subgroup analysis we compared DXA patients according to their osteoporotic status.

Results: Patients with DXA were on average 6 years older (54.27±11.12 vs 47.8±12.48 years, p<0.001), and were more likely to be female (67.8% vs 43.4%) than the patients without DXA. The duration of the disease was longer (6.67±3.85 vs 5.30±7.12 years, p<0.001) in the DXA group. CRP and ESR were also higher in the DXA group (10.27±6.01 vs 8.2±11.94 mg/L, p<0.001 and 17.10±7.62 vs 15.13±21.5±21/mill/1h, p<0.01, respectively). Patients with DXA had a longer cumulative prednisone exposure (5.42±21.00 vs 1.14±7.58 months, p<0.001).

In the DXA group, we had 545 patients, with valid DXA data in 266 patients. The prevalence of osteoporosis was 16.5%. Patients with osteoporosis were older than patients without osteoporosis (55.8±13.95 vs 52.89±9.68 years, p<0.01). There was a positive association between BMD and body mass index, additionally, higher age was associated with lower BMD. The other variables, including the disease activity, showed no correlation with the BMD.

Conclusion: Our analysis shows that PsA patients from the SCQM register with higher osteoporosis risk (female patients, with elevated inflammatory parameters and longer prednisone exposure) were more likely to be scanned by DXA. Further research is needed to elucidate the association between PsA and osteoporosis.

P 14
Osteoporosis (OP) diagnosis and treatment of women aged ≥70 years in primary care: results from a large European cross-sectional study
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Patients and methods: We analyzed data from 2443 consecutive patients included in the cohort between September 1997 and April 2010. We evaluated demographic and clinical characteristics assessed in the SCQM cohort, such as age, gender, body mass index (BMI), disease duration, smoking and alcohol habits, patient’s and physician’s global assessment, American College of Rheumatology (ACR) joint count, inflammatory activity measured by erythrocyte sedimentation rate (ESR), C-reactive protein (CRP), disease activity score (DAS 28), quality of life assessed by health assessment questionnaire (HAQ), rheumatoid factor, anti-CCP, HLA B27 status and medication use. First, we compared the patient group with bone density measurement (DXA) with the group with no DXA. In a subgroup analysis we compared DXA patients according to their osteoporotic status.

Results: Patients with DXA were on average 6 years older (54.27±11.12 vs 47.8±12.48 years, p<0.001), and were more likely to be female (67.8% vs 43.4%) than the patients without DXA. The duration of the disease was longer (6.67±3.85 vs 5.30±7.12 years, p<0.001) in the DXA group. CRP and ESR were also higher in the DXA group (10.27±6.01 vs 8.2±11.94 mg/L, p<0.001 and 17.10±7.62 vs 15.13±21.5±21/mill/1h, p<0.01, respectively). Patients with DXA had a longer cumulative prednisone exposure (5.42±21.00 vs 1.14±7.58 months, p<0.001).

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Conclusion: Our analysis shows that PsA patients from the SCQM register with higher osteoporosis risk (female patients, with elevated inflammatory parameters and longer prednisone exposure) were more likely to be scanned by DXA. Further research is needed to elucidate the association between PsA and osteoporosis.

P 15
Association between the soluble terminal complement complex C5b-9 (sc5b-9) and signs of active kidney disease in a Swiss SLE cohort
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Background: A possible role of the terminal complement complex C5b-9 in active SLE has yet to be elucidated. Its proinflammatory effects on a number of cells types, e.g. glomerular mesangial cells and synovial fibroboblasts, have been described.

Objective: To study whether sC5b-9 is associated with clinical disease activity in SLE and to compare it with C3, C4 and the split products C3a and C5b-9 by ELISA.

Methods
Study population and design: Patients from the Swiss SLE Cohort Study (SSCS, from St. Gallen centre, fulfilling the ACR criteria at inclusion) consecutively entered into a prospective observational study. Determined at two clinical visits, (≥ 6 months apart), compared with 18 healthy controls:
- clinical disease activity by clinical examination, SELENA-SLEDAI and SLICC Damage, SF-36, PGA, FACIT
- C3a and sC5b-9 by ELISA.
- standard of care routine laboratory parameters.

Statistics: Independent associations of continuous and categorical variables, studied by a mixed analysis of covariance (ANCOVA) models, followed by Spearman rank correlation analyses.

Results: 127 patients; age 51 ± 17 (mean ± SD) years (82% female), disease duration 5.8 [3.9-9.1] (median [IQR] years). Initial clinical manifestations: arthritis (60%), hematologic (57%), photosensitivity (47%), skin changes (35%), oral ulcers (34%), renal disease (16%). Lupus Low Disease Activity State in 87%, SELENA-SLEDAI (SLEDAI >0) of 49% (4.2 ± 3.1, mean ± SD).

IgG values were significantly associated with SELENA-SLEDAI (F = 4.94, p = 0.027) in a multivariate model, after adaptation for age, gender, CRP, ESR, ANA titre, dsDNA antibody value, complement factor C3 and C4.

Significant correlations/associations (univariate analyses) between:
1. sC5b-9 and haemoglobin (r = 0.001)
2. sC5b-9 and glomerular dysmorphic erythrocytes (r = 0.020)
3. dsDNA ab and sC5b-9 (r = 0.221, p<0.001) with IgG (r = 0.421, ps0.001)
4. C3a with sC5b-9 (r = 0.299, ps0.001), C3a with C3 (r = 0.318, p = 0.01), C3a with C4 (r = 0.137, p = 0.02)
Sensitivities/specificities (with regard to haematuria and glucerol enyratecytes): sC5b-9: 75/63% and 64/62%; C3: 8/69% and 27/69%; C4: 8/84% and 18/84%.

A significant association of C3a with routine laboratory parameters of standard of care and of sC5b-9 with overall disease activity or other components of the SLEDAI, could not be detected.

Conclusions: Soluble C5b-9, elevated during haematuria and increased glucerol enyratecytes, could play a role in the pathogenesis of SLE and be useful as a marker of active renal disease.

P 16

Severe myositis and perimyocarditis in anti-centromere positive systemic sclerosis complicated by thrombotic microangiopathy and renal insufficiency

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On February 2, a female patient (79 y) was admitted to the hospital after a fall. She was hemodynamically stable, but tachypnoeic with bibasilar rales. She was not able to lift her arms over 45° or to sit in an upright position. There were facial and palmar telangiectasia, digital ulcers, and skin thickening (face, forearms). In the echo, she had a diastolic dysfunction (I°, EF 60%) without regional motility alterations, but a pericardial effusion (1.1cm).

In her blood exams, a mild anemia, elevated muscle enzymes, cardiac biomarkers and CRP were detected (CK 3302 IU/L, CKMB 39 mcg/l, hsTrop 291 pg/ml, NTproBNP 1367 pg/ml).

Surprisingly, the high ANA titer of 1:10240 corresponded to positivity for anti–Centromere antibodies (abs) with absence of abs commonly associated with myopathy in systemic sclerosis (SSc) such as anti–Ku, anti–PM-Scl or anti–U1RNP.

On MRI, signal integrity was mainly increased in the thighs and gluteal muscles, which corresponded to focal perivascular inflammation, MHC I upregulation besides chronic neurogenic changes on muscle biopsy.

We therefore postulated an overlap syndrome of polymyositis / SSc with perimyocarditis and initiated a therapy with solumedrol i.v. for 3 days, followed by prednisolone 1mg/kg bw and azathioprin. For the next 5 days, we started amlopidin and iloprost i.v.

Since at follow-up, muscle enzymes and cardiac biomarkers were still elevated (CK 2502, CKMB 69, hsTrop 490), we initiated treatment with IVIG (2g/kg bw) with good biochemical response (CK 1605).

Despite having reduced the prednisolone dose rapidly below 10mg/d, slowly her renal function deteriorated without evidence of pre- or postrenal causes. Given the rise in blood pressure, we suspected scleroderma renal crisis and started the patient on increasing dosages of ACE inhibitors.

Concurrently, her hemoglobin decreased and the parameter for hemolysis were positive (haptoglobin 0.13g/l) without evidence of an unexplained primary hemolytic disorder (dCombs test neg. ADAMS13 activity 82%) leading to the diagnosis of a SSc-associated thrombotic microangiopathy.

Herein, we describe an unusual case of an anti-Centromere positive SSc patient with severe inflammatory myopathy and perimyocarditis. This is in contrast to the currently available literature, which supports the absence of muscular involvement and the rarity of renal complications in this specific clinic-serologic subtype in the absence of diffuse cutaneous involvement.

P 17

An unexpected cause of a persistent inflammatory syndrome in a scleroderma patient

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Background: A persistent inflammatory syndrome in a patient with scleroderma can be a sign of ongoing disease activity, but can also have other causes, such as infection, neoplasia or amyloidosis.

The case: We present the case of a 59-year-old female patient, with known limited cutaneous scleroderma. The manifestations at disease onset were dry eyes, arthritis, Raynaud`s, telangiectasia, livedo reticulasa and puffy fingers. ACA and anti-PM-Scl100-Ab were positive. She was well controlled under Methotrexate (MTX) and Hydroxychloroquine (HCQ) with the exception of persistent inflammation (ESR 64 mm/1h, CRP 62 mg/l). A CT scan of neck, chest and abdomen showed no infection or neoplasia. There was no monoclonal gammopathy. She consulted for a routine examination at our clinic and reported an intentional 10 kg weight loss during the last year, abdominal cramps, loose stool and fatigue. The symptoms did not improve despite MXT-dose reduction.

Further enzymes were normal. A gastroscopy showed a H. pylori neg. gastritis and the colonoscopy showed two polyps. Three months later, despite an increased proton-pump inhibitor dose, symptoms persisted and lower limbs oedema with night sweats developed. The patient was hospitalized for further investigation. Echocardiography and ECG were normal, lung function tests showed a slightly diminished Dlco (74%). Renal function was normal, the low albumin level explained the leg oedema. We repeated the gastroscopy, and the histopathological analysis of the duodenum showed normal mucosa, but some PAS and Warthin-Starry positive macrophages in the submucosa without lymphocytic infiltrate. PCR for Tropheryma whippelii was positive in saliva, stool and duodenum biopsy specimen. A treatment with Doxycycline was started and the HCo-dosage was increased. The patient also received nutritional consultation. Two months later, leg oedema and night sweats improved and she gained weight, but she developed painful, erythematous nodules on the limbs and trunk. The MRI of the calves revealed an extensive fascitis, interstitial lymphocytes, and diffuse interstitial infiltrates of immune reconstitution inflammatory syndrome treated with corticosteroids.

Conclusion: In case of persistent inflammatory syndrome with no apparent cause in a patient treated with immunosuppressive drugs, a WbCo-dosage should be suspected and searched for. There is a clear association between Whipple disease and scleroderma, therefore we think that the presence of this two diseases in our patient was fortuitous.

P 18

Is very early systemic sclerosis a combination of mild and early?

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Background: SSc has a high morbidity and mortality, therefore it is important to detect the disease at an early stage. Very early detection of SSc allows early management, which has been shown to profoundly impact on the disease course in different inflammatory rheumatic diseases. However, patients fulfilling criteria for the diagnosis of very early SSc could also be patients with a very mild, very slowly progressing, long-standing disease.

Objectives: To identify a subgroup of patients with long-standing, very mild SSc among the patients fulfilling the criteria for the very early diagnosis of SSc by analyzing clinical, epidemiological and immunological characteristics of the Zurich patient cohort.

Methods: Baseline data of the SSc patients from the University Hospital Zurich cohort are analyzed in this study. Demographic and disease characteristics of the patients enrolled between January 2009 and June 2018 into the Very Early Diagnosis of Systemic Sclerosis (VEDOSS) cohort were analyzed. Patients fulfilling the ACR/EULAR2013 criteria and patients with primary Raynaud phenomenon were excluded. Disease duration was calculated as the difference between the baseline visit date and the date of the first Raynaud’s phenomenon (RP) symptom reported by the patient. For further analysis, the cohort was divided into two subgroups using a cut off value of <5 years disease duration. Data were expressed as absolute and relative frequencies (n/total valid cases (%)) and percentages for categorical variables or as means ± SD and medians ± interquartile range for continuous variables.

Results: A total of 107 patients met the inclusion criteria. Disease duration was 4 years (1, 10.25) and 100/107 (93.5%) of patients had RP. The majority of patients had a short disease duration measured from first Raynaud attack of <5 years. However, 43/107 patients (40.2%) had a long-standing disease with long-standing Raynaud’s. Further analysis of the clinical characteristics of early patients with <5 years disease duration showed no significant differences in demographics and disease manifestations between the subgroups.

Conclusion: This analysis is showing that patients fulfilling VEDOSS criteria can include a subgroup of patients with very mild, long-standing disease. This observation has major impact on the management of
VEDO patients, as this subgroup requires different follow up and treatment strategies compared to VEDO patients with early, progressive disease.

P 19

Nintedanib reduced decline in forced vital capacity across subgroups of patients with systemic sclerosis-associated interstitial lung disease: data from the SENSICIS® trial

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Background: In the SENSICIS® trial, nintedanib reduced the progression of interstitial lung disease associated with systemic sclerosis (SSC-ILD) compared with placebo, as demonstrated by a significantly lower rate of decline in forced vital capacity (FVC) over 52 weeks (primary endpoint).

Objectives: To assess the effect of nintedanib on the rate of decline in FVC in the SENSICIS® trial across pre-specified subgroups defined by baseline characteristics.

Methods: Patients with SSC-ILD with onset of first non-Raynaud symptom ≤7 years before screening and ≥10% fibrosis of the lungs on a high-resolution computed tomography scan were randomised to receive nintedanib 150 mg twice-daily or placebo double-blind. The annual rate of decline in FVC (ml/year) assessed over 52 weeks (primary endpoint) was analysed in the overall population using a random coefficient regression model (with random slopes and intercepts) including FVC as covariates and treatment-by-time and baseline-by-time interactions. Analyses in subgroups by baseline characteristics included terms for treatment-by-subgroup and treatment-by-subgroup-by-time interaction.

Results: A total of 576 patients were treated (288 in each group). Most (75.2%) of patients were female, 51.9% had diffuse cutaneous SSc and 48.4% were taking mycophenolate at baseline. Mean ± SD age was 54.0 ± 12.2 years, and 21.4% of patients were aged ≥65 years. Generally, nintedanib had a consistent effect on reducing the rate of FVC decline across prespecified subgroups defined by baseline characteristics (p=0.05 for all treatment-by-time-by-subgroup interactions). The treatment effects estimates were comparable to the estimates of the primary analysis and the confidence intervals were overlapping. The analysis did not indicate a difference in the reducing effect of nintedanib across all subgroups assessed.

Conclusion: Nintedanib is effective at reducing ILD progression in a broad range of patients with SSC-ILD.

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Difficult to treat NXP2-positive polymyositis in a 38-year-old woman

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Background: NXP2-positivity occurs in up to 25% of juvenile dermatomyositis (DM) patients. In adults, NXP-2 antibodies are rare, but possibly associated with malignancy.

Case report: A 38-year-old woman was admitted to our ward with a creatin kinase of >18000 U/l. She had a 3 week-history of inflammatory pain and muscle weakness in the shoulder girdle, neck, and legs. The latter is done to foster protrusion of salivary glands and therefore to reduce the incision depth and potential nerve damage. We recently developed a new single-use device for MSG by 3D-printing in form of a lip clamp. For each MSG biopsy, we recorded if any assistance was needed during the procedure, occurrence of any complication, if salivary glands were obtained and if the quality of the salivary gland tissue sample was adequate for histologic analysis.

Results: 15 MSG biopsies were performed using the lip clamp on 15 patients with suspected Sjögren’s syndrome between August 2018 and February 2019. Using the lip clamp, the physician was able to perform all the biopsies without assistance. No complication occurred with a follow-up of 1 week for each patient. Salivary glands tissue samples were obtained in 13/15 of the patients using 1 incision. For 2 patients, a second incision had to be performed on the contralateral side of the lip during the same intervention because no glands were found on the first attempt. Quality of all the samples was adequate for histologic analysis. From February to May 2019 the device was temporarily unavailable, and we performed 10 MSG biopsies with routine procedure (with the need of an assistant) and obtained salivary glands tissue samples in 9/10 of the patients. We did not observe differences in terms of procedure time between both techniques.

Conclusion: The use of a single-use lip clamp facilitates MSG biopsy without needing assistance and potentially reduces invasiveness and collateral damage. Quality of the tissue samples obtained was adequate for histological analysis.

Conflict of interest: AD: none, DD: none, BB: none, TH: has developed the device and holds rights.
Dermatomyositis bei einer 66-jährigen Patientin mit schwerem Hautbefall

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son (20 mg/d bis 10 mg/d) ab Ende 02/2019 und danach eine Behand-
lung mit 15 mg Metronidazol wöchentlich begonnen. Ausser-
dem wurde eine Therapie mit Immunglobulinen geplant. Zusammenfas-
send ist festzustellen, dass die Diagnose einer seltenen Erkrankung häufig verzögert ist. Für das Krankheitsbild der Dermatomyositis sind ausreichend konklusive randomisierte Studien derzeit nicht verfügbar. Die Prognose ist von zusätzlichen viszeralen Beteiligung (z. B. Lun-
gen, Nieren, Malignität), Erhöhung der CK oder Sortypen abhängig.

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Efficacy and safety of tocilizumab in patients with giant cell arteritis and visual disturbances

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Background: Giant cell arteritis (GCA) affects cranial arteries and may lead to visual impairment and blindness. Tocilizumab (TCZ) has recently been approved for treatment of GCA, however, data on its effi-
cacy and safety in patients with initial visual affection is limited.

Objective: To study the outcome of patients with GCA and visual affect-
tion treated with TCZ.

Methods: We performed a retrospective single center study of all pati-
ents with GCA and visual impairment consecutively seen in our clinic between 4/2013 and 1/2019 who received TCZ.

Results: 16 GCA patients (13 women, 3 male) with a mean age of 76.3 + 9.7 yrs at GCA diagnosis and 25 affected eyes were treated with TCZ in addition to corticosteroids (CS). 2 patients experienced unilateral blindness while receiving iv pulse CS. AAION was diagnosed in 2025 eyes, APION in 1/25 eyes and occlusion of the central retina in 4/25 eyes. 14 patients were treated with TCZ iv 8mg/kg every 4 weeks, 2 patients received sc TCZ at 162mg every 2 weeks. All patients with visual symptoms received intravenous CS boluses, followed by predni-
son 1mg/kg/day with subsequent tapering. Concomitant treatment consisted of low dose ASS in 11/16, oral anticoagulants in 5/16 and statins in 9/16 patients. Mean disease duration before initiation of TCZ was 3.8 + 5.7 months. 13/16 patients started with TCZ within 2 months after diagnosis of GCA, in 3 patients, TCZ was started because of refractory and/or relapsing disease. Mean follow-up time is 24 + 20.4 months in 5/2019. Mean duration of TCZ therapy was 14.8 + 9.4 months. Mean duration on CS was 11.4 + 11.9 months. 9/16 patients stopped CS and have been steroid-free for a mean time of 14.7 + 8.3 months. 4/9 patients have discontinued TCZ and are drug-free at present for 8, 13, 35 and 39 months. 2 additional patients were able to extend the infusion interval. 0/12 eyes with BCVA (best corrected visual acuity) <20/200 recovered, however, 6/9 eyes with baseline BCVA between 20/200 and 20/40 improved during TCZ. None of the patients with initial unilateral eye involve-
ment, developed visual disturbances of the non-affected eye. Over-
all, TCZ was well tolerated. Vascular complications (TIA, aortic aneu-
rysam, pulmonary embolism) occurred in 3 patient. One patient died of concomitant cancer.

Conclusions: Although TCZ was unable to reverse unilateral blind-
ness, no new visual symptoms occurred during or after TCZ treatment and the majority of patients were able to stop or reduce GC.
Long-term outcome of tocilizumab for patients with giant cell arteritis: Results from part 2 of the GIACTA trial

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Introduction: Tocilizumab (TCZ) 162 mg administered SC weekly (QW) or every-other-week (Q2W) plus 26-week prednisone tapering resulted in higher rates of sustained glucocorticoid (GC)–free remission in patients (pts) with giant cell arteritis (GCA) than placebo plus 26-week (PBO+26) or 52-week (PBO+52) prednisone tapering in the 52-week, double-blind, randomized controlled GIACTA trial. We here analyzed long-term safety and maintenance of efficacy in GCA pts in a 2-year long-term extension (part 2) of this trial.

Methods: After 52 weeks, pts in clinical remission (CR, absence of flare per investigator assessment) stopped TCZ treatment upon entering part 2. Subsequent GCA therapy, including initiation/termination of open-label TCZ treatment was at the investigator’s discretion. Outcomes included maintenance of CR (no flare during part 2), flare, time to first flare, treatments received, cumulative GC dose, and safety. Treatment groups refer to originally assigned treatment (PBO or TCZ).

Results: 215/250 pts entered part 2 and 92% completed 3 years in the trial. 38/81 (47%) TCZ QW and 13/36 (36%) TCZ Q2W pts maintained CR during part 2. Of these, more pts (65%) were treatment-free (no NC and GC) vs original PBO pts (45%), with the highest proportion in the TCZ QW group (66%). Median time to first flare without TCZ was longer for pts in the original TCZ groups (TCZ QW, 575 days; TCZ Q2W, 428 days) than in the original PBO groups (PBO+26, 162 days; PBO+52, 295 days); TCZ QW patients remained flare-free the longest. Retreatment with TCZ effectively restored CR in part 2. Cumulative 3-year GC dose was lowest in the TCZ QW group (median dose [mg/day]: TCZ QW, 2372.8; TCZ Q2W, 2863.0; PBO+26, 5006.0; PBO+52, 5322.5). Rates of serious adverse events per 100 patient-years over 3 years were comparable for pts never receiving TCZ (23.2) and receiving ≥1 dose of TCZ (21.0; both p = 0.58). 38/81 (47%) TCZ QW and 13/36 (36%) TCZ Q2W pts maintained CR during part 2. Of these, more pts (65%) were treatment-free (no NC and GC) vs original PBO pts (45%), with the highest proportion in the TCZ QW group (66%). Median time to first flare without TCZ was longer for pts in the original TCZ groups (TCZ QW, 575 days; TCZ Q2W, 428 days) than in the original PBO groups (PBO+26, 162 days; PBO+52, 295 days); TCZ QW patients remained flare-free the longest. Retreatment with TCZ effectively restored CR in part 2. Cumulative 3-year GC dose was lowest in the TCZ QW group (median dose [mg/day]: TCZ QW, 2372.8; TCZ Q2W, 2863.0; PBO+26, 5006.0; PBO+52, 5322.5). Rates of serious adverse events per 100 patient-years over 3 years were comparable for pts never receiving TCZ (23.2) and receiving ≥1 dose of TCZ (21.0; both p = 0.58).

Conclusion: Nearly half the pts treated with TCZ QW maintained CR throughout part 2, though flares still occurred in the remaining pts once they discontinued TCZ treatment. Retreatment with TCZ restored CR in patients who experienced flare. Among pts maintaining CR in part 2, higher proportions of pts originally assigned to TCZ were treatment-free compared with those originally assigned to PBO. Cumulative GC doses over 3 years were lowest in patients originally assigned to TCZ. No new safety signals were observed with TCZ exposure in GCA pts during the 3-year study.

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Off-label use of rituximab in rheumatic diseases, a swiss tertiary centre experience

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Background: Rituximab (RTX) is licenced for the treatment of rheumatoid arthritis (RA) and ANCA-associated vasculitides. RTX is frequently used off-label to treat other auto-immune diseases (AID), especially connective tissue diseases (CTD). There are no published data about off-label use of RTX in AID in Switzerland.

Objectives: To describe off-label use of RTX in a real-life setting, when treating AID.

Methods: Retrospective cohort study of all patients treated with RTX in the Rheumatology Department between 2005 and 2017. Clinical efficacy of RTX after 12 and 24 months of treatment was classified as no response (NR), partial (PR) and complete response (CR). RTX discontinuation rate was analysed using Kaplan-Meier method. Occurrence of serious adverse events (SAE) and anti-RTX antibodies (ADA) were reported.

Results: 167 patients treated with RTX were identified: 29% for CTD, 62% for RA and 9% for other AID. RTX was used off-label in 74% of the patients according to Swiss official indications. No significant differences in terms of clinical response were observed between off-label and in-label use after 12 months (NR: 16%/14%, PR: 49%/48%, CR: 36%/38%, n = 103/29, p = 0.97) and 24 months (NR: 13%/10%, PR: 38%/30%, CR: 49%/60%, n = 76/20, p = 0.67), respectively. Clinical response after RTX treatment did not differ significantly between patients with CTD and RA after 12 months (NR: 10%/13%, PR: 50%/51%, CR: 40%/36%, n = 42/78, p = 0.81) and 24 months (NR:7%/10%, PR:32%/44%, CR:61%/46%, n = 28/59, p = 0.43), respectively. Survival curves of RTX treatment from CTD group closely matched that from RA group (HR 0.91 95% CI 0.61-1.38). Causes of RTX treatment discontinuation in patients with CTD (n = 26) and RA (n = 65) consisted of lack of efficiency (62%/55%), adverse event (19%/34%) and remission (19%/11%, p = 0.3).

SAE (n = 108) occurred in 34% of the patients and consisted of infectious SAE (43%) and perfusion-related AE (6%). 13%/22% of the patients with CTD/RA (n = 47/103) presented at least one infectious SAE (p = 0.15). 5 patients with RA and 3 patients with CTD died during RTX treatment. Low IgG levels were observed in 33% (46/141) of the patients according to Swiss official indications. No significant differences were observed in terms of serious adverse events (SAE) and anti-RTX antibodies (ADA) were reported.

Conclusion: Efficacy of RTX was similar in off-label vs. in-label use. RTX discontinuation rate was comparable in patients treated for CTD and RA in our population. Patients with RA were more prone to undergo adverse events by RTX than patients with CTD.
Methods
Retrospective cohort study using the Swiss Clinical Quality Management in Rheumatic Diseases (SCQM) registry. AxSpA patients initiating TNFi without previous DMARD (biologic or conventional synthetic DMARD (csDMARD)) use and with available Maastricht Ankylosing Spondylitis Enthesitis Score, modified to include the plantar fascia, (MASES) at start of treatment (BL) and after 6 months (± 3 months [mo] of follow up [FU]) were included. Presence of enthesitis was defined as at least 1 inflamed enthesis. Among patients (pts) with any entheses present at BL, pts with enthesitis at each MASES site was assessed at BL & 6-mo FU. Fisher’s exact test was used to assess significant enthesis resolution at each entheses site between BL & 6-mo FU.

Results
781 DMARD-naive pts with axSpA who initiated TNFi were identified. At BL, pts (67% male) were a median of 40 (interquartile range [IQR] = 32.5-49.2) years old, 59% were male, 94% were ≤ 60 years old, 7% were ≥ 60 years old. The majority of pts had axSpA (86%), followed by psoriatic arthritis (14%). At BL, 92% of pts had active enthesitis defined by the MASES, with a median of 2 (IQR = 0-5) entheses sites involved. At BL, 74% were receiving NSAID therapy and 45% were receiving csDMARD (predominantly methotrexate) therapy. Median disease duration was 9 (IQR = 3-18) years.

Conclusion
AxSpA patients initiating TNFi therapy had a significant increase in enthesitis resolution at each entheses site between BL & 6-mo FU, with most patients requiring a shorter therapy duration for resolution compared to csDMARD therapy. Further studies are needed to evaluate the long-term efficacy of TNFi in axSpA patients.
Conclusion: The primary and all major secondary endpoints for IXE were met at Wk 16 with no unexpected safety findings. IXE was superior to PBO for improving r-axSpA signs and symptoms and objective signs of inflammation.

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Sustained improvements in disease activity for up to two-years with ixekizumab in patients with active psoriatic arthritis who were either biologic-naïve or with previous inadequate response to tumour necrosis factor inhibitor therapy

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Background: Ixekizumab (IXE) is a high-affinity monoclonal antibody that selectively targets IL-17A and is approved for the treatment of psoriatic arthritis (PsA). The efficacy and safety of IXE 80mg every 4 weeks over two years of treatment in patients who were either biologic disease-modifying antirheumatic drug (bDMARD) naïve or tumour necrosis factor inhibitor inadequate responders (TNF-IRs) are presented.

Methods: Data were analysed from two double-blind, placebo (PBO)-controlled, Phase 2 trials in patients with active PsA who were bDMARD-naïve (SPIRIT-P1) or TNF-IR (SPIRIT-P2) were randomised to PBO, IXE 80mg every 4 weeks (IXEQ4W) or IXE 80mg every 2 weeks (IXEQ2W) (after a 160mg starting dose for both IXE Q4W and IXE Q2W or adalimumab (ADA) 40mg Q2W in SPIRIT-P1). At week 16, non-responder patients received rescue therapy. At week 24, patients on PBO or ADA in SPIRIT-P1 were re-randomised to IXEQ2W or IXEQ4W. Efficacy measures included American College of Rheumatology (ACR) 20/50/70 responses, Psoriasis Area and Severity Index (PASI) 75/90/100 responses, Leuds Enthesitis Index (LEI), Leuds Dactylitis Index-Basec (LDI-B), Health Assessment Questionnaire Disabiity Index (HAQ-DI) score, Minimal Disease Activity (MDA) and Nail Psoriasis Severity Index (NAPSI) score. Missing values were imputed by modified nonresponder imputation (mNRI) for categorical data or modified baseline observation carried forward (mBOCF) for continuous data. Safety analyses included patients receiving ≥1 dose of IXE.

Results: At week 108, patients treated with IXEQ4W demonstrated sustained improvements in ACR20/50/70 responses, Psoriasis Area and Severity Index (PASI) 75/90/100 responses, and mBOCF for continuous data. Safety analyses included patients receiving ≥1 dose of IXE. IXE showed sustained improvement in PROs in SPIRIT-P1 and -P2 (Population-bDMARDs naïve) and SPIRIT-P2 (TNFi-IR). Randomised patients treated with IXE Q4W vs PBO for 108 weeks reported:

1. ASAS improvement ≥20% (n = 38) vs 24.1% (n = 19; all NRI).

2. More pts with symptoms <5 yrs reached ASDAS-ID (40.5% [n = 32] vs 17.9% [n = 14]) and ASDAS-c2 (65.8% [n = 52] vs 52.6% [n = 41]; both LOCF).

Conclusion: IXE sustained improvement in PROs in SPIRIT-P1 and -P2 patients with shorter symptom duration (<5 yrs vs ≥5 yrs) showed greater improvements across multiple signs and symptoms of disease. Early CZP TX may be beneficial to nr-axSpA pts. References: 1. Rudwaleit M. Arthritis Rheum 2009;60:717–27; 2. Deodhar A. Arthritis Rheumatol 2018;70(S9):2073–4.

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Rapid and sustained improvements in patient-reported outcomes with ixekizumab in biologic-naïve and TNF-inaequate responder patients with psoriatic arthritis

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Background: Ixekizumab (IXE), a high-affinity monoclonal antibody that selectively targets IL-17A, has shown improvements in signs and symptoms of psoriatic arthritis (PsA) in patients who were biologic naïve and in patients who failed prior TNF-inhibitors (TNFi-inadequate responders [IR]). Here, we report the onset and duration of IXE treatment effect on patient-reported outcomes (PROs).

Methods: The PROs data were taken from two phase-3 trials: SPIRIT-P1 (Population-bDMARDs naïve) and SPIRIT-P2 (TNF-IR). Randomised patients treated IXE 80 mg every 2 weeks (Q2W) and every 4 weeks (Q4W) after 160 mg initial dose, or placebo. The following PROs were assessed from baseline up to 108 weeks: Joint pain visual analog scale (VAS), patient global assessment (PtGA), fatigue numeric rating scale (NRS), and health assessment questionnaire disability index (HAQ-DI).

Results: Patients treated with IXE Q4W dose in SPIRIT-P1 and -P2 studies reported rapid (as early as week 1) and consistent improvement in PROs throughout 52 weeks. Long-term treatment until week 108 with IXE showed sustained improvement in PROs in SPIRIT-P1 and -P2 studies, with mean change (±standard deviation) from baseline (IXEQ4W) in fatigue NRS (-1.9±2.7 and -1.8±2.8) and HAQ-DI (-0.6±0.5 and -0.4±0.6, respectively). Safety profile of IXE in patients with PsA is consistent with previously reported safety results from pooled data of phase 3 trials and no new or unexpected safety signals were reported.

Conclusion: These data demonstrate that patients with PsA treated with IXE achieve rapid and sustained improvements in PROs irrespective of prior biologic exposure.
Efficacy and safety of ixekizumab in the treatment of radiographic axial spondyloarthritis: 16 week results of a phase 3 randomised, double-blind, placebo-controlled trial in patients with prior inadequate response or intolerance to 1 or 2 tumour necrosis factor inhibitors

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Background: TNFi are recommended for patients with axSpA who do not respond to or tolerate NSAIDs, axSpA patients with inadequate response (IR) or intolerance to TNFi have not been exclusively studied in a clinical trial. In COAST-W (NCT02696798), we investigated the efficacy and safety of ixekizumab, a high-affinity monoclonal antibody that selectively targets IL-17A, in patients with active radiographic axSpA (r-axSpA) with prior use to 1 or 2 TNFi.

Methods: In this randomised, double-blind, placebo-controlled, Phase 3 trial, adult patients with IR/intolerance to 1 or 2 TNFi and an established diagnosis of r-axSpA (patients fulfilling ASAS classification criteria for axSpA, with radiographic sacroiliitis centrally defined by modified New York criteria) were recruited and randomised 1:1:1 to placebo (PBO) or 80-mg or 160-mg intravenous (IV) or subcutaneous (SC) ixekizumab every 2 (IXEQ2W) or 4 (IXEQ4W) weeks (wks), with either 80-mg or 160-mg starting dose (assigned 1:1). The primary endpoint was ASAS40 response rate at Wk16. Secondary endpoints included CFB in MRI spine and sacroiliac joint SPARCC scores. In addition, the CFB is reported for hs-CRP and the 4 patient domains used for calculation of the ASAS response: PGA, BASFI, spinal pain and BASDAI stiffness. Categorical outcomes were analysed by logistic regression with non-responder imputation. Continuous outcomes were analysed by mixed-effects model of repeated measures except MRI SPARCC scores (ANOVA using observed case). Safety was assessed.

Results: 316 patients were randomised to PBO (N = 104), IXEQ2W (N = 98) or IXEQ4W (N = 114). All patients possessed very active (mean BASDAI: 7.4±1.3) and long-standing disease (median duration of symptoms: 16.7 years); 90% had a prior IR and 10% were intolerant to TNFi. At Wk16, ASAS40 was significant with IXE [IXEQ4W = 25.4%; IXEQ2W = 30.6%] compared to PBO [12.5%]. Compared with PBO, IXE-treated patients showed significantly greater CFB in secondary endpoints including PGA, spinal pain and BASDAI stiffness, spinal MRI and SI inflammation, and high sensitivity CRP, at Wk16 and, as early as Wk1. Most TEAEs were mild/moderate. Serious AEs were consistent across arms. One death was reported (IXEQ2W) due to suicide which was not attributable to study drug per the blinded principal investigator.

Conclusion: The primary and all major secondary endpoints for IXE were met at Wk16 in patients with previous IR or intolerance to one or two TNFi, compared to PBO.

Efficacy and safety outcomes in patients with axial spondyloarthritis treated with certolizumab pegol: results from the 48-week run-in part of C-OPTIMISE

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Background: C-OPTIMISE is the first trial to evaluate whether certolizumab pegol (CZP) can be reduced/discontinued in patients with radiographic (r-)axSpA/ankylosing spondylitis (AS) and non-radiographic (nr-)axSpA achieving sustained remission after 48 weeks’ (wks’) treatment. We report interim efficacy and safety data for both axSpA subpopulations from the C-OPTIMISE trial.

Methods: C-OPTIMISE (NCT02505542) was open-label to Wk48 (Part A), followed by 48-wk randomization, double-blind, placebo-controlled treatment (full dose and half dose) to Wk96 (Part B). Patients with adult-onset axSpA of <5 years’ duration, fulfilling ASAS classification criteria, were recruited. In Part A, patients received CZP 400mg at wks0/2/4, then 200mg every 2 weeks (Q2W). Patients achieving sustained remission in Part A (ASDAS<1.3 at Wk52 and <2.1 at Wk56 [or vice versa], and <1.3 at Wk48) were eligible for Part B (secondary outcome). The primary outcome was the percentage of patients in Part B not experiencing a flare (not reported here). Missing values were imputed using non-responder imputation (NRI) or last observation carried forward (LOCF).

Results: A total of 736 patients were recruited in Part A (r-axSpA/AS: n = 407; nr-axSpA: n = 329). Mean (SD) time since diagnosis was 2.2 (1.7) years (r-axSpA/AS: 2.5 [1.8]; nr-axSpA: 1.8 [1.6]). At baseline, 98.5% patients had high/very high disease activity (ASDAS≥2.1); at Wk48, 52.7% (r-axSpA/AS: 52.6%; nr-axSpA: 52.9%) had inactive disease (ASDAS<1.3; LOCF). Of 736 patients, 43.9% achieved sustained remission (r-axSpA/AS: 42.8%; nr-axSpA: 45.3%; NRI). The treatment-emergent adverse event (TEAE) rate was 224.2/100 patient-years’ exposure; 4.5% patients discontinued CZP due to TEAEs. No new safety signals were identified.

Conclusion: The run-in phase of C-OPTIMISE shows that similar and substantial proportions of patients with r-axSpA/AS and nr-axSpA achieved sustained remission during 48 wks’ CZP treatment. No new safety signals were identified.

Comparative effectiveness research in observational settings: evaluating new two methods to analyse response rates

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Background: Comparing response rate (rr%) in observational studies is hampered by two major threats. 1. Confounding: Patient, disease, and treatment characteristics often differ for each drug. 2. Attrition bias: Assessing %rr after a set time excludes patients who discontinued their treatment, which may overestimate drug effectiveness.

Objectives: Propose two new methods (3 and 4) to compare %rr in patients with different baseline characteristics, while accounting for attrition and compare them to established methods (1 and 2). Sample illustration using CDAI low disease activity (≤10) rates in data from a collaboration of registries1 with 3448 patients treated by a biologic, either intravenously (IV: n = 2414) or subcutaneously (SC: n = 1034).

Methods

1. Complete case (CC) %rr is computed as the percentage of responders on total patients still on treatment at the given time point.

2. LUNDEX2: CC %rr is corrected for attrition by multiplying it by the Kaplan Meier estimates of the survival (SKM), thus considering all patients not on treatment as non-responders, irrespective of the reason for drug discontinuation.

3. Propensity Score Matching LUNDEX (PSM LUNDEX) A: Select patients in both exposure groups using propensity score matching B: Use the LUNDEX to compute the %rr.

4. CARRAC: Adjusted Response Rate with Attrition Correction by reason for drug discontinuation (CARRAC) A: Compute estimates of drug survival for the main reasons of drug discontinuation (e.g., ineffectiveness, adverse events). B: Estimate %rr using random effect IPD meta-analysis with estimates for each reason of drug discontinuation. C: Combine %rr estimates using weights of step A.

Results: Compared to CC analysis, differences in %rr between the SC and IV groups were smaller for the LUNDEX methods, larger for PSM LUNDEX, and close to CC for the CARRAC method. For PSM LUNDEX, overlapping propensity score only allowed to select 561 patient per group.

Conclusion: Both LUNDEX methods may underestimate the true response rates by considering all patients stopping treatment as non-responders, while complete case method may overestimate the %rr by considering patients stopping as having a similar %rr to patients continuing treatment. The CARRAC method, which accounts for attrition by reason for drug discontinuation, obtained %rr estimates in between complete-case and LUNDEX corrections. Simulations studies are needed to evaluate the best method.
An atypical chest pain
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A 50 years old man presented to the emergency department with widespread pain, especially at chest level, fever and night sweats. He referred fever with spikes up to 39 °C in the two days prior to hospitalization at the Department of Rheumatology. Physical examinations revealed a swelling with localized pain in the left sternoclavicular joint. Laboratory tests showed a CPR of 134 mg/l and an ESR of 70 mm/h. Uric acid is within the norm (263 mmol/l). The patient’s anamnesis is for a chronic gouty arthritis characterized by the presence of tophi and frequent arthritides, a type 2 diabetes poorly controlled, a lumbar radicular syndrome suggestive L5 on the left side and obesity that is why he underwent a gastric banding surgery. Social history: the patient declares drinking 2-3 liters of carbonated soft drinks a day.

Home therapy: Metformin, Sitagliptin, Gliclazide, Naproxen with partial benefit on pain and Febuxostat. Differential diagnoses of sternoclavicular swelling includes infectious, crystals or psoriatic arthropathy, Tumor pathology, SAPHO syndrome. An ultrasound scan performed at thoracic level showed the presence of effusion in the sternoclavicular joint. A thoraco-abdominal CT scan, performed in doubt of neoplasias, shows no masses but osteocutaneous non-specific alterations of the sternoclavicular joint. We performed a Dual energy CT (DECT) which report a gouty arthropathy at the sternoclavicular joints (in the literature only three similar cases are proved). Because of the poor therapeutic effects using Febuxostat and systemic corticosteroids, the patient was treated with Anakinra, an interleukin 1 receptor antagonist, which led, 6 months after the event, to a total remission.

Methods: Osteochondral tissue explants of osteoarthritic human knee tibial plateaus (n = 10) or lumbar facet joints (n = 10) were cultured for one week in the presence and absence of an inflammatory stimulus (1 μg/mL LPS). Specimens were left untreated (control) or treated with a senolytic agent (4.5 mg/mL quercetin) or inhibitor of TGF-beta receptor signaling (10μm SB-505124). Subchondral bone turnover (Pro-Collagen type I) and tissue inflammation (IL-6, MCP-1) was assessed by ELISA.

Results: Explanted tissues showed no appreciable loss of viability during culture and drug treatment. LPS challenge led to a 4- and 3-fold induction of IL-6 and MCP-1 tissue secretion, respectively. Subchondral bone turnover was not affected by inflammatory conditions. The therapeutic effect of TGF-beta signaling inhibition was revealed by a drastic reduction of pro-Coll1 (~75%) and IL-6 (~50%) secretion. Unexpectedly, MCP-1 secretion was significantly elevated (~200%) revealing a TGF-beta-dependent negative feedback mechanism. This side effect was specific for knee osteoarthritis and not observed in facet joint specimens. Senolytic treatment with quercetin did not affect bone turnover, yet strongly induced IL-6 tissue secretion under control (~400%) and inflammatory conditions (~200%).

Conclusion: Taking advantage of a preclinical model of human osteoarthritis, we established therapeutic efficacy of TGF-beta signaling inhibition on subchondral bone turnover in knee and spine. Elevated MCP-1 secretion upon TGF-beta-targeting and increased tissue inflammation using senolytics prompt careful evaluation of these potential disease-modifying agents transitioning from experimental to human osteoarthritis. Osteochondral explant models are highly valuable for determining joint-specific tissue responses.

Preclinical evaluation of targeting TGF-beta signaling and senescence in ex vivo models of human knee and spine osteoarthrititis
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Introduction: Histology remains the gold standard in morphometric and pathological analyses of osteoarthritic human tissues, because of its high resolution and cost-effectiveness. However, the experimental setup of histology is laborious and provides only a two-dimensional image of a single anatomical plane. Micro computed tomography (μCT) enables non-destructive three-dimensional visualization and morphometry of mineralized tissues and, with the aid of contrast agents, soft tissues. In this study, we evaluated phosphotungstic acid-enhanced PTA-μCT to visualize pathology in human facet joint degeneration.

Methods: Lumbar facet joint specimens were acquired from eleven patients undergoing decompression surgery. Fresh osteochondral specimens were immediately fixed in formalin and scanned in a benchtop μCT scanner (65 kV, 153 mA, 25 μm resolution). Subsequently, samples were decalcified in 5% formic acid, equilibrated in 70% ethanol and stained up to ten days in 1% PTA, which selectively binds to collagen. PTA-stained specimens were scanned at 70 kV, 140 mA, 15 μm resolution. Finally, specimens were dehydrated and processed for routine tissue histology (HE staining).

Results: While conventional μCT only displayed mineralized bone tissue, PTA-stained tissue samples showed X-ray attenuation in collagenous tissues including cartilage (collagen II, X), bone (collagen I) and bone marrow (collagen I, III, IV). Measurements of bone volume (r = 0.90, p = 0.01) and bone surface (r = 0.95, p = 0.004) were strongly correlated between conventional and contrast-enhanced CT methods. Image analyses of cartilage tissues enabled quantification of collagen loss in loaded versus unloaded regions of degenerated joints and visualization and quantification of cartilage cell (chondrocytes) numbers. Bone marrow signals corresponded with fibrovascular inflammatory cell infiltration in routine histology. Contrast-enhanced CT enabled quantification of inflammatory cell volume in bone marrow space.

Conclusions: PTA-enhanced μCT is a low-cost, non-toxic and highly feasible method for ex vivo 3D-visualization of osteoarthritic pathology in human joint tissues. The method enables bone morphometric analysis, as well as collagen distribution in all anatomical planes. Contrast enhanced μCT has several applications in bone and osteoarthritis research including 3D histopathological grading, tissue stratification, and imaging and analysis of aberrant collagen metabolism in osteoarthritic disease.
Raumforderungen in der infrapatellären Region
Tamborrini Giorgio


Modulation of neutrophil extracellular traps using apremilast (PDE4 inhibition)
van Breda S.V1,2, Rossi S1, Hasler P2

Increased propensity for neutrophil extracellular trap generation has been described in autoimmune diseases such as rheumatoid arthritis. Neutrophil extracellular traps are thought to contribute to disease propensity. Calcium signalling is known to be important for neutrophil extracellular trap generation. Thus, controlling this calcium signalling pathway may allow for regulation of autoimmune disease pathology. Apremilast is a selective phosphodiesterase 4 inhibitor that is currently approved for the treatment of psoriasis and psoriatic arthritis with a positive phase 3 on Behçet’s disease. Inhibition of phosphodiesterase 4 can elevate cAMP levels, decrease adenylate cyclase levels and thus modulate calcium release and store-operated calcium signalling. We hypothesised that by inhibiting phosphodiesterase 4 with apremilast, calcium release can be controlled and in turn decrease the propensity for neutrophil extracellular trap generation. Reduction in PMA induced ROS production for healthy control neutrophils when treated with apremilast was observed. A decrease in PMA and calcium ionophore-induced neutrophil extracellular trap generation was also observed. Apremilast treatment of rheumatoid neutrophils also displayed a decrease in spontaneous ROS generation and neutrophil extracellular trap generation. We also investigated the effect of phosphodiesterase 7 inhibition. Interestingly, this displayed an opposite effect to phosphodiesterase 4 inhibition. By reducing neutrophil extracellular traps through modulation of calcium signalling by phosphodiesterase 4 inhibition, the possibility of controlling neutrophil extracellular trap generation in certain autoimmune conditions might be possible.
HPR 1

Entwicklung von Intake-Kriterien für ein Case-Management bei PatientInnen mit hoher Verweildauer auf der Klinik für Rheumatologie

Maier J.1, Freyhof B.2, Mertz I.1, Adomeit P.1, Distler O.1,2

Ziele:

Ziele:
- Frühzeitsiges Erkennen der entsprechenden PatientInnen
- Frühe Prozesskoordination
- Reduktion der Leidens- Wartezeiten
- Rasche Symptomkontrolle und Selbstversorgung
- Reduktion der Verweildauerüberschreitung

Methode:

Ergebnisse:
- Die erkannten Zeitraum wurden insgesamt 14 entsprechende PatientInnen erfasst. Davon überschritten 12 die Zielverweildauer durchschnittlich 5.3 Tage. Lediglich zwei Betroffene überschritten die Zielverweildauer nicht.

Schlussfolgerungen:

HPR 2

Diagnostic test accuracy of clinical tests and ultrasound for the detection of cam and pincer morphology – a systematic review

Caliesz R1, Hilfiker R2

Background:
- Femoroacetabular Impingement (FAI) syndrome is seen as a predisposing factor for degenerative processes in the hip joint. Recognition and adequate intervention is needed to reduce the risk of premature degeneration. Several clinical tests for the diagnosis of FAI morphologies are proposed, but there is a lack of an actual systematic overview of the literature about the accuracy of these tests.

Objectives:
- To examine the diagnostic accuracy of clinical tests and ultrasound for the detection of pincer, cam or mixed type morphologies in people suspected of having FAI syndrome, and discuss the clinical utility of these tests.

Methods:
- A systematic search in PubMed, CINAHL, EMBASE and SPORTDiscus databases was conducted. Due to lack of data no meta-analysis was performed. Number of true and false positives, true and
HPR 4
A patient-centered approach for diagnosis and treatment of rheumatological diseases – a single center experience by an office based physician
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1Cabinet de Rhumatologie, Vevey, Switzerland

The complex diagnostic and therapeutic environment of chronic inflammatory diseases today challenges the modern physician in taking optimal decisions during all phases of disease management covering factors from patient satisfaction over practicability to cost effectiveness. In rheumatic diseases doctors still tend to focus on clinical parameters like tender and swollen joints. But even if these parameters improve, many patients experience insufficient subjective improvement to feel a notable difference to their quality of life. Inevitably, adherence decreases which - if unnoticed – leads to increased morbidity and mortality and is costly to manage.

Our center is designed to adapt to these conditions and offer our patients an approach that ensures patient satisfaction, adherence, practicability and thus therapeutic as well as economic outcome. With the intent of sharing best practice, this single center report describes a patient-centered approach and assesses patient satisfaction respectively.

In our model the interdisciplinary setting is assured by several cross-functional collaborations. Medical care through the physician is supported by easy accessible inhouse diagnostic procedures. Allied health professionals like physio- and ergotherapists cover preservation and rehabilitation of physical skills. The on-time drug delivery for treatment initiation, treatment application and patient support throughout therapy are conducted by the specialty pharmacy MediService and their specialized nurses. For covering emotional and mental care of the patient, we offer spiritual and pastoral support. Another unique point of differentiation is our individual educational support for patients in special life circumstances, e.g. nursing advice for female patients and their newborns.

Since March 2019 we assess patient satisfaction with a questionnaire on patient’s contentment. A four-scaled rating was evaluated on several parameters concerning the quality of care. Preliminary analysis revealed an average rating of 3.9 of 4 points for the question on how well patients feel taken care of. Hosting and support together were rated with 3.4 as well as the provision with information on disease and treatment.

Therefore, our clinic model not only suggests a practicable and proven combination of factors assuring patient satisfaction, adherence and therapeutic outcome but also contributes to health economy by an optimal care for rheumatology patients.

HPR 5
Dem Leiden eine Stimme geben
Die Erfassung des Leidensdrucks mittels Pictorial Representation of Illness and Self-Measure (PRISM) auf der Klinik für Rheumatologie im Universitätsklinikum Zürich
Freihof Brigitte1, Cymë Gashi2, Huber Patricia1, Jürgen Maier2
1Klinik für Rheumatologie, Universitätsspital Zürich; 2Medizinbereich Rheumatologie, Freyhof Brigitte1, Cymë Gashi1, Huber Patricia1, Jürgen Maier2


Deshalb wurde eine gemeinsame Dokumentationsstruktur entwickelt, getestet und Anfang 2020 evaluiert.

HPR 6
Betätigungsfokussierte Gruppendedukation bei Menschen mit chronischen Schmerzen
Bertschi Felicia1, 2, Schaufelberger Nina2
1Insepsital, Universitätssklinik für Rheumatologie, Immunologie und Allergologie; 2Zürcher Hochschule für angewandte Wissenschaften


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