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FM 1

PFAPA syndrome is linked to dysregulated IL-1β production

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Objective: PFAPA syndrome is an auto-inflammatory disease of unknown etiology that is characterized by recurrent fever, aphtosis, pharyngitis and cervical adenitis in young children. We hypothesized that it may be due to dysregulated IL1b production and studied the production of this cytokine *in vivo* and *in vitro*.
Methods: 12 PFAPA patients were studied during (IN) and outside (OUT) a febrile episode. Hematological profile, inflammatory markers and cytokine levels were measured in the blood. The capacity of LPS-stimulated PBMCs to secrete IL-1β was assessed by ELISA and active IL-1β production was visualized by Western blots. Genomic DNA was screened for common genetic variants of the MEFV, TNFRSF1A, MVK and NLRP3 genes.
Results: During a febrile attack, PFAPA patients revealed significantly increased monocyte and neutrophil counts, ESR, CRP, and serum amyloid A levels compared to outside an attack. MRP8/14 and S100A12 levels were also significantly increased during an attack. Stimulated PBMCs secreted significantly more IL-1β during an attack (IN 575 ± 88 pg/ml, OUT 235 ± 56 pg/ml; p <0.001), and this was in the active p17 form. IL-1β secretion was inhibited by ZYVAD a caspase inhibitor. Finally, 4 of 12 patients were found to be heterozygous for NLRP3 variants, whereas none had variants of MEFV, TNFRSF1A, and MVK genes.
Conclusion: The combined data strongly suggest that dysregulated production of IL-1β is at the base of the PFAPA syndrome. 4 of 12 patients were found to have known NLRP3 mutations, suggesting that mutations in inflammasome-related genes may underlie this auto-inflammatory syndrome.

FM 2

Evaluation of cardiovascular risk in Patients with RA: What is the added predictive ability of new cardiovascular biomarkers over established clinical risk scores?

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Introduction: Rheumatoid arthritis (RA) is associated with an increased risk of major cardiovascular events (MACE). Quantification of cardiovascular (CV) risk can be performed using well established clinical risk scores, such as the Framingham 10-years Global Cardiovascular Disease Score (FCVDS). It remains unclear whether the prognostic accuracy of the FCVDS can be improved by adding emergent biomarkers of CV risk, such as anti-apolipoprotein A-1 (anti-ApoA-1) IgG, N-terminal pro-Brain Natriuretic peptide (NT-proBNP), and oxidised LDL (oxLDL).
Objective: To determine whether the adjunction of 3 emergent CV biomarkers (anti-ApoA-1 IgG, NT-proBNP, oxLDL) to the FCVDS could improve its prognostic accuracy for MACE prediction in RA patients.
Methods: We performed an ancillary study (n = 118) derived from a single center prospective RA cohort published earlier (A&R, 2010:62(9):2640–50). Patients had no cardiovascular disease at baseline and were assessed for incident MACE over a median follow-up period of 9 years. We assessed discriminatory ability using the area under the ROC curve (AUC) and the integrated discrimination improvement (IDI) statistic. The added predictive ability of the aforementioned biomarkers was assessed by the increase in discrimination obtained by combining the biomarker and the FCVDS and compared to discrimination of the FCVDS alone.
Results: During a median follow-up of 9 years, MACE incidence was 16% (19/118). Individually, all 3 biomarkers were modestly predictive of MACE, with AUCs between 0.68–0.73. However, adding these biomarkers to established clinical risk factors (FCVDS) resulted in significant increase of predictive ability only for anti-Apo A1 IgG. The AUC improved from 0.72 (0.61–0.84) for FCVDS alone to 0.82 (0.72–0.92) for FCVDS + anti-ApoA-1 IgG, and the IDI by 0.98 (<0.001).
Conclusion: Among the emergent prognostic biomarkers tested in this study, anti-ApoA-1 IgG was the only independent predictor of MACE and the only biomarker that significantly improved the predictive ability of the Framingham CV risk score in RA.

FM 3

STIM1 controls store operated calcium entry in synovial fibroblasts and mouse myeloid cells and regulates inflammatory cytokines and IgG mediated phagocytosis

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Introduction: This study aims to assess the role of store operated calcium entry in inflammatory arthritis and antibody mediated autoimmunity.
Methods: STIM and Orai gene expression in mouse and human synovium, human fibroblast like synoviocytes (FLS) and cultured mouse macrophages and dendritic cells was determined by quantitative PCR, IHC and Western blot analysis. The role of STIM1, STIM2 and Orai1 was tested in FLS using siRNA knockdown. Inactivation of STIM1 and STIM2 in mouse myeloid cells was obtained by crossing STIM1 and STIM2 floxed mice with a LysM Cre knockin strain. Cytoplasmic calcium imaging was performed in Fura-2 loaded cells. In vitro phagocytosis of red blood cells opsonized with sheep IgG was assessed by confocal microscopy.
Results: STIM1, STIM2, Orai3 and Orai2 genes were overexpressed in synovial samples from patients with inflammatory arthritis (psoriatic and rheumatoid arthritis) compared to osteoarthritis and normal synovium. By immunohistochemistry, STIM1 overexpression was mainly localized to the synovial lining. Expression of STIM1, STIM2 and Orai1 protein and mRNA was reduced by >75% by siRNA transfection in human FLS. Store operated calcium entry was decreased by >75% in STIM1 and Orai1 knockdown FLS while STIM2 knockdown had no detectable effect. Synovial fluid, fetal bovine serum (10% FBS), histamine (50 μM) and platelet derived growth factor (20 ng/ml) induced STIM1 and Orai1 dependent cytoplasmic calcium fluxes in FLS. Compared to control transfected cells, the production of IL-33 and MMP-3 in STIM1 knockdown FLS co-stimulated with IL-1 and FBS was reduced by 49 ± 3% and 72 ± 5% while IL-6 release was slightly increased (20 ± 2%). In mouse bone marrow derived macrophages and dendritic cells, STIM1 but not STIM2 knockout abolished store operated calcium entry. Strikingly, STIM1 knockout macrophages and neutrophils had a 40% reduced capacity to phagocytose IgG coated red blood cells.
Conclusion: STIM1 dependent store operated calcium entry is involved in the production of IL-33 and MMP-3 by FLS and in IgG mediated phagocytosis by mouse macrophages and neutrophils. STIM1 may represent a novel target in inflammation and antibody mediated autoimmunity.

Posters

P 1

Home-based nurse support for RA patients – a feasibility study

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Introduction: In many countries, nurse support for RA patients at their homes produced improved coping skills and self-management. Nurse-led interventions were found to be safe, effective and acceptable. We conducted a pilot study to assess the acceptability of home-based RA support by a nurse in a Swiss context, and to identify factors that may influence its acceptability. Information from this pilot study may be useful in developping new care models for RA in Switzerland.
Methods: Home-based support and monitoring of RA by a trained nurse was offered to 30 eligible RA patients (22 females, 8 males) from two centres undergoing treatment with etanercept. Home visits were performed on up to 3 separate occasions over 10 months. After each visit, the nurse gave a feedback of her visit to the study coordinator and referring physician. Pre- and post-intervention interviews of the patients, the study nurse and the referring physicians were conducted. Reasons for participation/non-participation, patients' view of the home visits as well as socioeconomic profile, health,

experience with anti-TNF treatment, satisfaction with care, access to doctors, level of social/family support and use of patient support groups were recorded. Combined qualitative and quantitative approaches were used for analyses.
Results: 20/30 patients accepted the proposed intervention. 13 completed the study but all participated in the interviews. Decliners felt no need nor had time for the intervention. Participants viewed nurse visits as complementary to medical consultations, in terms of information and practical and psychosocial support. Preferred timing of visits is at disease onset or when treatment changes, and preferred setting is the home. Trust in the nurse is high. 12/13 participants would like to contact with the nurse. Factors influencing acceptance of home visits include health, treatment, and habitual care, structural and personal factors.
Conclusion: RA patients are willing to accept support and disease monitoring by a nurse delegated by their doctor. Her intervention is a valuable complement to medical consultations. Appropriate specialist nurse training as well as effectiveness and cost-effectiveness studies are needed in the Swiss context.

P 2

Evaluation of the Efficacy and the Safety of a Single Injection of 6 ml of Hyaluronate (Suplasyn-1 shot®) in Patients with Knee Osteoarthritis

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Introduction: Knee osteoarthritis (KOA) is a world wide spread painful disease. The 2008 OARSI recommendations for its management state that injections of intra-articular hyaluronate may be useful for the treatment of pain. Since recently, hyaluronate can be administered by a single 6ml injection. The aim of this daily life practice study is to evaluate the efficacy and the safety of this new medical device.
Methods: 95 patients (66 women) with KOA were enrolled in this open label, prospective trial to evaluate the efficacy and safety of Suplasyn-1 shot®. The mean age of patients was 68 years (range: 35–92 years). About 30% of the patients had a concomitant pain relieving treatment, mostly chondroitine sulfate (18%). 46% of the patients had already been previously treated with hyaluronate injections. Most of the patients choose the new treatment option (Suplasyn-1 shot®), for the easiness of administration and saving of time. 12% were treated on both knees. The injections were performed by a group of 21 rheumatologists located in all areas of Switzerland. Pain improvement was evaluated by a 4 step scale from unchanged to very much improvement.
Results: After a mean time of 3 weeks, pain was improved in 79% of the patients. Based on the judgment and standard care practice of the physicians, 78% of the patients had a second assessment after a mean time of 6 weeks after the injection. Pain was then improved in 72% of the patients. There was no difference in treatment outcome between patients treated the first time or treated previously with hyaluronate. Only three adverse events were reported: twice a pain at the site of injection which spontaneously waived, and once a local swelling that needed to be treated with a NSAID for 5 days. No systemic adverse event was observed.
Conclusion: In this KOA population, Suplasyn-1 shot® relieved pain in 3/4 of the patients after 3 and 6 weeks. Incidence of adverse events was very low. This new way of administrating 6 ml of hyaluronate simplifies the treatment, enhances pain control and reduces the risk of infection by reducing the number of intra-articular injections. Long-term results need to be generated in order to confirm the results of this study.

P 3

Surrogate markers of comorbidities: Impact of canakinumab versus triamcinolone acetonide in acute gouty arthritis patients

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Background: Many patients with gouty arthritis (GA) have pre-existing comorbidities such as hypertension (HTN), chronic kidney disease (CKD), and diabetes mellitus (DM), which can complicate and limit treatment options. IL-1β plays a key role in GA inflammation. Canakinumab, a fully human long-acting selective monoclonal anti-IL-1β antibody, is a potential new option for treating GA pain and delaying new flares.

Table: Change in parameters in patients with comorbidities from baseline to study end

Preferred term	Canakinumab 150 mg				TA 40 mg			
	n*	BL	EOS	Change from BL	n*	BL	EOS	Change from BL
Hypertension	N=131				N=139			
Sitting systolic BP (mmHg), mean	131	142	135	-6.9 (17.6)	139	140	136	-4.3 (15.8)
Sitting diastolic BP (mmHg), mean	131	86	83	-2.9 (10.7)	139	85	84	-1.6 (10.8)
Chronic Kidney Disease	N=33				N=22			
GFR (by MDRD mL/min/SA), mean	33	45	49	3.8 (11.6)	21	45	47	2.6 (6.7)
Microalbumin (mg/L), mean	33	408	326	-82 (180)	19	433	550	117 (588)
Sitting systolic BP (mmHg), mean	33	137	132	-5.7 (18.2)	22	137	139	1.7 (15.1)
Sitting diastolic BP (mmHg), mean	33	83	81	-1.9 (13.1)	22	82	85	2.7 (10.1)
Diabetes Mellitus	N=34				N=32			
Fasting blood glucose (mmol/L). Mean	32	7.38	7.32	-0.06 (2.23)	31	7.81	7.17	-0.63 (3.71)
HbIAc (%), mean	34	7.01	6.94	-0.07 (0.80)	32	6.94	6.73	-0.21 (0.56)

*n is the number of patients for the change from baseline summaries and includes only patients with a value at both baseline and end of study GFR, glomerular filtration rate, MDRD, modification of diet in renal disease study formula; SA, surface area, BP, blood pressure; TA, Triamcinolone Acetonide

Objectives: To compare the safety of canakinumab vs triamcinolone acetonide (TA) in GA patients with pre-defined comorbidities: results from two phase III studies.
Methods: In both studies, patients (β-RELIEVED, N = 230; β-RELIEVED-II, N = 226) aged ≥18–≤85 yrs and meeting ACR 1977 criteria for acute GA and contraindicated, intolerant or unresponsive to NSAIDs/colchicine, with onset of flares ≤5 days were randomized to receive a single dose of canakinumab 150 mg sc or TA 40 mg im and could receive retreatment for new flares only after 2 wks after previous flare.
Results: 225 patients received canakinumab and 229 patients received TA. A greater mean reduction in BP from baseline was observed in GA patients with HTN receiving canakinumab vs TA (table). In addition, microalbuminuria decreased with canakinumab and increased with TA, while GFR increased in both treatment groups. In GA patients with DM, fasting glucose and HbA1c levels remained stable.
Conclusions: HTN was the most frequent co-morbidity in this GA population. There may be a favorable impact on BP for patients treated with canakinumab vs TA. Further data are needed for the smaller subgroups of patients with CKD and DM.

P 4

A controlled trial of canakinumab vs triamcinolone acetonide in acute gouty arthritis patients: Results of the β-relieved study (response in acute flare and in prevention of episodes of re-flare in gout)

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Objectives: To evaluate the efficacy of canakinumab, a long-acting fully human monoclonal antibody selectively inhibiting IL-1β, vs. triamcinolone acetonide (TA) in treating acute flares and preventing recurrent flares in difficult-to-treat gouty arthritis patients.
Methods: In this 12-week, multicenter, double-blind, double dummy, active-controlled trial, patients (≥18–≤85 yrs) with gouty arthritis, who were unresponsive/ intolerant or contraindicated to NSAIDs/colchicine were randomized to receive either canakinumab 150 mg sc or TA 40 mg im.
Results: Of 230 patients enrolled, 228 (canakinumab: n = 113, TA: n = 115) received treatment. 214 (93%) patients completed the study and 16 (7%) discontinued (canakinumab: n = 6; TA: n = 10). Canakinumab was superior to TA in reducing VAS pain score from 12 h to 7 days. At 72 h post dose (1° endpoint) the difference was –11.4 mm (95% CI: –18.2, –4.6, p = 0.0005). Canakinumab delayed the time to first new flare vs TA with a significant relative risk reduction of 55% (p ≤0.001) within 3 months [HR: 0.45; 95% CI: 0.26, 0.76; p = 0.0014]. SAEs (canakinumab: n = 10, TA: n = 5) were not considered to be related to study medication by the investigators. No sc injection site reactions were reported.
Conclusions: This pivotal phase III study confirms the superiority of canakinumab over TA in relieving pain and reducing the risk of new flares in gouty arthritis patients unresponsive, intolerant or contraindicated to NSAIDs/colchicine.

P 5

Comparison of energy expenditure between patients with rheumatoid arthritis and healthy controls

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Introduction: Rheumatoid arthritis (RA) patients have an increased risk of cardio-vascular morbidity and mortality [1]. Among traditional risk factors, physical activity and energy expenditure have been poorly investigated. The present study aimed to compare energy expenditure and physical activity intensity reported by RA patients and controls.
Methods: One hundred and ten patients with RA and 440 age- and sex-matched controls were included in this study. Primary outcomes were assessed using the validated physical activity frequency questionnaire (PAFQ) [2]. For RA patients only, other measures included RA duration, disease activity (DAS28), functional status (HAQ), pain visual analogue scale (VAS) and fatigue VAS. Total energy expenditure (TEE) and the percentage of TEE spent in low- (TEE-low), moderate- (TEE-mod), and high-intensity (TEE-high) physical activities were calculated. Between groups comparisons were computed using conditional logistic regression. The effect of RA-specific measures on TEE was investigated using multivariate linear regression.
Results: The PAFQ was returned by 99 (90%) patients with RA (74% females, mean age 59.5) and 436 (99%) controls (75% females, mean age 58.5). TEE was significantly lower for RA patients compared to controls (resp. 2392 kcal (95% confidence interval: 2295–2490) and 2494 kcal (2446-2543), P = 0.027). Significant differences were obtained between RA patients and controls for TEE-low (resp. 77.5% (74.6–80.5) and 74.3% (73.0–75.7), P = 0.038) and TEE-high (resp. 7.1% (5.3–8.9) and 10.7% (9.6–11.7), P = 0.005) but not TEE-mod (resp. 15.4% (13.3–17.5) and 15.0% (14.0–16.0), P = 0.930). In RA patients, TEE was inversely associated with age (P = 0.027) and fatigue VAS (P = 0.028) but not with RA duration, DAS28, HAQ or pain VAS (P >0.05).
Conclusion: Physical activity of RA patients is more oriented towards low- than high-intensity activities, which results in a significantly lower TEE compared to control subjects, particularly with increasing age and fatigue. In conclusion, physical activity should be promoted among patients to manage cardiovascular risk in RA.

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P 6

Patient perspective on Rheumatoid Arthritis therapies in Switzerland: The Rheumatoid arthritis: insights, strategies (RAISE) survey. Hints to improve our practice

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Introduction: If the global RAISE survey [1] data from 8 European countries and Canada has helped us to better understand the patients perceptions of their disease, it's generalisability remains to be determined. The objective of the present survey was to investigate the perception and expectations of Swiss patients suffering from rheumatoid arthritis regarding their treatment, treatment process, and needs.
Methods: The structured questionnaire developped for the initial RAISE study was adapted by consensus of the authors. Eligible patients were either on biologic therapy (B) or biologic naïve and eligible for biologic treatments (N). Patients were recruited from both university and community-based rheumatologists (35 in all).
Results: 68 patients, 21 biologic naïve and eligible, and 47 biologic experienced were interviewed. Overall, responses were very similar with no significant differences between groups. 81% were women, mean age of 54. Despite our comparatively high density of rheumatologists, only 12% of first consultations were conducted by rheumatologists. 2.4 years occurred between onset of symptoms and diagnosis, a figure only partly explained by delay of referral. Patients seemed globally satisfied with the information they received: most physicians spoke in easily understandable terms (99%), and most (71%) were satisfied with the quality of the available information. While all patients reported improvement on their current treatment, around 10% described their current health status as bad or very bad, and up to 57% felt they needed a better treatment. Finally, if most patients on a biologic admitted this therapy was much more effective, a third of them was unable to self-inject.
Conclusion: RA management has greatly improved over the last decade, but the RAISE survey demonstrates us that there are still unmet basic needs with health quality perceived as suboptimal, unsatisfactory diagnostic delay and underestimated difficulties with self-applicated therapy.

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P 7

A novel screening strategy for preclinical rheumatoid arthritis (RA) in first degree relatives of patients with RA

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Introduction: Biomarkers and clinical risk factors of pre-symptomatic disease exist and suggest that screening at risk populations for early detection of RA is possible.
Objective: To assemble a prospective multicenter cohort of a population at increased risk of developing RA in first-degree relatives (FDRs) of RA patients.
Methods: This is an ongoing, prospective cohort study of individuals at increased risk of developing RA in FDRs of patients with active RA without clinical evidence of joint effusion or synovitis. The individuals are then followed yearly to determine the develop-ment of arthritis. The clinical and immunochemical characteristics of the cohort are described.
Results: We present the first consecutive FDRs of RA patients enrolled between 1st January 2009 to 31st December 2010: 302 FDRs from 5 centers have been identified. At inclusion, mean age is 41 years (SD 15), 75% are female, 93% are Caucasian, median duration of education is 13 years (IQR:12–16), median BMI is 23 (IQR: 21–26). On average, these individuals have 1.3 direct relatives with RA and 15% present at least one tender joint on examination. 18% of FDRs had at least one positive auto-antibody associated with RA (auto-AB): 14% were positive for rheumatoid factor IgM, 3% were positive for rheumatoid factor IgA, and 1% had anti–cyclic citrullinated peptide antibodies (anti-CCP 2 or 3.1). Individuals with at least one positive auto-AB were at higher risk of having tender joints on examination (OR: 3.23, 95% CI: 1.10–9.52).
Conclusion: The prevalence of auto-AB positivity and subtle signs of joint inflammation (joint tenderness) is somewhat higher among asymptomatic FDRs than what would be expected in a younger general population, suggesting that FDRs are indeed a group at higher risk of developing RA. The association between positive auto-Ab and joint tenderness suggests that auto-Ab are a valid intermediate marker of RA development in this population. FDR cohorts can be a valuable resource to decipher RA development and the relationship between genetic and environmental risk factors.

P 8

After failure of an anti-TNF it is unknown whether another anti-TNF or a new biological should be administered in second or third intention

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Introduction: After failure of a first anti-TNF agent, clinicians may chose to prescribe an alternative anti-TNF or switch to a newer biologic agent (Tocilizumab, Rituximab or Abatacept).
Objective: To compare drug retention rates of the newer biologics with those of alternative anti-TNF prescribed in second or third intention.
Methods: Longitudinal population-based Swiss RA cohort (SCQM-RA) including all patients treated with a second or third biological between 1997 and 2010. Drug survival was analyzed using a Cox proportional hazards model.
Results: Longitudinal population-based Swiss RA cohort (SCQM-RA) including all patients treated with a second or third biological between 1997 and 2010. Drug survival was analyzed using a Cox proportional hazards model.
Conclusion: In patients having experienced at least one inadequate response to a previous anti-TNF agent, we demonstrate significantly higher drug retention for biologics with a different mode of action compared to alternative anti-TNFs.

P 9

Anti-TNF therapy in acute sciatica reduces the long-term need for surgery: A three-year follow-up of a randomized double blind placebo controlled trial

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Introduction: Two subcutaneous injections of adalimumab in severe acute sciatica have demonstrated a significant benefit on the number of back surgeries in a short-term randomized controlled clinical trial [1]. This 3-year follow-up study aimed to determine whether the short-term benefit was sustained over a longer period of time.
Methods: Information on surgery was retrieved in 56/61 patients (93%). We used a Cox proportional hazard models to determine factors predisposing to surgery.
Results: Twenty-three (41%) patients had back surgery within 3 years, 8/29 (28%) in the adalimumab group and 15/ 27 (56%) in the placebo group, p = 0.038. Adalimumab injections reduced the need for back surgery by 61% (Hazard Ratio (HR): 0.39 (95% CI: 0.17–0.92). In a multivariate model, treatment with a TNF-α antagonist remained the strongest protective factor (HR 0.17, p = 0.002). Other significant predictors of surgery were a good correlation between symptoms and MRI findings (HR = 11.6, p = 0.04), baseline intensity of leg pain (HR = 1.3, p = 0.06), intensity of back pain (HR = 1.4, p = 0.03) and duration of sickness leave (HR = 1.01 per day, p = 0.03).
Conclusion: A short course of adalimumab in patients with severe acute sciatica significantly reduces the need for back surgery.

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P 10

P38 MAPK inhibitor-loaded particles for the long term intra-articular treatment of osteoarthritis

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Background: Cartilage damage observed in osteoarthritis (OA) is related to the presence of cytokines with pro-inflammatory and catabolic actions. Mitogen activated pathway kinases (MAPK) intervene in the regulation of cytokine expression and in the intracellular signals induced by cytokines. The purpose of this work was to formulate extended release formulations of nano- and microparticles containing two p38 MAPK inhibitors for the intra-articular treatment of OA.
Materials and Methods: Biodegradable VX-745- or SB203580-loaded particles of three different sizes were produced by emulsification/ evaporation. After preparation, particles were purified and freeze-dried. *In vitro* activity was assessed on two human fibroblast-like synoviocyts (FLS) lines. Cell viability was measured by MTT test and bioactivity evaluated by IL-6 production after IL-1β activation. Statistical analysis was performed using Student's t-test. In vivo tolerance was evaluated by injecting VX-745- loaded nano- and microparticles in the left knee of naïve mice. Histological evaluation was performed 4 and 22 days after injection.
Results: FLS viability was not decreased by blank nano- and microparticles or by VX-745 and SB203580. IL-6 production was not induced in resting FLS. Inhibition of IL-6 production was assessed in 24h stimulation experiments with IL-1 (1ng/ml). Batches of particles containing identical doses of the p38 inhibitor significantly inhibited the IL-6 release down to 44% ± 2.1%, 58% ± 1.3% and 65% ± 4.1% of controls for 25-, 2.5-µm microparticles, and nanoparticles, respectively. This inhibition pattern suggests that the extended release of the inhibitor can be controlled by modulating particle size. In vivo, VX-745 loaded particles did not affect cartilage integrity. Microparticles but not nanoparticles induced a mild synovial hyperplasia at day 4 after injection and remained in the synovium for the maximum duration of the experiment (22 days).
Conclusion: Identical doses of VX-745 loaded into nano- and microparticles differentially inhibit IL-6 release by actiavated FLS, suggesting that inhibitor release is modulated by particle size in vitro. Further *in vitro* and *in vivo* experiments are ongoing to test these promising novel formulations in different models of rheumatic diseases.

This work was supported by the De Reuter foundation.

P 11

Treatment of symphysitis pubis with one unique iv injection of Ibandronate: report of two cases

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Objective: Osteitis pubis is a noninfectious painful inflammatory disorder of the symphysis pubis. Etiologic factors are numerous, the most common are: osseous extension of adductor, enthesis due to sport overuse, irritation after urological and abdominal procedures, and systemic inflammatory disorders in particular spondylarthropathies. Many cases are idiopathic. The symptoms consist of regional chronic mechanical and sometime nocturnal pain. Diagnosis is usually confirmed by either bone scintigraphy or by MRI. There are no standard treatments but conservative approaches including rest and NSAIDS are generally recommended. In 2001, a good clinical and radiological response of three refractory cases with 3 to 6 monthly perfusions of pamidronate was reported [1]. Ibandronate is a much more powerful and long-lasting bisphosphonate than pamidronate, and has not yet been reported in literature to our knowledge in this indication.
Patients and Methods: We present two cases of idiopathic origin: one woman (63 years old) and one man (36 years old).The symptoms were present >3 months in the first patient and one year in the second. The diagnosis was confirmed by MRI which showed bone edema on both sizes of symphysis and in the second case bony erosions adjacent to the joint were seen. Both cases failed to respond to conservative measures. Both patients received one single direct iv Injection of 3 mg of Ibandronate.
Results: The injections resulted in a rapid (within a few days) resolution of pain that lasted more than 6 months in both patients. No side effects were observed. In the first case, an isotope bone scan performed 4 months after the injection showed no residual uptake. The second patient had a repeated MRI after 6 months. It demonstrated an attenuation of bone edema compared to the first MRI.
Conclusion: IV Ibandronate may constitute a safe and effective treatment option for patients with refractory osteitis pubis.

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P 12

Acute flare induced by the calcific tendonitis of the rotator cuff: inhibition of IL-1 a potential therapeutic target?

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Introduction: Calcific tendonitis of rotator cuff is observed on plain radiographs in 10% of adults, but remains asymptomatic in half these cases. Sometimes, these calcifications induce acute flares with massive inflammation similar to gout or CPPD crisis. Analgesics/ anti-inflammatory medications are usually not sufficient to controls symptoms in these situations. Local steroid infiltration with or without removal of the calcific deposition with a needle aspiration may be useful. A new approach could be IL-1 inhibitors. Indeed, basic calcium phosphate crystals are capable of stimulating the release of active IL-1β in vitro. These crystals trigger IL-1β release, in an analogous manner to MSU crystals in acute gout, suggesting that IL-1β blockade may be clinically useful.
Case presentation: This report describes a 70-year old woman with acute rest pain of the right shoulder since 48 hours. On examination, we found massive limitations of active and passive movements. The patient evaluated, on the visual scale, her symptoms at 10/10 the night and 5/10 the day. The radiography and showed a rounded, 8 mm calcification in the subscapularis tendon. The ultrasound aspect revealed a heterogeneous calcification partially non solid, surrounded by massive inflammation on Doppler. C-reactive protein and erythrocyte sedimentation rate were high (74 mg/ml, 54 mm/hour). The patient received subcutaneous injections of anakinra: 100 mg daily for 3 days (D1-D3). We evaluated the patient in our consult at day D1, D2, D3, D7, D16 and by phone at D70.
This treatment rapidly relieved the inflammatory symptoms (within a few hours with no relapse). The mobility of the shoulder, the biologics parameters improved and the size of the calcification as well the degree of inflammation regressed on ultrasound after 3 days.
Conclusion: This is the first report of a woman with an acute flare induced by calcific tendonitis who received anakinra. IL-1 inhibition may be a therapeutic target in calcific tendonitis. To analyse this response more precisely and elaborate definitive conclusions, a prospective pilot study is on-going in our ambulatory institute.

P 13

Reproducibility and feasibility of a 22 joints ultrasound score in rheumatoid arthritis: a study among rheumatologists with diverse expertise in musculoskeletal ultrasound

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Objective: To assess reproducibility and feasibility of a musculoskeletal ultrasound (US) score for rheumatoid arthritis among rheumatologist with diverse expertise in US, working in private or hospital practice.
Methods: The Swiss Sonography in Arthritis and Rheumatism (SONAR) group has developed a semi-quantitative score for RA using OMERACT criteria for synovitis and erosion. The score was taught to rheumatologists trained in US through two workshops. Subsequently, they were encouraged to practice in their office. For the study, we used 6 US machines of different quality, each with a different patient. 19 readers randomly selected among rheumatologists who have attended both workshops, were asked to score anonymously at least one patient. To assess whether some factors influence the score, we asked each reader to answer questionnaire describing his experience with US.
Results: 19 rheumatologists have performed 29 scans, each patient having been evaluated by 4 to 6 readers. Median time for exam completion was 20 minutes (range 15 to 60 mn). 53% of rheumatologists work in private practice. Graph 1 show the global grey scale score for each patient. Weighted kappa was calculated for each pair of reader using stata11. Almost all kappa of poor agreement were obtained with a low quality device or by an assessor who have previously performed less than 5 scores himself.
Conclusions: This is the first study to show an US score for RA feasible by rheumatologists with diverse expertise in US both in private and hospital practice. Reproducibility seemed to be influenced by the quality of device and previous experience with the score.

	Device 1	Device 2	Device 3	Device 4	Device 5	Device 6
Device quality	High	Low	High	High	Low	High
Median	0.45	0.38	0.58	0.47	0.22	0.62
Range	0.21–0.71	0.05–0.54	0.47–0.88	0.17–0.72	0.07–0.68	0.31–0.72

P 14

The metalloprotease meprin-α is a susceptibility gene for inflammatory bowel disease and contributes to the protective proteolytic barrier of the intestinal mucosa

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Introduction: The surface of the intestinal mucosa is endowed with a wide variety of proteases, which altogether represent a highly active exo- and endoproteolytic shield towards the gut lumen, capable of cleaving almost any polypeptide derived from nutrients and gut microbiota. Through the continuous extensive cleavage of polypeptides that escape complete digestion in the gut lumen and the cleavage of microbial surface proteins, the antigenic load of the mucosal immune system beneath the epithelial cell layer is dramatically reduced and the facultative adhesive-invasive capability of commensals are neutralized. Meprins are metalloproteases abundantly expressed by intestinal epithelial cells and highly enriched at the brush border membrane, thereby reinforcing the proteolytic barrier substantially. We thus expect that a deficiency of meprin activity increases the susceptibility for chronic inflammatory and autoimmune processes in the intestine and at extraintestinal sites.
Methods: The coding region including the 3'UTR of *MEP1A*, the gene encoding meprin-α, was sequence genotyped in a cohort of 379 colitis ulcerosa, 380 M. Crohn patients compared to 372 controls. The susceptibilty of meprin-deficient mice to chemically induced colitis was investigated in the DSS IBD model.
Results: A SNP in the 3'UTR of *MEP1A* was strongly associated with ulcerative colitis ($p = 2*10^{-7}$ and to a lesser extent with Crohn's disease ($p = 0.003$). Meprin-deficient animals displayed an increased susceptibility to intestinal inflammation in the DSS model.
Conclusion: We provide evidence for a protective role of meprins in IBD and speculate that the protease might also protect from other immune diseases.

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P 15

Transcriptomes distinguish active Rheumatoid arthritis from acute infection

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The etio-pathogenic influence by environmental and genetic factors on Rheumatoid Arthritis remains unclear. Infectious triggers have been postulated repeatedly, but could not be proven. A type 1 interferon (IFN) signature, which may be indicative for viral infections, was discussed for subgroups of RA patients.
In order to address the question of interaction between RA and infections, we compared peripheral blood gene expression profiles of RA with those of viral/bacterial infections and of patients treated with recombinant IFNβ. There was no viral or revealing type 1 IFN signature in RA detectable. RA profiles showed a mixed pattern of monocyte, T-cell and B-cell related genes and presented as a separate branch within the bacterial cluster.
In conclusion, RA profiles differ from classical infectious disease signatures and are closer to bacterial than viral/IFN patterns. Diagnosis of RA should be challenged if IFN patterns are observed.

P 16

Pro-inflammatory potential of human peripheral blood γδ T cells is reduced by pregnancy factors

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Introduction: During pregnancy, gammadelta T cells (γδ T cells) expand at the feto-maternal interface where they induce a tolerogenic milieu. Patients with rheumatoid arthritis (RA) experience a spontaneous improvement of their disease during pregnancy and an aggravation in the post-partum period. To figure out the role of γδ T cells in pregnancy induced remission of RA patients, numerical and functional changes of γδ T cells in the context of different pregnancy factors are analyzed.
Methods: The frequency and the intracellular cytokine profile of freshly isolated γδ T cells were analyzed by flow cytometry. The cytotoxic function was measured by chromium release assay. Phenotypic and functional changes of γδ T cells were investigated upon stimulation with pregnancy serum and invasive cytotrophoblast supernatant. Dells of patients were compared with cells of healthy controls.
Results: Ex vivo Vγ9 Vδ2 T cells (Vδ2) of patients and healthy controls showed a reduced proportion of Interferon gamma (IFNγ) positive Vδ2 T cells in the third trimester versus 8 weeks post-partum. Upon stimulation with isopentenyl-pyrophosphate, γδ T cells isolated during pregnancy secreted less IFNγ compared to those isolated in the post-partum period. Moreover, pregnancy serum reduced the expression of activating NKG2D receptor and increased the expression of the inhibitory NKG2A receptor on Vδ2 T cells. Regarding cytotoxicity, 3rd trimester serum could reduce the cytotoxic function of γδ T cells.
Conclusions: Pregnancy factors are able to reduce the pro-inflammatory potential of γδ T cells and might thereby be associated with pregnancy related disease remission of RA.

P 17

Flow cytometric detection of low level cryoglobulins

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Background: Cryoglobulins (Cg) are associated with several immunological phenomena, e.g. vasculitis. Detection of Cg,however, is difficult. It is performed by visual detection of precipitating molecules in cooled sera. Only if these precipitating molecules re-dissolve after re-warming to 37 °C the test is positive for Cg. This method has a big individual bias and low detection levels. As many vasculitic phenomena remain negative for auto-antibodies and detection levels are too high we hypothesise that Cg-associated autoimmune phenomena are not detected at the level of their occurrence. Consequently, a better method for detection of Cg is needed.
Objectives: In the presented study we analyzed whether and how sensitive flowcytometry may detect Cg.
Methods: Lipid micelles were diluted at different concentrations in PBS. Detection limits were assessed visually and by flowcytometry. Second, sera from 6 Cg positive patients were tested by flow cytometry for small precipitating molecules after keeping sera for 3 days at 4 °C. Third, sera of 92 consecutive patients suspected of being Cg positive during routine diagnostics were assessed by flow cytometry and the standard visual method for small precipitating molecules after 3 days at 4 °C.
Results: Artificial precipitates were produced by diluting lipid micelles in PBS. Dilutions of micelles ranged from 5.8 x 10^{-8}/µl to 1.5 x 10^{-4}/µl. The minimal dilution of lipid micelles was detected 3.1 x 10^{-6}/µl optically and 5.8 x 10^{-8}/µl by flow cytometry. In all sera of 6 patients known to be positive for Cg small precipitating molecules were detected by flow cytometry after keeping sera at 4 °C for 3 days. The precipitating structures re-dissolved after re-warming to 37 °C. Precipitates of two patients were labeled with anti-isotype antibodies to confirm that the molecules detected are immunoglobulins. Precipitates of the first patient were detected positive for IgM and the precipitates of the other patient were IgG and IgM positive. In parallel no precipitating molecules were found in cooled sera of 50 healthy control donors. Of the 92 patients analysed for Cg in parallel to routine diagnostics 15 samples displayed precipitates that re-dissolved after re-warming. Only 1 patient of these 15 patients was detected positive for Cg by the conventional optical method. All of these patients suffered from Cg associated diseases diseases: 1x Wegener's granulomatosis, 2x Raynaud`phenomenon, 1x papilitis, 1x systemic lupus erythematodes, 1x antiphospholipid syndrome, 1x arthritis, 2x Sjoegren's syndrome, 1x cerebral vasculitis, 1x neoplasm, 3x chronic infections, and 1x polyneuropathy.
Conclusion: Flow cytometry was 362.5x more sensitive than the visual method in detecting small precipitates. It positively confirmed the presence of Cg in 6 patients and did not detect any Cg in healthy control donors. When the method was tested in a cohort of 92 patients suspected of having Cg associated symptoms, the flow cytometry detected 15x more often Cg. We think that this new method may improve diagnostics in patients with Cg associated phenomena. The results need to be confirmed in a bigger cohort.

P 18

Subclinical peripheral synovitis detected by echography in patients with axial Spondyloarthritis

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Background: patients with axial Spondyloarthritis (SD), even without any obvious peripheral joint synovitis, often complain of pain in the joints of arms and legs. Several musculoskeletal ultrasound (US) scores developed in rheumatoid arthritis have demonstrated their capacity of discovering subclinical synovitis which were relevant in term of disease activity and for treatment strategies. None of these scores however have been, to our knowledge, applied to spondyloarthritis patients.
Objectives: to determine if subclinical synovitis can be detected by echography in patients with SD and if these synovitis are relevant compared with RA and controls.
Methods: the Swiss Sonography in Arthritis and Rheumatism (SONAR) group has developed a reproducible semi-quantitative score for RA using OMERACT criteria for synovitis. The score includes B mode and Doppler mode. 35 out of 40 enrolled SD patients fulfilling the 2010 diagnostic criteria were evaluated according to the SONAR score. In none of them, peripheral synovitis was clearly demonstrated, although some have or reported recurrent peripheral joint pain. The score was also applied to 20 matched controls and 40 consecutive RA patients (RA). 19 of them were in remission (DAS: <2.6), 10 with a low activity (DAS: 2.6 <>3.4) and 11 with a moderate activity disease (DAS: 3.5 <>5.1). All the patients and the controls had a complete clinical, biological and auto-evaluation assessment (joint pain and swelling counts, DAS28, HAQ, BASDAI BASMI, BASFI, m-SACRAH). The ultra-sonographer was blind to all these parameters.
Results: a B mode score >8, was set up as a cut-off value for significant synovitis as only 10% of the controls (median: 5.9 ± 2.2) and 90% of active RA had a higher score .34% of SD had significant synovitis which remained mostly mild. Their median B mode score (12 ± 1.6) was higher but not significantly than in remission Ra (7.1 ± 3.4). Only active RA (DAS >3.5) had significant higher echographic scores: B mode (17 ± 11), Doppler score and cumulative score for synovitis grade >1. BASDAI, BASFI, BASMI, m-SACRAH, DAS28 and CRP were not significantly different in SD patients with or without synovitis.
Conclusions: some patients with axial Spondyloarthritis have subclinical but significant peripheral synovitis detected by echography. The impact of these synovitis remains uncertain as their presence does not seem to significantly influence disease activity and function evaluation tools.

P 19

Destructive Arthropathy in a 75-year old Woman

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A 75-year-old Swiss woman developed pain and swelling in the left ankle after a long hike in fall 2009. In an orthopedic consultation in 01/2010, deformed feet and a mid-foot collapse on both sides was described. Adjusted orthopedic shoes led to a marked improvement. After a distortion in 03/2010, she developed important swelling in the left ankle with significantly elevated inflammatory parameters.
MR imaging excluded osteomyelitis and conventional radiographs were consistent with a calciumpyrophosphat arthropathy, an aspiration of the left ankle was not successful. Treatment with corticosteroids and – because of the destructive course-, methotrexate started as well as prophylaxis with colchicine. In 06/2010 the left upper ankle joint was infiltrated with lidocaine/triamcinolone and the subtalar joint was infiltrated with triamcinolone, and an orthopedic shoe was adapted. These measures showed improvement of symptoms and inflammation in the blood for 4 months. In 12/2010, the same symptoms reappeared. Aspiration of synovial fluid from the left ankle yielded 103000 cells (97% polynuclear, cultures negative). Due to the suspicion of septic arthritis on one hand and crystal induced arthritis on the other hand, therapy with ceftriaxon and prednisolon was started. A second MR imaging revealed an advanced destructive arthropathy, suspected osteomyelitis (tarsal bones, talus, calcaneus, ankle, lower ankle, distal tibia) and small abscesses on the dorsum of the foot. There were no signs of diabetes mellitus. The bone biopsy showed a moderate granulocytic infiltration, PAS and Gram negative, with negative staining (Congo) and missing crystals. Culture and PCR for tuberculosis were also negative. A Pirogoff amputation was performed, in intraoperative bone biopsy no specific pathogen was found.
Discussion: Finally, the cause of this destructive foot arthritis remains unknown. The clinical and radiological presentation looks like Charcot arthropathy on one hand. On the other hand destructive calciumpyrophosphat arthropathy is suspected, due to conventional radiography as well as important inflammatory changes in synovial fluid and blood and good response to anti-inflammatory therapy. We started a new therapy with etanercept and colchicine.

P 20

Leg pain as primary manifestation of granulomatosis with polyangiitis (Morbus Wegener)

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Case report: A 54-years old male presented with a one-year duration of swelling and localized pain of his legs in 2006 for suspicion of nephrotic syndrome. Pain had in part responded to a self-medication with NSAID. Nephrologic work-up was negative. The patient was transferred to Rheumatology and started on sulfasalazine for his non-specified leg pain. In 2008 he suffered fulminant pneumonia and acute renal insufficiency accompanied by bloody nasal discharge. Wegener's granulomatosis was diagnosed, cyclophosphamide was given with two i.v.-boli of 1400 mg each and in progressive disease followed by rituximab with 4 doses of 500 mg each accompanied by tapering dosages of glucocorticoids. Due to partly remitting disease oral glucocorticoids were continued as baseline medication. Leg pain remained the main complaint. As the patient evaded medical follow-up he decided for glucocorticoids for pain control in dosages of 20–50 mg prednisone equivalent per day. In 2011 he changes medical service due to the leg pain and suspected concomitant cellulitis.

Immunological work-up reveals high c-ANCA levels with PR-3 positivity, renal insufficiency, low-grade proteinuria and clinically a localized painful swelling of his right tibia. MRI and bone scintigraphy show an inflammatory process. Tibial muscle and periostal biopsy demonstrate a necrotizing vasculitis as well as a periostitis with heterotopic ossifications. Kidney biopsy confirms active pauci-immune glomerulonephritis. Five years after the initial manifestation the diagnosis is confirmed by histology and the patient is free of pain after resection of his inflammatory leg ossifications. Re-Induction therapy is now being installed with rituximab and low-dose glucocorticoids followed by azathioprine as maintenance therapy. Features of long-standing glucocorticoid therapy remain present.
Conclusion: Necrotizing vasculitis in granulomatosis with polyangiitis can primarily present as localized limb muscle pain. Histologic evaluation even of atypic lesions appears reasonable for rapid confirmation of active disease and guidance of treatment. Unnecessary and potentially harmful medication can thus be avoided as well as mimickry of severe organ involvement.

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P 21

Spinal gout mimicking septic spondylodiscitis

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A 86-year-old patient in septic condition with a history of chronic back pain and suspicion of septic spondylodiscitis was referred to our hospital. From the patients history a moderate renal insufficiency and a gouty arthritis with formation of tophi was known. Laboratory examinations revealed a CRP of 340 mg/L, a creatinine of 160 umol/l, an anemia of 100 g/l and an increased uric acid of 513 umol/L. Trans-esophageal echocardiography showed no evidence for bacterial vegetations, blood cultures and eubacterial PCR were negative. X-rays showed an advanced degeneration of the spine. MR Imaging documented a spondylodiscitis of LWK1/2 with abscess formation in the psoas muscle indicative of a septic spondylodiscitis. CT guided puncture of the psoas abscess as well as additional surgical biopsy yielded no evidence of pus or bacterial or fungal material and respective cultures of tissue remained negative. However, the polarized light microscopy of the tissue sections showed needle-shaped uric acid crystals.
Discussion: Gouty tophus involving the spine and mimicking a psoas abscess is exceptionally rare. This differential diagnosis should be kept in mind when clinical evidence for tophaceous gout is given and puncture as well as biopsy does not show pus and / or an infectious agent. Suspicion for this diagnosis should arise when CT scans show a degenerative as well as a lytic process involving the upper and lower border of adjacent vertebral bodies. The MRI shows a hypointense tophus with inflammation of adjacent soft tissue. Therapy of spinal involvement of gout is not different from conventional gout therapy. In refractory situations or contraindications for glucocorticoids and NSAIDs, a therapy with IL-1RA should be considered.

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