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**Prediction of Progression of Interstitial Lung Disease in Patients with Systemic Sclerosis: The SPAR Model**

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**Background:** The natural disease course of interstitial lung disease associated with systemic sclerosis (SSc-ILD) is highly heterogeneous. Currently, no data are available to distinguish a progressive disease course from a stable course when mild interstitial lung disease (ILD) is diagnosed in patients with systemic sclerosis (SSc).

**Objectives:** This study was aimed to identify predictive clinical characteristics and establish a prediction model for the progression of mild ILD at 1-year follow-up in SSc patients.

**Methods:** Patients with SSc from two independent prospective cohorts were included in this observational study. All patients fulfilled the American College of Rheumatology/European League Against Rheumatism (ACR/EULAR) 2013 criteria, had mild ILD at baseline diagnosed by HRCT (ILD extent <20% lung involvement on HRCT), available baseline and follow-up pulmonary function tests, at least one annual follow-up visit, and no concomitant pulmonary hypertension or airflow obstruction. ILD progression was defined as a relative decrease in FVC ≥15%, or FVC ≥10% combined with DLCO ≥15% at 1-year follow-up. Candidate predictors for multivariate logistic regression were selected by expert opinion based on previous studies and clinical significance. Multiple imputation was used to address missing data. A prediction model for ILD progression was established in the derivation cohort and validated in the multinational validation cohort.

**Results:** A total of 25/98 and 25/117 SSc patients showed ILD progression in the derivation and validation cohort, respectively. Lower SpO₂ after six-minute walk test (6MWT) and arthritis ever were identified as independent predictors for ILD progression in the derivation, validation, and pooled cohorts (Figure). The optimal cut-off value for SpO₂ after 6MWT and arthritis ever were identified as independent predictors for ILD progression in the derivation, validation, and pooled cohorts (Figure).

**Conclusions:** The evidence-based SPAR prediction model developed in our study might be helpful for the risk stratification of patients with mild SSC-ILD in clinical practice and cohort enrichment for future clinical trial design.

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**Minimal spinal radiographic progression over 2 years in longstanding nonradiographic axial spondyloarthritis (nr-axSpA) in comparison to ankylosing spondylitis (AS):**

**Objective:** To compare spinal radiographic progression in patients with nonradiographic axial spondyloarthritis (nr-axSpA) versus ankylosing spondylitis (AS).

**Methods:** Patients fulfilling the Assessment in SpondyloArthritis international Society (ASAS) classification criteria for nr-axSpA in the Swiss Clinical Quality Management Cohort (SCQM) with available lateral radiographs of the cervical and lumbar spine at 2 years (±1y) intervals were included in the study. Radiographs were scored by 2 readers according to the modified Stoke Ankylosing Spondylitis Spine Score (mSASSS). Progression was defined as worsening of the mean mSASSS by ≥2 units over 2 years. The relationship between type of axSpA (nr-axSpA vs. AS) and radiographic progression over time was investigated using binomial generalized estimating equations (GEE) fitted using multiple imputation of missing covariate data. The analyses were adjusted for factors known to affect radiographic progression (baseline radiographic damage, sex, length of radiographic interval, previous treatment with TNFi, eosinophils and the Ankylosing Spondylitis Disease Activity Score (ASDAS)).

**Results:** A total of 88 nr-axSpA patients and 418 AS patients with 128 and 597 radiographic intervals, respectively, fulfilled the inclusion criteria. Mean (SD) disease duration at first radiograph was 10.0 (9.9) years in nr-axSpA and 14.0 (9.8) years in AS (p < 0.001). Both groups presented with similar disease activity levels at baseline: BASDAI 4.6 (2.0) vs. 4.2 (2.3), p = 0.26 and ASDAS 2.8 (0.9) vs. 2.8 (1.1) for nr-axSpA vs. AS, respectively. Mean mSASSS at baseline was 0.9 (1.5) in nr-axSpA and 6.8 (12.7) in AS, p < 0.001. While 35% of AS patients already had syndesmophytes at baseline, this was the case in only 9% of nr-axSpA patients. The proportion of patients on TNFi was 19% vs. 36% for nr-axSpA and AS, respectively. Mean (SD) spinal radiographic progression was 0.16 (0.62) units in nr-axSpA and 0.92 (2.78) units in AS (p = 0.01). In the adjusted longitudinal model a trend for lower spinal radiographic progression was found in nr-axSpA vs. AS (odds ratio 0.40 (95% confidence interval 0.14; 1.09), p = 0.07).

**Conclusion:** Patients with longstanding nr-axSpA (mean 10 years of disease duration) presented with minimal risk of radiographic progression and, accordingly, had only minimal spinal progression over 2 years. After adjustment for confounding factors, nr-axSpA patients showed a trend towards a smaller progression in comparison to AS.
Smoking Behaviour and the Severity and Progression of Organ Manifestations in Systemic Sclerosis: a Longitudinal European Scleroderma Trials and Research Group Study


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Background: SSC is a rare, multisystem autoimmune disorder. The pathogenesis is characterised by a microangiopathy to which hypoxia and oxidative stress may contribute. Tobacco inhalation induces free radicals and vasoconstriction, and promotes vascular damage. So far, data available with regards to a role of tobacco exposure with SSC severity and progression are scarce. We aimed to assess the associations of smoking with the speed of worsening of lung involvement, skin involvement, and digital ulcers (DU) in the EUSTAR database.

Methods: Adult SSC patients with a follow-up visit 12–24 months after baseline and available data on their smoking habits were included. Associations of severity and progression of organ involvement with smoking history and the lung function index (FEV1/FVC ratio) were assessed using multivariable regression analyses adjusting for age, sex, autoantibody status, disease duration, SSC subset. Missing data were imputed using multiple imputation.

Results: Of the 3,319 patients included (mean age 57 years, SD 14; 85% female; 29% diffuse SSC), 66% of patients stated that they never smoked; 23% were ex-smokers and 11% were current smokers. The average ex-smoker had smoked 18 pack-years (SD 21) during a time of 19 years (SD 12) and quit smoking 15 years (SD 13) ago. The average current smoker smoked 27 pack-years (SD 30) during a time of 30 years (SD 13). Never-smokers had a higher baseline FEV1/FVC ratio than previous and current smokers (p < 0.001). On average, the FEV1/FVC ratio changed from 96.5 (SD 14) at baseline to 96.0 (SD 13) at follow up. In current smokers, the ratio decreased significantly faster during the observation period than in never smokers after adjustment (β = −4%, p < 0.001). This was not observed in ex-smokers (p = 0.7). The baseline mRSS and the mRSS decline were clinically comparable across smoking groups and were also not clinically significant associated with the CSI. Although heavy smoking (more than 25 pack years) increased the odds of DU by almost 50%, there was no robust adverse association of smoking with DU development.

Conclusions: The adverse effect of smoking on bronchial airways that is known in the general population is replicated in the SSC population. The lack of a robust, measurable adverse effect of smoking on the speed of worsening of cutaneous and pulmonary SSC manifestations argues against a major role of tobacco associated free radicals and vasoconstriction in the pathogenesis of SSC vasculopathy and fibrosis.

FREE COMMUNICATIONS SSR

SSRO 4

A standardized gnobiotic mouse model to evaluate host-microbe interactions in colitis


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The intestine harbors trillions of microbes that live in a mutualistic relationship with its host. These symbions have profound effects on the host by shaping the immune system and by providing essential metabolic compounds. Alterations in this sophisticated host-immune-microbiota crosstalk have been associated with the development of acute and chronic intestinal inflammatory disorders such as Cohn's disease and ulcerative colitis (inflammatory bowel diseases). Accordingly, differences in the microbial composition have been shown to critically impact on the immune system, thus providing a strong rationale for the standardization of the microbiota. Here we describe a novel gnobiotic mouse model to investigate the host microbial relationship during acute and chronic colitis in which germ-free (GF) mice are colonized with the recently described stably defined moderately diverse mouse microbiota 2 (sDMDDm2). The sDMDDm2 consists of 12 well-defined symbiotic bacterial strains, however, to successfully induce colitis it is necessary to include the pathobiont Helicobacter typhlonius (H. typh.) in the sDMDDm2 flora. In the adoptive CD4+ T cell transfer model of colitis, GF Rag1-/-mice colonized with sDMDDm2 + H. typh. develop colitis with a comparable pathogenesis, but slower kinetic than mice from our in-house SPF facility, i.e. both groups of recipient mice accumulate CD4 T cells, monocytes and neutrophils at intestinal sites and display a similar overall colon histopathology. Importantly, due to the reduced microbial complexity, we were able to follow the dynamics of the microbiota at a bacterial species level, which surprisingly showed that during acute colitis, H. typh. is outcompeted by the other members of the community but recovers during remission of the disease. The precise mechanisms how H. typh. boosts the inflammatory response in our gnobiotic mouse model still remains to be elucidated and is subject of current investigations. Nonetheless, the described model offers as yet unavailable possibilities to study in parallel the host immune response and its relationship with microbiota on a species level. Moreover, the model is universally applicable and is independent on the microbial status of the local animal facilities and thus antagonizes contradictory results in disease models.

FREE COMMUNICATIONS SSAI

SSAI 1

Autophagy in lymphatic endothelial cells dampens Rheumatoid arthritis

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Lymph node (LN) stromal cells (LNSCs) are essential to the structure and function of the LN, supporting hematopoietic cell migration, interactions, and hormone synthesis. Recently, LNSCs, in particular the lymphatic endothelial cells (LECs), have been shown to endogenously

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express antigens (Ags) otherwise restricted to a small number of peripheral tissues. Direct presentation of peripheral tissue Ags (PTA) by LECs to CD8 T cells results in their deletion. Studies have shown that LECs express significant basal MHCII levels in the steady state and further up-regulate MHCII upon inflammation. In addition, our recent unpublished data show that LECs are competent at autophagy and target autophagosomes to MHCII-loading peptide compartments. Autophagy is an endogenous process necessary for the turnover of organelles and intracellular proteins, therefore maintaining cellular homeostasis and directing cell fate. Whether this pathway can be used by LECs to load peptides onto MHCII molecules and shape peripheral CD4+ T cell responses in vivo remains unknown. Alterations of autophagy regulation contribute to the progression of various rheumatic diseases, including Rheumatoid arthritis (RA), a systemic autoimmune disease resulting in severe inflammation associated to bone and joint damage. Several studies have shown that autophagy is upregulated in RA synoviocytes and promote RA-associated synovitis. In this project, we evaluate the contribution of autophagy in the ability of LECs to present auto-Ags and impact auto-reactive CD4 T cells responses and/or regulatory T cell (Treg) homeostasis in RA pathogenesis. To assess the contribution of autophagy in MHCII-mediated Ag presentation by LECs, we genetically abrogated autophagy in LECs and analyzed the impact on T cell responses and disease development in collagen-induced arthritis mouse model. Our first results show that mice in which autophagy has been disrupted in LECs developed an exacerbated disease and exhibit an impaired Treg population. Moreover, similar disease exacerbation is observed in mice genetically deficient for MHCII expression in LECs. Therefore, autophagy in LECs could play an immunoregulatory role, via MHCII-mediated Ag presentation, during RA development. We are currently deciphering the molecular and cellular mechanisms implicated in RA attenuation by autophagy in LECs.

SSAO 3

Functional anti-TIGIT antibodies modulate T cell responses in vivo

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The selective engagement of inhibitory receptors plays an important role in maintaining immune homeostasis and their divergent expression gives rise to a broad range of pathologies such as autoimmunity, cancer and chronic infections. Blocking antibodies directed against inhibitory receptors such as PD-1 and LAG-3 showed great efficacy as anti-cancer drugs in the clinics because of their potential to restore T cell responses in vivo. TIGIT is a novel co-inhibitory receptor that has recently gained attention as a potential regulator of T cell exhaustion in the context of cancer as well as in ameliorating autoimmune disorders. In order to study the immune modulatory properties of TIGIT, we generated a panel of functional anti-TIGIT antibody clones using hybridoma cultures and tested them in both autoimmune and cancer models. We found that the administration of the agonistic anti-TIGIT antibody ameliorated autoimmune disease severity in EAE, whereas administration of the blocking anti-TIGIT antibody in combination with anti-PD-1 blockade showed a synergistic anti-tumor effect in models of colon carcinoma and glioblastoma. Collectively, our data demonstrates that TIGIT modulation can be used to effectively regulate T cell responses and disease outcome in vivo and provides further insight for the development of novel therapeutic approaches.

SSAO 4

Rgs1 critically regulates the generation and re-activation of intestinal tissue resident memory CD8 T cells

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Tissue resident memory T cells (TRM) are recently characterised subsets of memory cells that are preferentially localized in non-lymphoid barrier tissues such as the skin, lung and intestinal mucosa. In a previously infected host, they mediate an enhanced, rapid immune response at the site of pathogen re-entry. Currently, however, little is known about the requirements for the generation, maintenance and re-activation of TRM cells in situ. We observed that in resident intestinal T cell subpopulations (Regen G protein-coupled receptor (GPR 17), also known as G-Protein Signaling 1) is significantly increased in comparison to their circulating T cell counterparts. Since Rgs1 has been previously reported to modulate chemotaxis of lymphoid cells, we directly assessed whether enhanced Rgs1 activity in T cells is a prerequisite for the generation, long-term retention, and re-activation of non-recirculating TRM in the intestinal mucosa. By monitoring TRM cell generation upon oral Listeria monocytogenes infection, we currently define the functional relevance of increased Rgs1 levels for TRM cell formation, maintenance and re-activation in the intestinal mucosa. We found, that absence of Rgs1 significantly reduces the capacity of intestinal TRM cells to mount a secondary immune response upon reinfection with L. monocytogenes. We also observed significant differences between transcriptional profiles of Rgs1-deficient versus wild-type de novo differentiated intestinal TRM cells. Collectively, the ongoing studies are expected to yield mechanistic insight into TRM cell biology in general and may reveal the pathways that regulate their maintenance and re-activation, both during homeostatic, and inflammatory conditions, notably also during chronic remitting relapsing inflammatory disorders.

SSAO 5

Mitochondrial pyruvate carrier inhibition during CD8 T cell priming enhances central memory differentiation and anti-tumoral activity

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T cell fate is tightly linked with specific metabolic characteristics. Effector CD8 T cells use aerobic glycolysis in the fermentation of pyruvate to lactate, while long-lived memory CD8 T cells are characterized by mitochondrial metabolism, mainly through fatty acid oxidation. However, it remains unclear if pyruvate can be metabolized in the mitochondria during naïve T cell priming, and whether this contributes to effector versus memory precursor differentiation. We have found that inhibiting the mitochondrial pyruvate carrier with the small molecule UK5099 during T cell priming, unexpectedly led to an increase in mitochondrial oxygen consumption, driven by fatty acid oxidation. This metabolic adaptation was accompanied by an increased surface expression of the central memory marker CD62L, and adoptive transfer of UK5099-treated CD8 T cells into melanoma tumor-bearing mice, resulted into a more potent tumor control compared to adoptive transfer of DMSO-treated cells. A much higher proportion of adoptively transferred UK5099-treated CD8 T cells formed central memory cells. Furthermore, upon mitochondrial pyruvate carrier inhibition, T cells infiltrating the tumor were characterized by a reduced PD-1 expression and increased cytokine production. This metabolic adaptation was accompanied by an increased proliferation of CD8 T cells in vitro re-stimulation. Thus, this study shows that metabolic adaptations induced during early CD8 T cell priming can lead to long-lasting central memory T cell differentiation, resulting in an increased anti-tumor control.

SSAO 6

Enforced PGC-1α expression promotes CD8 T cell persistence and anti-tumor immunity

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CD8 T cells mount protective responses against viral/bacterial infections and cancers. Memory CD8 T cells can provide long-term protection against tumors, which depends on their enhanced proliferative capacity, long-term self-renewal and unique metabolic machinery to sustain cellular fitness. Memory CD8 T cells harbor higher mitochondrial respiration and rely on oxidative phosphorylation (OXPHOS) and fatty acid oxidation (FAO) to fulfill their metabolic demands. However, it remains unknown whether enforced mitochondrial biogenesis promotes CD8 T cell memory formation and persistence in vivo. Peroxisome proliferator-activated receptor γ coactivator 1-alpha (PGC-1α) is a master regulator of mitochondrial biogenesis and controls pathways known to be crucial in memory formation, we thus hypothesized that overexpression of PGC-1α in CD8 T cells might improve cell fitness and memory lineage
Correlation of in-vivo oral food challenge with in-vitro basophil activation test in hazelnut allergic patients  
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Introduction: The diagnosis of food allergy including hazelnut is based on the case history, skin prick test and/or hazelnut specific IgEs. Concerning severity, oral food challenge (OFC) is still the golden diagnostic standard. The risk of anaphylaxis is the drawback of this resource-intensive procedure. In this study, we investigate the correlation between OFC and the basophil activation test (BAT) as “a provocation in the test tube”. BAT has already shown its value in the diagnosis of peanut allergy and was able to predict the result of OFC in two thirds of the cases. In this proof-of-concept study we analyze if the BAT correlates to the OFC in hazelnut sensitized patients.

Method: We analyzed three defined groups: (A) positive case history of hazelnut allergy (n = 54), (B) positive case history of birch pollen allergy and clinically asymptomatic sensitization to hazelnut (n = 17), (C) non-allergic controls (n = 9). We performed skin prick tests with birch pollen and hazelnut extracts and prick-to-prick tests with native hazelnuts. Hazelnut allergic participants (A) underwent double-blind, placebo-controlled food challenge (DBPFC), Group B and C participants had an open challenge. BAT with hazelnut extract, recombinant Cor a 1 (Cor a 1) and recombinant Cor a 1 (Cor a 8) was performed in all participants.

Results: The percentage of CD63 and CD203c positive basophils in BAT upon stimulation with different concentrations of hazelnut extract and rCor a 1 correlated with the result of hazelnut challenges and showed significant differences between the three study groups. In addition, BAT positivity after stimulation with hazelnut extracts in group A increased with symptom severity in DBPFC not reaching statistical significance.

Conclusion: Our study groups significantly differ in the degree of BAT positivity correlating with OFC. For the discrimination of clinical severity by BAT alone, the number of patients with distinct severity groups was too low to reach statistical significance. Thus, BAT supplements the diagnostic armamentarium in the diagnosis of hazelnut allergy but needs further investigation to effectively replace OFC.

Correlation of in-vivo oral food challenge with in-vitro basophil activation test in hazelnut allergic patients

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Background: AIDs are rare but not negligible conditions in Switzerland. A national study through the JIRcohorte database is ongoing aiming to evaluate the number of pediatric and adult patients with AIDs in Switzerland, in order to study clinical presentation, treatments and long term complications. We report the results of the study until May 2018. AIDs included diagnosis of Systemic onset juvenile idiopathic arthritis (JSJIA), 16 with FMF, 12 with CAPS including 5 with Muckle-Wells syndrome (MWS) and 1 with chronic infantile neurological cutaneous and articular syndrome (CINCA), 6 with MKD and 3 patients with TRAPS. Three patients with TRAPS had IL-6 receptor antagonist (anti-IL-6R) were used for treatment in 64% of our patients. The prevalence in our pediatric population under 18 years old is 19.4 per 100,000 children. The total number of children with AID is estimated at 310 in Switzerland.

Conclusion: AIDs are rare but not negligible conditions in Switzerland. A national study through the JIRcohorte database is ongoing aiming to evaluate the number of pediatric and adult patients with AIDs in Switzerland, in order to study clinical presentation, treatments and long term complications.

Results: A total of 70 patients were enrolled, including 60% females. The median age of last visit was 11 years [TA1]. Patients were distributed as follows: 34 patients with SJIA, 16 with FMF, 12 with CAPS including 5 with Muckle-Wells syndrome (MWS) and 1 with chronic infantile neurological cutaneous and articular syndrome (CINCA), 6 with MKD and 3 patients with TRAPS. Three patients with TRAPS had IL-6 receptor antagonist (anti-IL-6R) were used for treatment in 64% of our patients. The prevalence in our pediatric population under 18 years old is 19.4 per 100,000 children. The total number of children with AID is estimated at 310 in Switzerland.

MTBVAC vaccination promotes immune recognition to multiple M.tb expressed antigens as compared to BCG

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In 2016, it was estimated that 10.4 million fell ill with tuberculosis (TB). The disease is now the ninth leading cause of death worldwide and the leading cause from a single infectious agent, ranking it above HIV/AIDS. The bacille Calmette-Guérin (BCG) vaccine, which is still widely used, has been shown to prevent severe forms of TB in children. However, there is currently no vaccine that is effective in preventing TB disease in adults, either before or after exposure to TB infection. Strategies for improving vaccination for TB include candidates to prevent the development of TB, and candidates to help improve the outcomes of treatment for TB disease. MTBVAC, a candidate vaccine, is a strain of M.tb, attenuated via deletions of the phoP and fabD26 genes. Primarily, it will be used as a BCG replacement vaccine in neonates and secondarily as a booster vaccine in adolescents and adults. We have previously shown that MTBVAC is a safe and immunogenic vaccine in a phase 1 clinical trial in Lausanne. As part of investigating the potential differential immune protection that may be imparted by MTBVAC over BCG, we compared the immune recognition of the M.tb phase specific as well as lipid antigens. PBMC from MTBVAC and BCG vaccinated volunteers at D0, D28 and D210 were stimulated with 18 protein and 5 lipid TB antigens. We observed no immune recognition of the immunodominant antigens ESAT6 and CFP10 post vaccination, which was expected as MTBVAC does not secrete these antigens and they are absent from BCG. However, there was increased immune recognition of both Ag85B and TB10.4 immunodominant antigen in the MTBVAC group as compared to BCG post vaccination. There was also increased recognition of the latency antigens Rv2626, Rv2628 and Rv1733 and the in vivo expressed antigen Rv3034 in MTBVAC but not BCG vaccinated volunteers at D28. Importantly, the antigen recognition signature of the MTBVAC vaccinated was more similar to that of the latent TB infected (LTBI) but disease protected group. M.tb also possesses a cellular envelope rich in complex lipids and carbohydrates that play key roles in its virulence and pathogenesis. Indeed, vaccination with MTBVAC, the causative but attenuated form of Mtb promoted increased liporabinomannan, lipomannan and total lipid- specific CD8+ T- and NK-cell responses. Thus far, we demonstrate that vaccination with MTBVAC promotes a more M.tb specific T-, B- and NK-cell immune response than BCG.

SSAIO 12

MTBVAC vaccination promotes immune recognition to multiple M.tb expressed antigens as compared to BCG

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SSAIO 13

Design and characterization of near-native Ebola GP vaccine candidates: implications for immunogenecity

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In 2016, it was estimated that 10.4 million fell ill with tuberculosis (TB). The disease is now the ninth leading cause of death worldwide and the leading cause from a single infectious agent, ranking it above HIV/AIDS. The bacille Calmette-Guérin (BCG) vaccine, which is still widely used, has been shown to prevent severe forms of TB in children. However, there is currently no vaccine that is effective in preventing TB disease in adults, either before or after exposure to TB infection. Strategies for improving vaccination for TB include candidates to prevent the development of TB, and candidates to help improve the outcomes of treatment for TB disease. MTBVAC, a candidate vaccine, is a strain of M.tb, attenuated via deletions of the phoP and fabD26 genes. Primarily, it will be used as a BCG replacement vaccine in neonates and secondarily as a booster vaccine in adolescents and adults. We have previously shown that MTBVAC is a safe and immunogenic vaccine in a phase 1 clinical trial in Lausanne. As part of investigating the potential differential immune protection that may be imparted by MTBVAC over BCG, we compared the immune recognition of the M.tb phase specific as well as lipid antigens. PBMC from MTBVAC and BCG vaccinated volunteers at D0, D28 and D210 were stimulated with 18 protein and 5 lipid TB antigens. We observed no immune recognition of the immunodominant antigens ESAT6 and CFP10 post vaccination, which was expected as MTBVAC does not secrete these antigens and they are absent from BCG. However, there was increased immune recognition of both Ag85B and TB10.4 immunodominant antigen in the MTBVAC group as compared to BCG post vaccination. There was also increased recognition of the latency antigens Rv2626, Rv2628 and Rv1733 and the in vivo expressed antigen Rv3034 in MTBVAC but not BCG vaccinated volunteers at D28. Importantly, the antigen recognition signature of the MTBVAC vaccinated was more similar to that of the latent TB infected (LTBI) but disease protected group. M.tb also possesses a cellular envelope rich in complex lipids and carbohydrates that play key roles in its virulence and pathogenesis. Indeed, vaccination with MTBVAC, the causative but attenuated form of Mtb promoted increased liporabinomannan, lipomannan and total lipid- specific CD8+ T- and NK-cell responses. Thus far, we demonstrate that vaccination with MTBVAC promotes a more M.tb specific T-, B- and NK-cell immune response than BCG.
Background: Despite many vaccine candidates at various development stages, no vaccine has yet been approved for human use against Ebola virus (EBOV) infection. Humoral responses of EBOV survivors mainly target the surface glycoprotein GP, and anti-GP neutralizing antibodies have been associated with protection against EBOV infection. To be elicited in an appropriate manner, neutralizing antibodies require a suitable conformation of the antigen, which remains difficult to be controlled with current viral vector-based approaches.

Objective: We propose a vaccination strategy based on a near-native recombinant GP protein as a promising candidate to elicit epitope-specific neutralizing antibodies and protect against EBOV infection.

Methods: We engineered and expressed several variants of soluble GP proteins in CHO cells, including: a wild type GP; a mucin-like domain-deleted GPΔmuc; two GPΔmuc variants added with trimerization motifs in the C-terminus in order to favor their native trimeric conformation. The designed immunogens have been extensively characterized by means of size exclusion chromatography, circular dichroism and ELISA to assess binding to mAbs. The effect of the GP variants in inhibiting the neutralizing activity of mAbs in an infection assay was assessed on a murine leukemia virus-derived retroviral pseudotype platform. Moreover, we explored the GP variants to characterize the immune response elicited in volunteers of the ChAd3-EBOV trial.

Results: Near-native structure was retained upon removal of the mucin-like domain, which also allowed unmasking of critical neutralizing epitopes. Inclusion of the trimerization motifs resulted in proteins showing the highest breadth of reactivity with several conformational mAbs, among which KZ52 and a panel of murine neutralizing antibodies recognizing BSF and in neutralization of pseudotype infection assay. We also showed that the ChAd3 vaccine raised a volunteer-specific antibody response directed against a prevalence of linear rather than conformational epitopes, the former leading to a less favourable outcome in neutralization assays.

Conclusion: We have developed trimeric EBOV GP’s showing superior antigenic profiles than those of the monoclonal wild type protein, and we have supported the importance of suitable antigen conformation for induction of neutralizing antibodies. These GP candidates are currently being tested in pre-clinical animal models for immunogenicity and protection.

Role for gut immune response during neuroinflammation: fact or fiction?

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Background: Multiple sclerosis (MS) and its animal model, the experimental autoimmune encephalomyelitis (EAE) are characterized by demyelination and inflammation of the central nervous system. The development of this disease is under the control of both genetic and environmental factors. The relationship between intestinal immune responses and neuroinflammation remains unclear.

Aim: To investigate the role of the gut immune responses during EAE and assess their contribution during neuroinflammation.

Methods: Active and adoptive transfer model of murine EAE were used. Histological evaluations were performed to assess intestinal morphology and inflammatory infiltrates. Immune cells isolated from the intestinal lamina propria were analyzed by flow cytometry, and specific myelin reactive CD4+ T cells in the intestinal compartment were further evaluated ex vivo. Gene expression profiles of inflammatory markers and antimicrobial peptides were performed by RT-qPCR. Intestinal microbes changes were evaluated by metatranscriptics based on 16S rRNA marker gene.

Results: We observed altered intestinal immune responses coupled with increased expression of inflammatory markers in the gut during EAE and importantly, even before neurological symptoms. At the peak of EAE disease, morphological changes were observed in the intestinal tract. Simultaneously, a significant accumulation of pro-inflammatory CD4+ T cells was detected within the intestinal lamina propria. Interestingly, blocking the migration of lymphocytes in the intestine was associated with a delayed disease progression in the adoptive transfer model but not in the active model. Finally, EAE was associated with changes in the relative abundance of specific intestinal bacterial taxa.

Conclusion: Altered gut associated immune responses with an accumulation of pro-inflammatory cells in the lamina propria were observed in two different EAE models together with a dysbiosis.
Blocking the migration of pro-inflammatory CD4+ T cells in the intestinal compartment alters the EAE disease course pointing towards a contribution of the gut-brain axis in EAE development. Although the link between the gut immunity and MS has yet to be clarified, a better understanding of how immune cells are generated and regulated in the intestine during EAE could support innovative approaches to dampen neuroinflammation by targeting the gut-brain axis.

S0SAI 17

Premises, promises, and challenges of analyzing longitudinal flow cytometry data: Application to temporal immune response induced by the yellow fever vaccine YF-17D

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YF-17D is a live attenuated virus that mediates lifelong protection. Besides antibodies, it induces a highly robust CD8+ T cell response. Improved understanding of the highly coordinated sequence of immunological events underlying the remarkable immunogenecity of the YF vaccine has however only recently paved the way to optimal optimization of vaccines and other immunotherapies. To this end, we have recently embarked on a multi-omics approach to characterize the longitudinal human immune response to priming vs. boosting with the YF vaccine YF-17D. Here, we present the results of this longitudinal flow cytometry approach, in which circulating immune cells were profiled up to six months post vaccination using multiplex flow cytometry. Although time course studies hold great potential in deciphering the temporal dynamics of continuous immunological processes, an adequate and reliable measurement of the resulting time-series data remains challenging in part due to small sample sizes, imprecisely spaced time points, noisy measurements, and multi-dimensionality of immunological data. In addition, the temporal order and dependence of repeated measures front-end individual immune compartment correlation structure in the data, which if ignored can lead to loss of information and reduced statistical power. In the first part, we describe unique characteristics of our flow cytometry data and highlight advantages as well as challenges associated with the longitudinal nature of the data. In the second part and in an attempt to identify immunological features with distinct temporal patterns in priming vs. boosting vaccination, we take the audience on an adventurous yet informative journey through data quality control and preprocessing, visualization, and model development. More specifically, we aim to provide immunologists with a non-technical overview of both classical and modern statistical approaches to analyzing longitudinal biological data. In doing so, we highlight various roadblocks that we faced in analyzing our data set, and share the remedies that we found useful in overcoming those barriers. In the third and final part, we delve more into understanding the interactions of immunological features over time using a network analysis approach, and sketch a natural and fruitful approach to analyze and interpret longitudinal flow cytometry data in the context of human immune response induced by vaccination against yellow fever.

S0SAI 18

TLR2 signaling in non-hematopoietic skin cells induces neutrophil recruitment and lesion resolution in Leishmania major infection

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Leishmania major (L. major) is a protozoan parasite that is transmitted by sand flies bites and is highly virulent. Understanding the modes and extent of infectivity of the pathogen has led to unique insights on the immune system in the context of human immune response induced by vaccination against yellow fever. In consequence, the roles of TLR2 signaling, which mainly occurs in non-hematopoietic cells, is critical in the recruitment of the first wave of neutrophils that allows transient parasite survival, delaying further control of infection.

S0SAI 19

Premises, promises, and challenges of analyzing longitudinal flow cytometry data: Application to temporal immune response induced by the yellow fever vaccine YF-17D

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S0SAI 20

The thioredoxin-1 system is essential for fueling DNA synthesis during T-cell but not B-cell metabolic reprogramming and proliferation

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The thioredoxin-1 (Trx1) system is a key player of the cellular redox balance and a sensor of energy and glucose metabolism. Here we report critical c-Myc-dependent activation of the Trx1 system during Th1 response. The crucial role of Trx7-signaling in neutrophils was further demonstrated using neutrophin C57BL/6 Genista mice. Neutropenic mice co-injected with C57BL/6 neutrophils at the time of infection were able to heal their lesions, whereas development of a Th1 response in neutrophils failed. Conversely, neutrophin mice infected with Trx7/-/- neutrophils developed unhealing lesion and showed only partial parasite burden. In contrast, neutrophin mice infected with Trx7/-/- neutrophils showed impaired effector functions including decreased release of reactive oxygen species and neutrophil extracellular trap formation. In contrast to C57BL/6 mice, that were able to heal their lesion, Trx7/-/- mice developed a chronic unhealing lesion with partial control of parasite burden. In this system we investigated the importance of endosomal TLR7 signaling in neutrophils early after infection and its impact on disease outcome. Twenty-four hours after infection Trx7/-/- mice infected simultaneously with L. major harbored a higher frequency of infected neutrophils containing a greater number of parasites per cell when compared to neutrophils of C57BL/6 mice. Furthermore, in response to L. major, Trx7/-/- neutrophils showed impaired effector functions including decreased release of reactive oxygen species and neutrophil extracellular trap formation. In contrast to C57BL/6 mice, that were able to heal their lesion, Trx7/-/- mice developed a chronic unhealing lesion with partial control of parasite burden. In this system the role of endogenous TLR7 signaling in neutrophils is essential for control cutaneous leishmaniasis.

S0SAI 21

Premises, promises, and challenges of analyzing longitudinal flow cytometry data: Application to temporal immune response induced by the yellow fever vaccine YF-17D

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SSRP 1

Chronic compartment syndrome in localised scleroderma
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Introduction: Pan-sclerotic morphea is a rare form of localized scleroderma. Cutaneous lesions touch symmetrically the trunk and limbs and can extend to widespread skin sclerosis, but, without vascular or visceral involvement. Circumferential limb lesions may induce a compartment syndrome and trophic changes due to reduced blood-supply. Chronic compartment syndrome is a seldom condition found mostly in athletes, occurring because of repetitive loading or overloading of extremities in the extremities. Very few cases of scleroderma-patients with this pathology are described in the literature.

Case presentation: A 36 years old patient presents progredient myalgia and moderate weakness in the legs after a few minutes’ walk, without symptoms at rest. She had a history of juvenile pan-sclerotic morphea since the age of 10, with multiple topical treatments without effect. She presented sclerotic and partially atrophic skin-involvement of the trunk, arms, forearms and upper legs and had secondary flexion-contracts of elbows and knees, without distal skin-involvement, nor Raynaud-phenomenon. Normal CRP, ESR, creat.-kinase, ANA 1:80. Ab against Scx, centromere, RNA-polymerase III, THT, fibrillarin, PrSc, Ku negative. Normal video-capillaroscopy. Normal echocardiography and heart-MRI. Pulmonary function tests: mild restriction due to chest-wall-sclerosis. Normal MRI of the lumbar and dorsal spine and angiologic evaluation. Compartment pressure in the right rectus femoris muscle was 55 mm Hg at rest (normal ≤15), 60 mm Hg after a 12 minutes’ walk, sinking to 48 at rest in less than 5 minutes, in a physiological pattern. Chronic compartment syndrome due to skin sclerosis of the upper-legs was diagnosed. Conservative approach with analgesics and lymphatic drainage was chosen. Patient reported an improvement when cycling and to a lesser extent when walking. Adding immunosuppressive medication like methotrexate or mycophenolate mofetil might help diminish the skin sclerosis and indirectly the pressure in the affected compartment.

Conclusion: This case report illustrates the fact that pan-sclerotic morphea can induce a symptomatic chronic compartment syndrome. Treatment is not well codified. Lymphatic drainage should be undertaken and, if unsuccessful, fasciotomy should be discussed. Immunosuppressive agents like glucocorticoids, methotrexate or mycophenolate mofetil might help diminish the skin sclerosis and indirectly the pressure in the affected compartment.

SSRP 2

Racial differences in SSc disease presentation: a European scleroderma trials and research group (EUSTAR) study
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Background: Genetic and environmental factors play a significant role in SSc. African Americans are known for a higher SSc incidence, an earlier age of onset, and a greater frequency of ILD and PH than white patients. Data on black patients mostly stem from African Americans and studies on SSc in Asians are mostly from outside Asia and lack direct comparison with other racial groups. We aimed to further evaluate differences of SSc presentation between races cross-sectionally.

Methods: Characteristics of self-reported white, Asian and black SSc patients from the EUSTAR cohort were compared across racial groups; survival/logistic regression analyses were used to adjust for potential confounders.

Results: 9161 white, 341 Asian (208 from within, 133 from outside Asia) and 198 black patients (82 from within, 116 from outside Africa) were included. Asian and black patients were on average 10 years younger than white patients (p <0.001). Black patients developed the first non-Raeynaud’s phenomenon feature of SSc faster than Asian and white patients (all p <0.001) also after adjustment (HR[blacks] 1.4, p <0.001; HR[Asians] 1.1, p = 0.06 vs whites). ACA predominated in white patients (whites 42%, Asians 16%, blacks 10%; p <0.001) and Scl-70 in Asian patients (whites 35%, Asians 47%, blacks 34%; p <0.001). The prevalence of diffuse skin involvement was similar in Asian (28%) and white patients (26%), but more common in black patients univariably (56%; p <0.001); however in multivariable analysis Asians patients were less likely to have diffuse SSc than white patients (OR 0.7, p = 0.009) while black patients were more likely (OR 2.7, p <0.001). The prevalence of PH (defined as PAPsys ≥40 mm Hg by echocardiography) was lower in white patients (whites 12%, Asians 18%, blacks 17%; p = 0.004; OR[Asians] 2.7, p <0.001, OR[blacks] 1.2, p = 0.005 vs whites). Asian had a higher prevalence of an impaired DLCO (i.e. ≤80% of predicted; 84%) than black (74%) or white patients (70%; p <0.001) also in multivariable analysis (OR[Asians] 2.4, p <0.001, OR[blacks] 1.2, p = 0.24 vs whites). Both, Asians (44%) and black patients (50%), had a higher prevalence of a reduced FVC (i.e. ≤80% of predicted) compared to white patients (23%, p <0.001) univariably and multivariably (OR[Asians] 2.5, p <0.001, OR[blacks] 2.4, p <0.001 vs whites).

Conclusions: Asian SSc patients had high prevalences of Scl-70, PH and of a reduced DLCO and FVC. Black SSc patients in contrast had a fast disease onset and a high prevalence of diffuse skin involvement.

SSRP 3

Mitochondrial DNA mutations and respiratory chain dysfunction in idiopathic and connective tissue disease-related lung fibrosis
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Background: Recent data have implemented reactive oxygen species (ROS) in the aetiology of interstitial lung disease (ILD) and sarcoidosis sclerosis. We aimed to investigate the role of large-scale somatically acquired mutations in mitochondrial DNA (mtDNA) and consecutive respiratory chain dysfunction as a trigger of ROS formation and lung fibrosis.

Methods: Mitochondrial function and mitochondrial DNA (mtDNA) were analysed in lung biopsies from 30 patients with idiopathic or
connective tissue disease (CTD)-related ILD and 13 controls. Fifteen ILD patients had a CTD and 14 patients had idiopathic ILD; in one ILD patient this information was unavailable. From 17 patients paired biopsies from both upper and lower lobes were available. Control samples were taken from lung cancer resections in which there was no histological evidence for ILD.

Results: Malondialdehyde (MDA), a marker of ROS formation, was elevated in ILD biopsies (p = 0.044). The activity of the mitochondrial respiratory chain (cytochrome c-oxidase/ succinate dehydrogenase [COX/SDH]-activity ratio) was depressed in ILD (median 0.10, IQR 0.04–0.13) compared with controls (0.12, IQR 0.11–0.18; p < 0.001) as was the expression of the mtDNA encoded COX subunit 2 protein normalized for the nucleus-encoded COX subunit 4 (COX2/COX4-ratio; ILD-median 0.5–0.5; controls 2.2, IQR 2.1–2.2; p < 0.001). Wild-type mtDNA copies were slightly elevated in ILD (ILD-median 419, IQR 323-527; control 315, IQR 267-471; p = 0.088). The common mtDNA deletion was present at low levels in controls (median percentage of mtDNA deletions 0%, IQR 0–3%) and at high levels in ILD (17%, IQR 0–32%; p < 0.001). Among the 17 ILD patients of whom we had simultaneous biopsies from upper and lower lobes, the median MDA content and the mtDNA deletions were 30% and 53% higher in the lower lobes than in the upper lobes (both p < 0.001). The median COX2/COX4-ratios and the median COX/SDH-activity ratios were however, 41% and 35% lower in the lower lobes compared to upper lobe biopsies (both p < 0.001). There was no association of mitochondrial-patient characteristics with the differences between CTD and idiopathic ILD. Age was associated with mtDNA deletions (p = 0.055) and with low COX2/COX4-ratios (p = 0.022).

Conclusions: Our data support the role of mtDNA-mutations and respiratory chain dysfunction as a trigger and perpetuator of ROS formation in both, idiopathic interstitial pneumonitis and ILD of patients with CTD.

Progressive Skin Fibrosis is Associated with Lung Function Decline and Poorer Survival in Patients with Diffuse Cutaneous Systemic Sclerosis: a European Scleroderma Trials and Research (EUSTAR) Analysis

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Background: Short disease duration and low baseline modified Rodnan skin score (mRSS) have been identified as independent predictors of progressive skin fibrosis in patients with diffuse cutaneous systemic sclerosis (dcSSc), using the EUSTAR database. However, whether worsening skin fibrosis is an appropriate surrogate marker for nosent or deterioration of visceral organ disease and overall survival in dcSSc has been questioned.

Objectives: To determine whether progressive skin fibrosis is associated with visceral organ progression and mortality in dcSSc over follow-up.

Methods: We performed a survival analysis of the EUSTAR database including patients with dcSSc, fulfilling the ACR criteria, with baseline mRSS ≥7 in 2009 or later, valid mRSS at 12 ± 3 months after baseline, and ≥1 available annual follow-up visit. Progressive skin fibrosis was defined as an increase in mRSS ≥5 units and ≥25% from baseline to 12 ± 3 months later. Disease outcome was defined as occurrence of one of the following new events during follow-up based on expert group consensus: relative decrease in FVC ≥10%; LVEF <45% or relative decrease in LVEF >10% for patients with baseline LVEF <45%; pulmonary hypertension globally judged on echocardiography by the treating physician; renal crisis; all-cause death. The association between skin progression and disease outcomes over follow-up was evaluated by Kaplan-Meier analysis, log-rank test and multivariate Cox regression. Multiple imputation was used to handle missing values.

Results: Among 215 patients (78 (76.%) had progressive skin fibrosis within 1 year (median follow-up 3.4 years). Survival analyses indicated that skin progressors had a significantly higher probability of FVC decline ≥10% (53.6% vs 34.4%, p < 0.001) and all-cause death (15.4% vs 7.3%, p < 0.003) than non-progressors (Figure). The subanalyses with either baseline mRSS ≥22/51 or disease duration ≥15 months also revealed these findings. Multivariate Cox regression confirmed that skin progression was independently associated with higher probability of FVC decline ≥10% (HR 1.79, 95% CI 1.20–2.65) and all-cause death (HR 2.58, 95% CI 1.31–5.09).

Conclusions: Progressive skin fibrosis within 1 year is associated with lung function decline and poorer survival over follow-up in dcSSc. This evidence-based finding is helpful for cohort enrichment in clinical trials for both skin and lung fibrosis, and for risk stratification in clinical practice.
Objective: This study assessed whether using a test meal instead of standard water swallows to perform HRM increases sensitivity and can detect clinically relevant, abnormal motility in already very early SSc and whether this finding is associated with subsequent disease progression.

Methods: This prospective, longitudinal cohort study recruited 68 consecutive SSc patients (group #1: 32 established disease (ACR/EULAR 2013 and ACR 1980 criteria fulfilled); group #2: 24 early disease (only ACR/EULAR 2013 fulfilled); group #3: 12 very early disease (clinical expert diagnosis of SSc, no classification criteria fulfilled) and 72 healthy controls. HRM evaluated oesophageal motility for water swallows and a solid test meal using validated methods.

Results: SSc patients had less frequent effective oesophageal contractions during the test meal compared to healthy controls. Notably, this was detected even in very early disease (0.15, 1.0, 2.1/min for group #1, #2 and #3, vs. 2.5/min in health, p < 0.001; p < 0.001 and p < 0.009, respectively). No other significant abnormality on HRM was found in patients with very early disease (group 1). Ineffective motility at baseline was associated with a higher modified Rodnan skin score at baseline. Moreover, at mean 18 (10–31) months follow-up, the presence of ineffective motility at baseline was associated with progressive skin disease in the overall SSc cohort (p < 0.010). In a secondary analysis, below-average lower oesophageal sphincter pressure was associated with progression of skin disease and organ disease, in particular interstitial lung disease (p < 0.009).

Conclusion: Ineffective motility for the presence of ineffective motility at baseline was associated with progressive skin disease for the overall SSc cohort (p < 0.010). In a secondary analysis, below-average lower oesophageal sphincter pressure was associated with progression of skin disease and organ disease, in particular interstitial lung disease (p < 0.009).

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Anti-TNF Treatments for Women with Chronic Inflammatory Diseases: Comparing Attitudes and Perceptions of Physicians in Europe and the US


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Background: High disease activity in Women of Childbearing Age (WoCBA) with chronic inflammatory diseases (CID) is associated with increased risk of pregnancy complications and adverse outcomes; disease control is therefore important. Tumour necrosis factor antagonists (anti-TNFs) are effective treatments, but data on their utilisation for this patient (pt) group are limited.

Objectives: To understand physicians’ attitudes towards treating WoCBA pts with ant-TNFs during pregnancy and lactation, and differences between Europe- and US-based physicians.

Methods: The online survey was conducted in the US (Jul-17 and EU5 (France, Italy, Spain, UK, Germany; Nov-Dec-17) by SERMO RealTime. WoCBA were defined as female pts ages 18–45. Participants included rheumatologists (RH), gastroenterologists (GI), dermatologists (DM) and obstetricians/gynaecologists (OB). We present data for RH and OB.

Results: 203 US healthcare professionals (HCPs) participated (50 RH, 50 OB) and 401 EU5 HCPs (152 RH, 114 OB); over half of their female CID pts were WoCBA. EU5 HCPs were less inclined to prescribe anti-TNFs for WoCBA; US RH (43%) had the highest proportion of WoCBA prescribed anti-TNFs (EU5 RH: 33%). Both US and EU5 HCPs comfort with prescribing anti-TNFs declined with onset of family planning. EU5 RH (61%) and OB (78%) were more likely to recommend stopping anti-TNFs before conception than US HCPs (RH: 46%; OB: 62%); similarly, >50% EU5 RH and OB agreed that women should stop anti-TNFs’ post-conception (US RH: 34%; OB: 54%). These findings may be due to more US HCPs strongly agreeing on making disease control during pregnancy a priority (US RH: 42%; EU5 RH: 25%) and that controlled disease reduces risk of pregnancy complications (US RH: 42%; EU5 RH: 28%), as well as more EU5 (34%) than US RH (12%) being very concerned about adverse events in pregnant pts on anti-TNFs. More EU5 (16%) than US RH (6%) strongly believed breastfeeding pts should not take anti-TNFs, although a high degree of uncertainty was noted.

Conclusions: Our survey shows variability in confidence in clinical management of WoCBA with CID, highlighting differences in physicians’ attitudes. Uncertainty and concerns about anti-TNFs for WoCBA pts are common, emphasising a need for better information/ education of HCPs on appropriate anti-TNF use during pregnancy and breastfeeding.

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Fears and Misconceptions of Women with Chronic Rheumatic Diseases on their Journey to Motherhood


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Background: EULAR Points to Consider give guidance on management/treatment of Women of Childbearing Age (WoCBA) with chronic rheumatic diseases (CRD). However, it is unclear if these patients (pts) feel adequately supported making informed treatment decisions around pregnancy and breastfeeding.

Objectives: To understand perspectives of WoCBA with CRD regarding decision making (DM) and preparedness, and assess whether clinical practice provides adequate support.

Methods: WoCBA (18–45 years) from Germany, France, UK, Italy, Spain (EUS), the US and Japan, participated in an online survey (Jul–Oct-17, InSites Consulting). Pts had moderate-severe CRD and were pregnant/had been pregnant in the past 2–5 years.

Results: 822 participants had CRD and resided in the EUS (n = 306), US (n = 293) and Japan (n = 23). 49% stated they had actively planned their most recent pregnancy. 46% WoCBA visited a healthcare professional (HCP) before pregnancy, of whom 53% consulted a rheumatologist. Guidelines recommend addressing family planning/ pregnancy in WoCBA pts before conception, but 69% pts had initiated these discussions. 54% WoCBA delayed their decision to become a mother; the main fear (46%) was passing on health issues to their child. During pregnancy, 82% pts visited an obstetrician/gynaecologist (OB/GYN), 68% a rheumatologist; 65% had a treatment plan aligned between different HCPs. Stopping treatment during pregnancy was largely driven by fear of harming the foetus (78%) 22% of pts on anti-TNFs (n = 113) decided to stop treatment at the start of pregnancy; 47% were advised to stop by their HCP. Although 89% pts reported discussing breastfeeding with an HCP, 66% mothers felt they had to decide between treatment and breastfeeding. While information provided was generally satisfactory, pts felt they lacked information on the impact of treatment on pregnancy (37%) and breastfeeding (24%).

Conclusions: Despite current recommendations, WoCBA with CRD have fears and misconceptions about the journey to motherhood, due to lack of guidance and inconsistent information. Survey findings suggest that treatments needed to delay their treatment are linked to a need for greater awareness of disease management options. Access to this information, earlier consultation with specialists and aligned treatment plans could help prevent unnecessary decisions.

A FAMILY CASE OF ADA 2 DEFICIENCY WITH CECR1 MUTATION

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Introduction: ADA2 deficiency (DADA2) is an immunological disease recently described caused by an autosomal recessive mutation in the ADA gene encoding the DADA2 enzyme. DADA2 is causing various and heterogeneous manifestations including: systemic inflammation; vasculititis; thrombotic events; cytopenia; immune deficiency or autoimmunity. Timely diagnosis and treatment are crucial to prevent cerebral strokes as well as other multisystemic serious complications of the disease.

Objectives: We describe here a 4-year old Caucasian child diagnosed with DADA2 in the context of positive family history.

Materials and Methods: Case report.
**Results:** 4-year-old boy, originated from Portugal, presenting with persistent fever in the last 3 months, lower limbs pain, systemic inflammation, anaemia, lvedo, IgM and IgA hypogammaglobulinemia. The personal history showed failure to thrive since the age of 2 years old. Family history demonstrated a consanguinity and a fourth degree relative diagnosed with DADA2 (homozygous R169Q mutation). After exclusion of infectious and oncologic causes, genetic analysis was performed and showed the presence of the same mutation with functional tests confirming the absence of DADA2 enzyme activity. After diagnosis, oral steroids were introduced with recovery of symptoms and inflammatory markers within 3 weeks, followed by anti-TNFalpha therapy. Genetic testing of the family is ongoing.

**Discussion & Conclusion:** We describe here a case of DADA2 prominently diagnosed during the positive family history. Early diagnosis of DADA2 seems to be essential to prevent serious complications of the disease, highlighting the importance of genetic testing in all family members. However, the management of presymptomatic patients remains a matter of controversy. In the absence of biomarkers predicting the onset of the disease, a close and regular follow-up is recommended.

**Longterm outcome in real life patients with giant cell arteritis (GCA) and polymyalgia (PMR) treated with tocilizumab (TCZ)**

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**Background:** High-dose corticosteroids (GC) are the mainstay of treatment in GCA, but relapses are frequent when doses are tapered. Recently, RCT’s have demonstrated efficacy and safety of TCZ in patients with GCA with a significant proportion of patients with GC free remission. However, data on efficacy and safety of TCZ in real life patients and during longterm follow-up are still limited.

**Methods:** In our single-center cohort, 36 patients with GCA and 6 patients with PMR have been treated with TCZ (8 mg/kg/month) in addition to GC between 2013 and 2018. Safety and efficacy of TCZ were analysed retrospectively.

**Results:** 42 patients (29 female, 13 male) with a mean age of 68 + 9 years were included in this analysis. Apart from typical clinical manifestations, diagnosis was mainly based on US of temporal arteries (n = 23), MR angiography (n = 36), CT angiography (n = 14) and/or PET CT (n = 8). 12/36 GCA patients received TCZ as part of their initial treatment strategy, whereas 25% of patients had refractory disease. There was a clear trend over time to use TCZ in patients with earlier disease and more frequently in patients without previous use of other immunosuppressives. Mean treatment duration was 18.2 + 9.6 months, with treatment still ongoing in 35/42 patients. The majority of patients achieved GC free clinical remission (28/42 + 67%). In 12 patients, who went in GC free remission, TCZ was stopped. Only 6 patients, with 4/6 suffering from PMR, stayed in GC free and TCZ free remission during follow-up. 3 patients relapsed after 3, 11 and 11 months, were restarted with TCZ and GC and achieved GC free remission again. 3 patients were died with varying long-term follow-up. Infectious complications occurred in 3 patients, two cases with herpes zoster, one RSV pneumonia and one case with bronchitis. TCZ was restarted in all patients. 3 patients developed vascular complications during follow-up, 1 patient with stroke (but coexisting with herpes zoster, one RSV pneumonia and one case with bronchitis).

**Conclusions:** In summary, our data show that in this real life patient cohort TCZ is safe and efficacious in improving signs and symptoms of disease and results in GC free remission in the majority of patients. However, sustained remission without TCZ was infrequently observed. Our data suggest that patients with GCA with or without involvement of cranial arteries benefit from continuous treatment with TCZ.

**Inhibition of Cathepsin S leads to suppression of antigen specific T cell responses from patients with primary Sjögren Syndrome**

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**Background:** Primary Sjögren syndrome (pSS) is an autoimmune disease characterized by an infiltration of T and B cells into exocrine gland tissue and its subsequent destruction. Antigen presenting cells, including B cells, foster T cell activation and anti-SS-A/SS-B producing plasma cells, eventually leading to disease progression and systemic complications.

**Objectives:** Cathepsin S (CatS) is crucially involved in MHCII processing in pSS mouse models and patients. In this translational study we investigated the ex vivo effects of the CatS inhibitor RO5459072 in different bio-compartments, including specific T cells, of pSS patients and healthy controls.

**Methods:** Ex vivo CatS activity was assessed in different bio-compartments of 15 pSS patients and 13 healthy controls and in presence or absence of RO5459072 using commercial activity and quantification assays. In addition, antigen (5 µg/mL SS-A, 5 µg/mL SS-B, 5 µg/mL Influenza H3N2; 2 µg/mL Tetanus Toxoid and 100ng/mL, SEB) specific T cell responses were examined using 2x105 PBMC/well IFN-γ/IL-17 Dual ELISPOT (48h incubation) and 5x104 PBMC/well Brdu proliferation assays after (72h incubation) in presence or absence of RO5459072.

**Results:** pSS patients showed significantly higher CatS activity in tear fluid than healthy controls (two-tailed t-test p < 0.01). RO5459072 significantly suppressed CatS activity in tears of pSS patients (two-tailed t-test p < 0.01). Four patients exhibited strong SS-A/SS-B specific IFN-γ responses, whereas no specific IL-17 secretion could be detected. Four patients showed antigen specific proliferation to autoantigens. CatS inhibition by RO5459072 exerted a strong and dose-dependent suppression of T cell responses towards SS-A and SS-B antigen.

**Conclusion:** CatS activity in tear fluid seems to be a relevant biomarker for pSS disease activity. RO5459072 is a potent inhibitor of CatS and of antigen specific T cell responses which are considered relevant for the pathogenesis of pSS.

**Tobacco smoking effects on clinical, serological and histological manifestations of Sjögren’s syndrome, a cross-sectional study of the OASIS cohort**

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**Background:** Previous studies showed that tobacco smoking in patients with primary Sjögren’s syndrome (pSS) is negatively associated with a histopathological focus score and anti-Ro/anti-La serological positivity.

**Objectives:** To evaluate the association of tobacco smoking history with clinical, serological and histological features of patients with pSS.

**Methods:** Cross-sectional study of patients with suspected pSS or known pSS at the time of recruitment into the OASIS cohort between 2014 and March 2017. Patients all fulfilled the ACR-EULAR 2016 classification criteria for pSS and 57 presented with sicca symptoms without pSS. The rate of current/previous smoking was respectively 5%/23% in the pSS group and 11%/33% in the sicca-non pSS group; 73%/56% of the patients with pSS/sicca-non pSS never smoked (p = 0.19). Patients with pSS who ever smoked, compared to those who never smoked, had a higher body mass index (BMI) (29.8 ± 5.8 versus 26.8 ± 5.7 kg/m², p = 0.04), lower IGG levels (13.0 [10.0–16.6] versus 16.0 [12.4–21.7], g/l, median [IQR], p = 0.03), a higher ESSDAI (6.0 [5.0–10.0] versus 4.0 [2.0–6.0], median [IQR], p = 0.02) and a higher ESSPRI (7.3 [5.3–8.7] versus 6.0 [4.3–6.7], median [IQR], p = 0.02). Anti-Ro/La positivity did not differ between both groups. Tear and saliva production, assessed by Schirmer’s test and unpaired t test, Mann-Whitney test and Chi-square test when appropriate. P ≤0.05 was considered statistically significant.

**Results:** Among the 174 patients included in the cohort, 82 fulfilled the ACR-EULAR 2016 classification criteria for pSS and 57 presented with sicca symptoms without pSS. The rate of current/previous smoking was respectively 5%/23% in the pSS group and 11%/33% in the sicca-non pSS group; 73%/56% of the patients with pSS/sicca-non pSS never smoked (p = 0.19). Patients with pSS who ever smoked, compared to those who never smoked, had a higher body mass index (BMI) (29.8 ± 5.8 versus 26.8 ± 5.7 kg/m², p = 0.04), lower IGG levels (13.0 [10.0–16.6] versus 16.0 [12.4–21.7], g/l, median [IQR], p = 0.03), a higher ESSDAI (6.0 [5.0–10.0] versus 4.0 [2.0–6.0], median [IQR], p = 0.02) and a higher ESSPRI (7.3 [5.3–8.7] versus 6.0 [4.3–6.7], median [IQR], p = 0.02). Anti-Ro/La positivity did not differ between both groups. Tear and saliva production, assessed by Schirmer’s test and unpaired t test, Mann-Whitney test and Chi-square test when appropriate. P ≤0.05 was considered statistically significant.

**Conclusion:** Patients with pSS who ever smoked showed a higher BMI, ESSDAI and ESSPRI and lower IGG levels compared with patients with pSS who never smoked at inclusion in our cohort. In contrast with published data, they did not differ in terms of autoantibody profile and minor salivary gland histological features.
SSRP 13

Pregnancy Outcomes and Disease Activity in Women with Axial Spondyloarthritis: A Systematic Literature Review

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Background: Women with axial spondyloarthritis (axSpA) are often affected by the disease during their reproductive years [1], but reports on disease activity (DA) and pregnancy outcomes (PO) in these patients (pts) are sparse. In women with ankylosing spondylitis (AS), also currently termed as radiographic axSpA, a higher risk of DA flares and prevalence of adverse PO have been reported vs healthy controls (cts); however, in non-radiographic (nr)-axSpA pts, such data are virtually non-existent [2].

Objectives: To review available evidence on the relationship between axSpA DA and pregnancy outcomes, including foetal outcomes.

Methods: A systematic literature review was conducted in Oct-17 by searching EMBASE® and MEDLINE®; the Cochrane Database of Systematic Reviews, and the Database of Abstracts of Reviews of Effects. Publications were systematically screened for English language articles on observational studies of axSpA pts reporting PO or DA during pregnancy. Studies utilising agents contraindicated in pregnancy were excluded. Supplementary searches of selected, 2016–17 conference proceedings and bibliographies of relevant review articles were also conducted.

Results: 2216 publications were reviewed, with 20 publications on 15 unique studies meeting the inclusion criteria. When utilising the validated DA measurement instruments, BASDAI or ASDAS-CRP, 5 studies (3 prospective, 2 retrospective) reported active disease both during pregnancy and postpartum in most pts. PO in axSpA pts were compared with healthy cts in 6 studies (3 prospective, 2 retrospective, 1 case-control), the 3 largest of which (including 1 prospective) revealed higher risk or odds of pre-term births in axSpA pts. Higher rates or risk of low birth weight/small-for-gestational-age neonates were seen in pts vs cts in 2/5 studies reporting such outcomes. Stillbirths, miscarriages or foetal loss/abortion were found to occur at similar rates in both populations.

Conclusions: Robust, prospective data on DA during pregnancies of women with axSpA are limited. This data suggests that there may be a small increase in pre-term births; no signal for increased pregnancy loss was detected. Further research is needed to investigate relationships between maternal DA and PO in axSpA.


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SSRP 14

CLINICAL SPECIALTY SETTING AS A DETERMINANT FOR DISEASE MANAGEMENT IN PATIENTS WITH PSORIATIC ARTHRITIS: RESULTS FROM LOOP, A CROSS-SECTIONAL, MULTI-COUNTRY, OBSERVATIONAL STUDY

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Background: Evidence suggests that timely and effective management can influence long-term outcomes in patients (pts) with psoriatic arthritis (PsA); however factors influencing treatment management decisions are not well understood.

Objectives: To evaluate the association between clinical specialty setting and time to inflammatory musculoskeletal symptom onset to PsA diagnosis and to different management steps in pts with diagnosis of PsA.

Methods: LOOP is a large cross-sectional, multi-center, observational study conducted in 17 countries across Western and Eastern Europe, Latin America and Asia. Adult pts (≥18 years) with a suspected or established diagnosis of PsA routinely visiting a rheumatologist (rheum), dermatologist (derm) or non-rheum/non-derm site were eligible to participate. Each enrolled patient in the study was assessed by both rheum and derm. Main endpoints assessed were time from inflammatory musculoskeletal symptom onset to PsA diagnosis, time from PsA diagnosis to first csDMARD and to first bDMARD, and time from first csDMARD to first bDMARD.

Results: Of the 1483 pts enrolled in this study, 1273 pts with a confirmed diagnosis of PsA were included in this analysis. A majority of pts were recruited by rheums (671, 52.7%), followed by derms (541, 42.5%), physiatrists (36, 2.8%), and other specialties (25, 2.0%). PsA was first suspected by a rheum in 726 (57.0%) pts and by a dem in 541 pts (42.5%). Pt demographics and disease characteristics were mostly comparable between rheum and derm settings. Disease activity was higher in PsA pts in derm setting compared with rheum setting. The mean time from symptom onset to PsA diagnosis was 24 months (mo) in rheum setting and 1 mo longer for derms. In rheum and derm settings, the mean time from PsA diagnosis to first csDMARD was 11 and 25 mo, respectively; whereas the mean time to first bDMARD was 52 and 55 mo, respectively. The mean time from first csDMARD to first bDMARD was 42 mo for rheum; while it was 26 mo shorter for derms.

Conclusions: Although the duration from symptom onset to PsA diagnosis was similar between rheum and derm setting, there were differences in the timing of introduction of different DMARD classes. Notably, mean time from first csDMARD to first bDMARD was 3 months longer in rheum setting. Pts in derm setting had significantly higher disease activity. These data lend further support to the need for rheum-derm collaborative approach to optimize management of PsA pts.

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Lower spinal radiographic progression in female versus male patients with axial spondyloarthritis: data from the SCQM cohort

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Objective: To compare spinal radiographic progression in male versus female patients with axial spondyloarthritis (axSpA).

Methods: Male and female patients fulfilling the Assessment in SpondyloArthritis international Society (ASAS) classification criteria for axSpA in the Swiss Clinical Quality Management Cohort (SCQM) with available lateral radiographs of the cervical and lumbar spine every 2 years (±1 year) were included in the study. Radiographs were scored by 2 readers according to the modified Stoke Ankylosing Spondylitis Spine Score (mSASSS). Progression was defined as worsening of the mean mSASSS by ≥2 units over 2 years. The relationship between gender and radiographic progression over time was investigated using binomial generalized estimating equations (GEE), fitted using multiple imputation of missing covariate data. The analyses were adjusted for factors known to affect radiographic progression (baseline radiographic damage, classification status (nonradiographic axSpA versus ankylosing spondylitis), length of radiographic interval, previous treatment with TNF inhibitors and the Ankylosing Spondylitis Disease Activity Score (ASDAS)).

Results: A total of 317 male and 189 female patients with 463 and 263 radiographic intervals, respectively, were included. Male patients presented at first radiograph with higher mean ± SD ASDAS levels (2.9 ± 1.1 vs. 2.7±1.0, p = 0.04), higher BASMI levels (2.3 ± 2.0 vs. 1.6 ± 1.6, p <0.001) and a higher mSASSS (7.8 ± 13.5 vs. 2.2 ± 6.7, p <0.001). A higher proportion of male patients were HLA-B27 positive (84% vs. 71%, p = 0.002), had elevated CRP levels (46% vs. 27%, p <0.001) and had syndesmophytes at first radiograph (40% vs. 15%, p <0.001). Mean (SD) spinal radiographic progression was 1.06 ± 3.00 units in men and 0.34 ± 1.43 units in women (p <0.001). In the adjusted longitudinal Cox regression model, male gender was an independent risk factor for spinal progression was found in men vs. women (odds ratio 1.9 (95% confidence interval 1.07; 3.36, p = 0.03).

Conclusion: Men presented with more risk factors for spinal radiographic progression in the SCQM cohort. After adjustment for these observed differences, the risk for progression was twice as high in men than in women.

EMH MEDIA
Dose adjustments of individual TNF inhibitors and drug survival without dose increase in patients with axial spondyloarthritis: results from the SCoM cohort
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Background: Survival rate of a first tumor necrosis factor inhibitor (TNFi) seems not to be influenced by the choice of TNFi in axial spondyloarthritis (axSpA). However, these results might be confounded by the fact that the extent of dose adjustments (either dose alterations or changes in the length of the interval between administrations) may differ between individual TNFi. In particular, a differential potential of immunogenicity has been described for the different anti-TNF agents.
Methods: Patients fulfilling the Assessment in Spondyloarthritis international Society (ASAS) classification criteria for axSpA in the Swiss Clinical Quality Management (SCQM) cohort were included in the current study if a first TNFi was started after recruitment and if a baseline visit was available. Time to ineffectiveness (drug retention without an increase in dose) was defined as the time between treatment initiation and either drug discontinuation or a dose increase of at least 10%. Differences between TNFi were analyzed with multiple adjusted Cox proportional hazards models and multiple imputation for missing baseline covariate data (gender, SpA-type, disease duration, comorbidity with conventional DMARD, BASDAI, elevated CRP, education, number of alternative TNFi on the market).
Results: Nine hundred and eighty-seven patients were included: adalimumab (ADA) n = 344, etanercept (ETA) n = 243, golimumab (GOL) n = 194, infliximab (IFX) n = 206. Patients on corticosteroids or methotrexate (MTX) were excluded because of the limited number of patients fulfilling the inclusion criteria (n = 11). The proportion of patients with a dose reduction of their first TNFi during follow-up was similar between the different anti-TNF agents: ADA 18%, ETA 20%, GOL 19%, IFX 14%. In all groups, there were significant differences between individuals. An increase in dose was more often found in patients treated with IFX: ADA 2%, ETA 1%, GOL 1%, IFX 16%, p < 0.001. However, no significant differences in time to ineffectiveness were observed in multiple adjusted analyses: hazard ratio for IFX vs. ETA (HR) 1.3 (95% CI 0.9; 1.87), p = 0.16; HR 1.0 (0.72; 1.38), p = 1.00 for ADA vs. ETA; HR 0.85 (0.60; 1.21), p = 0.37; GOL vs. ETA and HR 0.91 (0.67; 1.23), p = 0.54 for ETA vs. subcutaneously administered monoclonal antibody TNFi.
Conclusion: Drug retention without dose increase during follow-up is comparable in axSpA patients treated with different anti-TNF agents.

Identification of Methotrexate-Induced Pulmonary Toxicity Cases in a Fully Searchable Routine Clinical Database
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Background: Methotrexate (MTX) remains the favoured disease-modifying anti-rheumatic drug for the treatment of rheumatoid arthritis (RA) and is frequently used in other inflammatory conditions. However, side effects are frequent and toxicity is of concern, especially since MTX-induced pulmonary side effects, including pneumonitis, are potentially fatal. Estimates of MTX-induced pneumonitis in the literature range from 0.3% to 7.5% of exposed cases (Barrera et al., 1994; Kremer et al., 1997).
Objectives: We aimed to identify and characterise MTX-induced lung injury in patients exposed to low-dose MTX at the Rheumatology Division of the Kantonsspital Aarau, Switzerland.
Methods: The revised diagnostic criteria for adverse pulmonary events due to MTX treatment as defined by Kremer et al (Kremer et al., 1997) were used to categorise MTX-induced lung injury. The electronic patient files of the Rheumatology Division are stored in a NoSQL-database (MongoDB), which is fully addressable by the Solr search platform (Apache LuceneTM). The entire database was searched for terms associated with methotrexate exposure and potential pulmonary side effects.
Results: Of 9'550 cases, 11 fulfilled the criteria for definite MTX-induced pulmonary injury, while three additional patients could be classified as suffering from probable MTX-induced pulmonary side effects. To determine the number of exposed cases, the case files were queried for the mention of MTX and related terms. 1'947 case files contained a reference to MTX. In a random sample of 395 of these cases, an exposure to MTX was verified in 328 (83%). Assuming a calculated exposure of 1'639 cases, MTX-induced lung injury was present in 0.85%.
Conclusions: In a comprehensive survey of patients exposed to MTX in a fully searchable routine clinical database, MTX-induced pulmonary injury occurred in a low frequency.
did not improve. Blood tests showed an increased angiotensin converting level to 99 μU/l (normal range: 12–68) and lymphopenia with a CD4 count at 531/mm³ (546–1855). The chest CT scan showed symmetric mediastinal and hilar lymphadenopathies and pulmonary micronodules. An endobronchial ultrasound-guided biopsy of mediastinal lymph nodes (EBUS-TBNA) was performed. The pathologic examination revealed non-necrotizing granulomatous inflammation. Microbiological tests were negative for Mycobacterium tuberculosis (PCR-negative). The diagnosis of sarcoidosis was established. ADA and MTX were discontinued and prednisone 50 mg daily was started in association with hydroxychloroquine 400 mg daily. After one year, prednisone was tapered down to 15 mg daily. The respiratory symptoms disappeared with complete resolution of hilar lymphadenopathies and disappearance of most micronodules on the chest CT scan. As prednisone dosage was reduced under 15 mg daily the patient experienced a flare of cutaneous and articular signs of PsA. A treatment with secukinumab was started at a dose of 150 mg SC with complete resolution of clinical signs of PsA allowing for prednisone discontinuation without subsequent sarcoidosis relapse.

Discussion: We present here a case of pulmonary and mediastinal sarcoidosis that could be considered as a late complication of ADA treatment (after 9 years of treatment). Indeed, similar observations have been described during treatment with TNF-alpha blockers (etanercept, adalimumab, infiximab). The remission of sarcoidosis occurs generally within one year after withdrawal of the TNF-alpha blockers and corticosteroid therapy is necessary in approximately 2/3 of the cases. Of note, we did not observe a relapse with anti-IL-17A therapy so far.

Conclusion: Rheumatologists should be aware that sarcoidosis can occur as a paradoxical adverse event in patients on TNF inhibitors.

SSRP 20

Do we prescribe too many opioids? An analysis of analgesics prescription patterns at discharge from the rheumatology ward of a Swiss teaching hospital with a focus on opioids

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Background: Opioids prescription for non-cancer pain has recently come under intense scrutiny as opioid abuse has become a major public health issue, primarily in the USA.

Objectives: To evaluate analgesics prescription, especially opioids, at discharge from our rheumatology ward.

Methods: We prospectively recorded analgesics prescription patterns of paracetamol, nonsteroidal anti-inflammatory drugs (NSAIDs), weak opioids (tramadol/codeine) and strong opioids (opioids) at discharge for all patients hospitalized in the Rheumatology Department between May 2017 and October 2017. Statistical analyses consisted of descriptive statistics and univariate/multivariate logistic regression. P ≤ 0.05 was considered statistically significant.

Results: We analysed 154 hospital inpatient stays of 146 patients. At discharge, paracetamol, tramadol/codeine, NSAIDs and opioids were prescribed for 47%, 25%, 22% and 10% of patients at a fixed dosage, respectively. Tramadol/codeine (n = 39) and opioids (n = 36) with a fixed dose were either prescribed alone (13%, 26%), combined with paracetamol (46%, 8%), NSAIDs (15%, 47%) or combined with both (26%, 17%), respectively. Tramadol/codeine and opioids were never combined. Patients hospitalized for debilitating osteoarthritis, severe low back pain and osteoporotic fracture had the highest rate of opioids prescription at discharge (38%, 35%, 35%, respectively). Opioids at fixed dose were more often prescribed for patients transferred to a nursing home (100%) or a transitional care unit (38%) than for patients discharged home (17%). Moreover, opioids prescription at discharge was negatively associated with home discharge in multivariate analysis (0.29, 0.12 to 0.72, adjusted OR, 95%CI). Multivariate logistic regression analyses identified age at admission (1.02, 1.00 to 1.04) and concomitant DMARDs prescription (2.79, 1.01 to 7.74) as predictors of opioids prescription at discharge (adjusted OR, 95%CI). Length of inpatient stay predicted (1.05, 1.00 to 1.09, adjusted OR, 95%CI) opioid prescription at discharge in crude analysis but not when adjusted for other factors.

Conclusion: Opioids were prescribed less often than other analgesics and mainly at fixed doses. They were most frequently combined with NSAIDs or prescribed as monotherapy. In the population studied, age at admission and concomitant DMARDs prescription were independent on opioids prescription at discharge. Opioids prescription negatively predicted home discharge.

SSRP 21

Measurements of Functioning in Patients with Chronic Low Back Pain: Validity of Functional Scales

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Background: Functional impairment is seen as the leading consequence of chronic low back pain. The study aimed to determine the validity and specificity of various scales in the measurement of physical function.

Methods: In a prospective cohort study, patients were measured at baseline (before) and after a specific, 4 week interdisciplinary pain management program by the Short Form 36 (SF-36), the Multidimensional Pain Inventory (MPI), the Oswestry Disability Index (ODI), the back performance scale (BPS) and the 6 minute walking distance test (6WD). Cross-sectional and longitudinal construct validity was quantified by bivariate correlations and with use of factor analysis. Specificity was examined by comparing effect sizes (ES).

Results: Patients (n = 142) were on average 47.8 years old (SD = 11.8) and 61.0% were female. Cross-sectionally, only some correlations between the function scales reached moderate levels (maximum: r = 0.67 between SF-36 physical functioning and the 6MD). The factor “physical function” ranked only on the second position (28.6% explained variance) behind the “psychosocial” factor (37.4%). On that, the SF-36, the BPS and the 6WD, but not the MPI nor the ODI showed high factor loads (>0.80). Longitudinally, all correlations between function scores were low to moderate (max. r = 0.46 between MPI interference with pain and ODI). The latter two scales ask also about pain. Consistently, the highest explanatory factor was “condition-specific symptoms and impairment” (25.3% explained variance), on which the two later scales loaded maximal together with MPI pain to severity. The “function test” factor summarizing maximal factor loads of the BPS and the 6MD ranked on third position (16.1%) behind the “psychosocial” factor (19.9%). The MPI interference with pain and the ODI (function), the simultaneous inclusion of pain blurs the construct of specific function content. In contrast to those, the generic SF-36 (physical functioning) showed highest functional specificity and construct overlap to the functional performance tests.

Conclusions: Overall, construct overlap of physical function scales was moderate to weak and the construct of physical function explained limited variance of state and change of health in chronic low back pain. On the condition-specific instruments, namely the MPI interference with pain and the ODI (function), the simultaneous inclusion of pain blurs the construct of specific function content. In contrast to those, the generic SF-36 (physical functioning) showed highest functional specificity and construct overlap to the functional performance tests.

SSRP 22

Multidimensional minimal clinically important differences (MCID) in knee osteoarthritis after comprehensive rehabilitation: a prospective evaluation from the Bad Zurzach Osteoarthritis Study

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Background: Changes in health or symptoms should not only be detected by statistical significance tests, they have also to be perceived by the person affected. The subjective perception of outcome effects defines the minimal clinically important difference (MCID). The aim was to determine MCIDs for improvement and worsening in various health dimensions in knee osteoarthritis under conservative therapy.

Methods: Health, symptoms and function were assessed by the generic Short Form 36 (SF-36) and the condition-specific Western Ontario and McMaster Universities questionnaire (WOMAC) in n = 190 knee osteoarthritis patients before and after comprehensive rehabilitation intervention (3-month follow-up). By means of construct-specific transition questions, MCIDs were defined as the difference between the “slightly better/worse” and the “almost equal” transition response categories according to the “mean change method”. The bivariate MCIDs were adjusted for sex, age, and baseline score to obtain adjusted MCIDs by multivariate linear regression. They were further standardized by (baseline) effect sizes (ES), which is the mean score difference between baseline and follow-up divided by the group’s standard deviation.

Results: Adjusted ES for pain were ES = 0.33 for improvement / -0.33 for worsening on the WOMAC and 0.50/-0.37 on the SF-36. For function, they resulted in 0.50/-0.37 (WOMAC) and 0.20/-0.34 (SF-36).
The corresponding levels were 0.63(-0.38 on WOMAC stiffness, 0.14/-0.44 on SP-36 mental health and 0.38/-0.30 on SP-36 general health.

Conclusions: This study presents MCIDs over a comprehensive range of health dimensions, which can be generalized for samples with different characteristics regarding sex, age and baseline score levels. For most scales, a score change of ≥1/3 to 1/2 standard deviations of the baseline scores is – on group level – subjectively perceivable for persons affected by knee osteoarthritis. This helps to rate the clinical impact of therapy effects.

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Nerve growth factor, TrkA and substance P is expressed in different compartments of human osteoarthrosis facet joints

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Background: Chronic low back pain is frequently linked to facet joint osteoarthritis (FOA). Repeated pain induces neuron-derived molecules with further downstream inflammatory stimuli. This mechanism is termed neurogenic inflammation (1) with nerve growth factor (NGF) being the most important NGF, regulates substance P (SP) expression as another pivotal peripheral neurogenic pro-inflammatory molecule. Thus, NGF appears as a promising target for novel pain medications. Despite of rapidly progressive OA (ROPO) in some selected cases, NGF inhibitors (NGFi) have thus shown significant efficacy in peripheral OA and to some extent also in low back pain. Therefore, further specification of NGF signaling in FOA is necessary.

Objectives: To evaluate the expression of its high affinity transmembrane tyrosine kinase A (TrkA) receptor and SP in different compartments of FOA.

Methods: Human FOA specimens of six donors undergoing spine surgery were examined. OA severity was graded on HE-stained tissue sections. NGF, TrkA and SP expression was evaluated by indirect immunohistochemistry with monoclonal antibodies. New bone formation was assessed by staining for osteocalcin.

Results: FOA had low (n = 2), intermediate (n = 2) and high (n = 2) inflammatory bone marrow infiltrates. NGF expression was found in capsular tissue, in degenerated cartilage, and in active bone marrow infiltrates. TrkA was found in all bone marrows and capsular tissues but not in cartilage. TrkA expression colocalized with osteocalcin in subchondral bone, suggesting a link to new bone formation. Cells strongly positive for SP were detected in the bone marrow. NGFi might thus be effective by targeting inflamed joint tissue and receding NGF may also have an impact on bone remodeling. The latter mechanism needs further investigation also regarding the potential onset of ROPAO.

Conclusions: In this study we define tissue compartments of the NGF axis in human FOA. The findings indicate the presence of neurogenic inflammation. NGFi might thus be effective by targeting inflamed joint capsule or subchondral bone marrow. NGF may also play a role in bone remodeling. The latter mechanism needs further investigation also regarding the potential onset of RPOAO.

References

A refractory tenosynovitis of the wrist

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INTRODUCTION: Mycobacterium malmoense belongs to slow-growing non-tuberculous mycobacteria (NTM) species. Mostly seen in pulmonary infections or lymphadenitis. In case of a slow-growing mycobacteria, should be suspected and searched for, if confronted with therapy-resistant tenosynovitis. Diagnosis delay can lead to major functional impairment. Given increasing occurrence of slow-growing NTM (teno-) synovitis, in case of an unclear rheumatic condition it is important to rule out this type of infection before initiating any immunosuppression therapy.

CONCLUSION: Slow-growing bacteria, such as non-tuberculous mycobacteria, should be suspected and searched for, if confronted with therapy-resistant tenosynovitis. Diagnosis delay can lead to major functional impairment. Given increasing occurrence of slow-growing NTM (teno-) synovitis, in case of an unclear rheumatic condition it is important to rule out this type of infection before initiating any immunosuppression therapy.

Background:

A 65 y. old female patient presenting with right wrist pain and paresthesia. A carpal tunnel syndrome was diagnosed.

Mycobacterium malmoense belongs to slow-growing non-tuberculous mycobacteria (NTM) species. Mostly seen in pulmonary infections or lymphadenitis. Diagnosis is often delayed, mostly because of difficulty to culture it.

Encountered in isolated (teno-) synovitis. Diagnosis is often delayed, mostly because of difficulty to culture it.

CONCLUSION: Slow-growing bacteria, such as non-tuberculous mycobacteria, should be suspected and searched for, if confronted with therapy-resistant tenosynovitis. Diagnosis delay can lead to major functional impairment. Given increasing occurrence of slow-growing NTM (teno-) synovitis, in case of an unclear rheumatic condition it is important to rule out this type of infection before initiating any immunosuppression therapy.

Background:

A 65 y. old female patient presenting with right wrist pain and paresthesia. A carpal tunnel syndrome was diagnosed. During carpal tunnel release, tenosynovitis of wrist-fluxor-tendons was seen. Despite two synovectomies, tenosynovitis recidivated, causing significant functional impairment. Patient also complained about bilateral shoulder pain and left wrist pain. Clinical examination showed no other synovitis. Laboratory showed mild inflammatory syndrome (CRP 32, ESR 28).ANA 1:160, neg. antibodies against Scl, polymyositis, RF, ACPAs. Normal calcium, phosphate and TSH. HIV, viral hepatitis serology and TB spot negative. Biopsy of synovial tissue showed nonspecific chronic synovitis and standard culture was negative. Hands X-ray: no erosions, bases CD 4/millimeter 0.1. Wrist-MRI: erosive carpal synovitis, massive flexor tenosynovitis. Ultrasound: synovitis of MCP joints 2-4 and of right knee, bilateral subacromial bursitis. First joint aspiration of wrist failed, and culture of rinsing fluid did not show mycobacteria at 8 weeks. A further, successful aspiration showed crystals, no culture of mycobacteria was ordered. CT scan, colonoscopy and gynecological examination without neoplasia. A seronegative polyarthritis was suspected. Immunosuppressive treatment with glucocorticoids and methotrexat showed no significant improvement, but had side effects (psychomotor agitation and weight-loss). A third synovectomy showed “rice-like" aspect of synovial tissue. Histological analysis showed non-tuberculous granulomatous inflammatory infiltrates. After 26 days of incubation, Mycobacterium malmoense was identified. Immunosuppression was stopped and antibiotic therapy with ethambutol, rifampicin and clarithromycine was initiated.

CONCLUSION: Slow-growing bacteria, such as non-tuberculous mycobacteria, should be suspected and searched for, if confronted with therapy-resistant tenosynovitis. Diagnosis delay can lead to major functional impairment. Given increasing occurrence of slow-growing NTM (teno-) synovitis, in case of an unclear rheumatic condition it is important to rule out this type of infection before initiating any immunosuppression therapy.

Background:

Chickenpox is a common childhood disease caused by a herpes virus. Adult patients are rare, usually with a severe disease and high risk of long-term sequelae. We report on 65 y. old female patient presenting with right wrist pain and paresthesia. A carpal tunnel syndrome was diagnosed.

Mycobacterium malmoense belongs to slow-growing non-tuberculous mycobacteria (NTM) species. Mostly seen in pulmonary infections or lymphadenitis. Diagnosis is often delayed, mostly because of difficulty to culture it.

CONCLUSION: Slow-growing bacteria, such as non-tuberculous mycobacteria, should be suspected and searched for, if confronted with therapy-resistant tenosynovitis. Diagnosis delay can lead to major functional impairment. Given increasing occurrence of slow-growing NTM (teno-) synovitis, in case of an unclear rheumatic condition it is important to rule out this type of infection before initiating any immunosuppression therapy.
Clinical features of 35 patients with 172 spontaneous vertebral fractures after denosumab discontinuation: a single center observational study

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Introduction: Denosumab discontinuation (DD) induces an increase of B-crosslapses above baseline values for two years, and a complete or partial loss of the BMD gain after one year. This rebound effect is associated with spontaneous clinical vertebral fractures (SCVF) in 1 to 10% of patients. We report the clinical characteristics of 35 patients with SCVF after DD evaluated at our center from July 2015 to March 2018.

Methods: We report the cases of 35 patients who received Denosumab 60mg every 6 months for 2 to 11 doses. All were on calcium and vitamin D during and after DD. VF have been documented by MRI. A wide biological assessment, performed at the time of fracture, was strictly normal. A secondary cause of osteoporosis was excluded.

Results: Thirty-five cases, man 66.3 ± 9.6 years, experienced 172 SCVF (median 5) in the 11.6 ± 2.8 months (median 11; min 7, max 20) following the last denosumab injection. Eight women received a bisphosphonate before Denosumab, and nine women received antihormonal inhibitors with denosumab. Eleven women had prevalent osteoporotic fracture. Twelve women had vertebraladows with 58 new SCVF in the following days. The mean B-crosslapses value at the time of SCVF was 1523 ± 588 pg/Ml. B-crosslapses were lower with the number of denosumab doses (R2 = 0.28). The number of SCVF was inversely associated with age: 5.4 ± 2.0 vs 2.8 ± 1.3, < vs > 65 years (p < 0.001). The delay between DD and the occurrence of SCVF increases with age: 10.4 ± 1.3 vs 12.7 ± 2.7 months, < vs > 65 years (p = 0.008). The mean reasons for DD were end of AI or no more osteoporosis (15), omission (7), patient’s wish (5), AFF or dental intervention (4).

Conclusion: After denosumab discontinuation, women < 65 years have a higher number of SCVF and in a shorter period than women over 65 years. SCVF are a very severe and frequent clinical complication after DD. A close follow-up for 2 years after DD is necessary. Studies are urgently needed to better define who and when to treat with denosumab, as well as strategies to avoid SCVF after DD.

**INTEROBSERVER AGREEMENT OF THE OMERACT ULTRASONOGRAPHIC CRITERIA FOR THE DIAGNOSIS OF CALCIUM PYROPHOSPHATE DEPOSITION DISEASE AT THE WRIST, AMONG PANEL OF RADIOLOGISTS AND RHEUMATOLOGISTS**

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Objectives: To assess whether the high level of inter-observer agreement of US for the detection of Calcium Pyrophosphate Deposition Disease (CPPD) in the triangular fibrocartilage complex (TFCC) of the wrist found by the experienced rheumatologists of the OMERACT group2 could be reproduced in real life.

Methods: The OMERACT US criteria for identification of CPPD were utilized for this exercise on pre-recorded static images using a dichotomous score among several radiologists (n = 2) and rheumatologists (n = 5) with varying level of experience in musculoskeletal ultrasonography (range: 2–10 years). Firstly, the same 15 US images of the wrist that had been evaluated by the OMERACT group2 could be reproduced in real life.

Results: The mean overall agreement and kappa values on the procedure appear to be an important aspect with regards to the absence of strict standardisation of US procedure and inferior image quality. For comparison, the performance on the local radiographs was similar (0.70 and 0.47 respectively).

Conclusions: Our results confirm that the new OMERACT US definitions for assessing wrist CPPD are reliable when applied to pre-recorded static images. Scanning technique and standardisation of the procedure appear to be an important aspect with regards to the assessment of CPP deposition at the wrist.

**Retroperitoneal flares of pseudogout secondary to hypomagnesemia in the context of a Crohn’s disease**

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Background: Hypomagnesemia (hypoMg) is a classical cause of chondrocalcinosis and is generally due to renal loss. We present here a rare case of hypoMg secondary to short bowel syndrome after ileo-cecal resection for Crohn’s Disease. Joint manifestation is characterised by pseudogout mimicking peripheral spondylarthropathy.

Case Report: A man born in 1952 was diagnosed with Crohn’s disease at the age of 28. He underwent ileo-cecal resection 14 years later. Though he suffered profound watery diarrhoea thereafter, he never received any treatment. He was a non-prednisone, usually at a dose of 5 mg daily. In 2015, he began to feel pain in his joints with morning stiffness. Several times a year, he had to raise prednisone doses during a few days because of acute migrating flares. Serum uric acid was low (336 mmol/L). Spondylarthropathy associated with Crohn’s disease was questioned but X-rays showed typical chondrocalcinosis in his knee, wrist and tarsal joints. Hemochromatosis was ruled out. In 2016, a knee aspiration during an acute access showed inflammatory synovial fluid containing numerous Calcium pyrophosphate crystals. A secondary cause of chondrocalcinosis was looked for, which highlighted severe chronic hypoMg (0.31 mmol/L, normal range 0.70-1.10) with low magnesuria. Prednisone dose could then be tapered; parenteral Mg supplementation, but no anti-TNF, was prescribed.

Mecanism: This is an outstanding case of severe and chronic hypoMg associated with short bowel syndrome after ileo-cecal resection. Mg deficiency results from accumulation of extracellular PPI which facilitates PPiCA formation. Calcium pyrophosphate deposition disease (CPPD) is probably proportional to duration and severity of hypoMg. Parenteral Mg replacement therapy is often mandatory, as in our case, but does not prevent from recurrent flares.

Conclusion: CPPD should not be mistaken for Crohn’s spondylarthropathy in patients with chronic longstanding watery diarrhea which could lead to hypoMg.

**Early-onset gout and progressive renal failure in two patients with uromodulin (UMOD) mutations**

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Background: Single gene mutations are rarely associated with clinical gout, although some composite phenotype should prompt genetic evaluation. Among these, pathogenic variants in UMOD gene are responsible for familial hyperuricemic juvenile nephropathy or medullary cystic kidney disease type 2.

Case presentation: Patient 1 is 28-year-old and reported recurrent acute episodes of mono or oligo-arthritis and inflammatory low back pain since 20 years of age. He had a positive family history for gout. Knee aspiration showed bloody synovial fluid with urate crystals. Laboratory findings revealed hyperuricemia, renal impairment and presence of HLA-B27. MRI of the sacrum showed left sided sacro-iliitis with erosions. There was no evidence of crystal deposit on DECT-scan. A biopsy of the sacro-iliac joint revealed no crystals and culture was sterile. Based on these findings, we made a diagnosis of HLA-B27 positive SpA as well as gout. In 2017, genetic analyses revealed a pathogenic mutation (p.Pro236Leu) in the UMOD gene. Patient 2 is a
32-year-old male presenting with acute episodes of gout since he was 20. At the age of 23, laboratory findings showed renal impairment and marked hyperuricemia. A kidney biopsy showed typical tubulo-interstitial nephritis. He had a positive family history for gout and renal failure. He was lost to follow-up and developed, eight years later, tophaceous gout with further worsening of renal function function (eGFR 30 ml/min/1.73 m²). Hands and feet radiographs showed juxta-articular bone erosions without joint space narrowing, DECT of the hands demonstrated uric acid deposition in the flexor tendon of the right 3rd digit and was clinically associated with a trigger finger. UMOD sequencing revealed a pathogenic heterozygote point mutation (p.Asp196Gly).

Conclusion: In patients presenting with early-onset gout, hypertension and/or progressive renal impairment, UMOD mutations, albeit rare, should be considered. Most of these patients progress to end-stage renal disease between the fourth and seventh decades of life, although penetrance and expressivity vary both between and within families. Autosomal dominant transmission of the disease has implications for family members and requires genetic counselling.

Gout outcomes in Switzerland: Data from the Basel gout cohort. A prospective single center Swiss cohort
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Objective: To analyse treatment and outcome of gout patients at a tertiary Swiss hospital.

Methods: Consecutive gout patients presenting between January 2013 and April 2017 at the University Hospital Basel were prospectively included. At inclusion and 3 and 12 months thereafter, gout specific parameters were recorded.

Results: 117 patients (98 men) with a mean age of 67.1 years (standard deviation, SD 15.2) were included. At the time of inclusion 73.6% of the patients presented with a flare. Tophi were detected in 24.6% and arthritis in 73.5% (n = 86) of the patients. From these 86 patients with arthritis the joint manifestation was oligo- or polyarticular in 35.5% of the patients. Frequent comorbidities were hypertension (72.2%), kidney disease (54.6%) and obesity (29.1% of the patients in 53.5 % of the patients. Frequent comorbidities were hypertension (72.2%), kidney disease (54.6%) and obesity (29.1% of the patients in 53.5% of the patients). Frequent comorbidities were hypertension (72.2%), kidney disease (54.6%) and obesity (29.1% of the patients in 53.5% of the patients). Frequent comorbidities were hypertension (72.2%), kidney disease (54.6%) and obesity (29.1% of the patients in 53.5% of the patients). Frequent comorbidities were hypertension (72.2%), kidney disease (54.6%) and obesity (29.1% of the patients in 53.5% of the patients).

Conclusion: At the 12 months FU 41.7% of the 48 presenting patients reported flare(s) during the preceding 9 months. 38.2% of the presenting patients achieved the SUA target (360 µmol/l) at the 3 months-FU and 57.1% at the 12 months-FU. The median dosage of allopurinol and febuxostat at the 12 months-FU were 200 (IQR 100, 300) and 80 (IQR 70, 80) mg/d, respectively. In 22 patients upitation or adaption of ULT was done over the 12-months-FU period.

Conclusions: Gout incidence peaks with age, flares are frequent and the SUA target is often not achieved. In gout patients careful but prompt upitation or adaption of ULT is mandatory to achieve the SUA target. In our cohort the management of ULT was suboptimal. Strategies to improve care in gout patients are needed. Better patient education and the broader introduction of guideline-oriented treatment might be solution approaches.
Objective and Methods: To summarise changes in absolute neutrophil counts (ANC), absolute lymphocyte counts (ALC), platelet counts, and haemoglobin (Hgb), and associated adverse events, with baricitinib and placebo treatment.

Methods: To summarise changes in absolute neutrophil counts (ANC), absolute lymphocyte counts (ALC), platelet counts, and haemoglobin (Hgb), and associated adverse events, with baricitinib and placebo treatment.

Results: BARI treatment was associated with a decrease in ANC and an increase in ALC and platelets, which stabilized and returned to baseline with prolonged treatment or treatment discontinuation. Neutropenia (<1000 cells/mm³) was rare (<1%) and was not associated with higher risk of overall or serious infections. Lymphopaenia was associated with slightly higher rate of overall infections. Incidence of overall and serious infections in ALL-BARI-RA set was 29.9 and 3.9 per 100 patient-years, respectively. More BARI 4-mg (2.3%) as compared to placebo-treated (1.3%) patients had platelet count ≥600x10⁹/L. In 6-study placebo-controlled set (0-24 weeks), 5 BARI 4-mg-treated patients (vs 0 placebo-treated) had "deep vein thrombosis" (DVT) and/or "pulmonary embolism" (PE). Incidence of overall and serious DVT/PE in ALL BARI-RA set remained low at 0.5 and 0.3 per 100 patient-years, respectively. The proportion of patients with high platelet levels (≥600x10⁹/L) was comparable between patients with DVT/PE vs those without DVT/PE (at baseline: 0 vs 0.5%; post-baseline: 6.5% vs 3.3%). With long-term BARI treatment, Hgb levels decreased transiently before returning to levels slightly higher than baseline at Week-52. Incidence of severe treatment-emergent shifts in Hgb (grade ≥3 to grade ≥5) was low across all treatment groups (<0.5%).

Conclusions: No associations were observed between ANC decrease and infections or thrombocytosis and DVT/PE. BARI treatment was not associated with an increased incidence of erythrocytosis-related events or anaemia as compared to placebo. Few patients interrupted/discontinued BARI due to TE laboratory abnormalities.
Comparative Effectiveness of Tocilizumab as Monotherapy Versus TNF inhibitors in Combination with Conventional Synthetic Disease Modifying Antirheumatic Drugs in Bio-naive Patients with Rheumatoid Arthritis

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Background: In randomised controlled trials, subcutaneous tocilizumab (TCZ sc) has been found non-inferior to intravenous TCZ (TCZ iv) for the treatment of rheumatoid arthritis (RA) patients. However, to our knowledge, there are no observational studies comparing these two different routes of administration in routine care.

Objective: To compare the real-world effectiveness of TCZ sc and TCZ iv in RA patients.

Methods: We included RA patients treated with TCZ from 8 European registries. We compared drug retention using Kaplan-Meier and Cox models. The proportions of patients achieving CDAI remission and low disease activity (LDA) at 1 year were compared using LUNDEX correction with comparison of confidence intervals by bootstrapping.

Results: 2896 patients were retrieved from the collaborative registries before January 2017, including 2469 TCZ iv and 427 TCZ sc. Baseline demographics were similar between both groups, but patients in the TCZ iv group had a more severe disease activity, with higher DAS28, CDAI, tender joint count (TJC), swollen joint count (SJC), and ESR.

Conclusion: In routine care across 10 European countries, the proportion of patients reaching CDAI low disease activity (LDA) and remission at 1 year were similar if treated with TCZ mono or TNFi combo. The proportions of patients reaching CDAI low disease activity (LDA) and remission after one year were adjusted for attrition with the LUNDEX index.

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Comparative effectiveness of subcutaneous versus intravenous tocilizumab in a pan-European collaboration of registries

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Comparison of clinical and ultrasound measures of disease activity in a large national ‘real life’ cohort of RA patients

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Background: Measures of disease activity, such as the clinical disease activity score (DAS) or ultrasound (US) scores can be sometimes yield discordant results. The objectives of this study were to determine the proportion of patients presenting discordances between a DAS and an US assessment in patients followed in a large national registry.

Methods: All patients with at least one concomitant US and DAS score assessment during 2 years in the Swiss registry for inflammatory arthritides (SCQM) were included. Disease activity was categorized as remission, low to moderate and high activity disease based on previously established cut-offs both for the DAS and the US scores. Discordance was operationally defined by differing disease activity states between clinical (DAS) and imaging (DAS) scores. A longitudinal analysis was performed in all the patients with at least two subsequent visits. Results: 2369 assessments were included, of which 1196 (50.4%) were found discordant. The proportion of discordant assessments did not differ significantly by the level of clinical disease activity or the level of US categories except more frequent (10%) in both high activity disease groups. Disease activity was equally frequently over-estimated by the clinical (DAS) and imaging (US) scores. A longitudinal analysis was performed in all the patients with at least two subsequent visits.

Results: 2369 assessments were included, of which 1196 (50.4%) were found discordant. The proportion of discordant assessments did not differ significantly by the level of clinical disease activity or the level of US categories except more frequent (10%) in both high activity disease groups. Disease activity was equally frequently over-estimated by the clinical (DAS) and imaging (US) scores. A longitudinal analysis was performed in all the patients with at least two subsequent visits.

Conclusion: Discordance between US and clinical data is frequent. However, they are of similar frequency regardless of disease activity level.
presence of tenosynovitis was the main US associated factor. For 1181 patients with sequential DAS and US assessments, the proportion of discordances during the follow up remained unchanged overtime. However initial discordances/concordances changed over-time in up to 30% of the cases.

Conclusion: Discordances between DAS and US assessments appear to be higher than expected in real life both. Both outcome measures can potentially over or under-estimate of the level of disease activity when compared to the alternative assessment modality.

SSRP 38

Only very high radiographic progression affects HAQ-DI scores, from the Swiss SCGM cohort

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Background: The aim of treatment of rheumatoid arthritis is to control disease activity and to inhibit joint damage. Progression of damage is analysed by conventional radiographs. High radiographic progression has, to our knowledge, not been analysed in detail.

Objectives: To analyse RA patients depending on their individual peak radiographic progression.

Methods: We selected for the highest (peak) radiographic progression in every individual patient of the Swiss registry SCGM with at least two scored sets of radiographs. The individual radiographic progression was analysed as change of Ratingen erosion scores/year (follow up 1998–2015). The baseline disease characteristics were compared using standard descriptive statistics (Kruskal-Wallis or chi square tests). The change of DAS 28 and HAQ-DI scores before and after peak progression were analysed with the Wilcoxon signed rank tests.

Results: Of the 4 033 patients in the analysis 3 049 patients had a peak radiographic progression rate between 0 and ≤10/year. 77.3 between 10 and ≤20, 150 between 20 and ≤30, and 61 of >30 (defining groups 1–4). Rheumatoid factor and ACPA were more frequent in patient groups with higher peak radiographic progression. Peak radiographic progression at a rate >20/year (groups 3 and 4) were not detected after December 2012. When the rate of radiographic progression before and after peak progression was analysed, 69.7%, 74.7%, 76.9%, and 93.3% of the patients had a peak progression of 25% lower as compared to peak progression before and after peak progression, respectively for patients in groups 1 to 4. The disease activity, as assessed by DAS 28, was significantly higher in all patient groups before peak progression and lower thereafter (p < 0.001). Average HAQ-DI scores increased after peak radiographic progression in group 4 (p = 0.005) whereas it is stable or even decreases among the patients of the other patient groups.

Conclusions: These data show that high radiographic progression is rare and gets last over the last years. Higher disease activity precedes radiographic peak progression. Radiographic progression before and after the individual peak radiographic progression was far lower as compared to the time of radiographic peak progression. Only the highest individual peak (change of Ratingen score >30/year) radiographic progression was followed by an increase of HAQ-DI scores.

SSRP 39

Managing checkpoint inhibitor induced inflammatory arthritis in metastatic melanoma

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Immune checkpoint inhibitors (ICI) have a major impact in the treatment of metastatic melanoma. Immune related adverse events (irAEs) may occur during immune checkpoint inhibitor therapy often causing ICI treatment interruption. Inflammatory arthritis (IA) is the most common rheumatologic irAE, clinically resembling a rheumatoid arthritis (RA) like disease. In contrast to RA however, treatment algorithms are not well defined. Furthermore, the most commonly used immunosuppressant’s such as systemic steroids, methotrexate (MTX) and TNF-alpha inhibitors have been controversially debated in reducing ICI efficacy and de novo melanoma occurrence. We describe two patients suffering from ICI induced grade 2 IA. In both patients, ICI treatment was withheld, systemic steroids administered (0.5 mg/kg/KG) and rapidly tapered. TNF-alpha inhibitor adalimumab (40 mg qw2) was initiated in one of two patients due to recurrent disease activity, leading to immediate symptom control. 2 months after withholding ICI therapy, treatment was successfully re-initiated in both patients. Current irAE management guidelines recommend withholding ICI in grade 2+ IA along with systemic steroid therapy interruption. If symptoms persist, achievement of aggressive steroid tapering, disease modifying anti rheumatic drugs (DMARD) such as MTX, leflunomide, TNF-alpha inhibitors and IL-6 receptor antagonists are recommended. However, no preferred sequence is defined. In metastatic melanoma, overall survival (OS) and response rate (RR) was not reduced through systemic steroid or infliximab treatment due to ICI induced irAE, encouraging the early use of systemic steroids in the management of irAE. MTX is considered the first line DMARD in RA. There are no data evaluating the effect of MTX on ICI induced melanoma patients. Despite the initially described role of TNF-alpha in tumor necrosis, recent data has not shown a significant increase in de novo melanoma occurrence upon TNF-alpha inhibition. Furthermore, TNF-alpha is suggested to be a mediator of ICI treatment resistance, ameliorated through TNF-alpha inhibition. In addition, TNF-alpha inhibitors, in contrast to MTX, provide immediate symptom control, allowing rapid re-initiation of ICI therapy, and may be beneficial in the treatment of ICI-induced IA.

SSRP 40

Classification criteria in Systemic-onset Juvenile Idiopathic Arthritis (SJIA): Evaluation of the Yamaguchi and ILAR ‘modified’ criteria in a SJIA population

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Introduction: Early diagnosis of systemic-onset juvenile idiopathic arthritis (SJIA) is crucial in order to avoid long-term complications. However, the existing International League of Associations for Rheumatology (ILAR) classification criteria for SJIA have been criticized. A substantial percentage of SJIA patients fail to fulfill them, mostly because of the absence of arthritis, or due to the exclusion criteria requiring radiographs of hands (≤30) and feet (≤61) when compared to the alternative assessment modality.

Objective: To evaluate the existing Yamaguchi and ILAR classification criteria as well as a new set of ILAR ‘modified’ criteria, in an international cohort of SJIA patients.

Methods: This is a multicentre, retrospective and inclusion cohort study, through the international platform JIRchopte. The existing ILAR classification criteria, a new set of modified ILAR classification not including HLAB27 testing and the Yamaguchi criteria were applied in SJIA patients followed in one of the participating centers in Switzerland, France, Belgium and Morocco. 50 SJIA patients with no more than one missing criteria in the database were enrolled (sex ratio 1:1) and compared to a control group of 46 patients with other systemic and articlar inflammatory diseases.

Results: Only 56% of SJIA patients enrolled (28/50) fulfilled the ILAR classification criteria for SJIA. Among the 22 patients who failed to fulfill the ILAR criteria, 4 (19%) had no arthritis, 9 (41%) had no other systemic manifestations than fever at diagnosis, 1 (5%) had family history of psoriasis, and in 8 patients (36%) HLAB27 testing has not been performed. ILAR ‘modified’ criteria identified 74% (37/50) of SJIA patients. Their sensitivity and specificity in the discrimination of SJIA patients from the control group were of 74% and 100% respectively, a Youden index of 0.74, and an area under the curve (AUC) of 0.95. ILAR ‘modified’ criteria identified 74% (37/50) of SJIA patients. Their sensitivity and specificity in the discrimination of SJIA patients from the control group were of 46% and 93% respectively, a Youden index of 0.39, and an AUC of 0.69.

Conclusion: A substantial percentage of SJIA patients (44%) failed to meet the ILAR classification criteria as well as a new set of ILAR ‘modified’ criteria, in an international cohort of SJIA patients. A substantial percentage of SJIA patients (44%) failed to meet the ILAR classification criteria as well as a new set of ILAR ‘modified’ criteria, in an international cohort of SJIA patients.

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Conclusion: A substantial percentage of SJIA patients (44%) failed to meet the existing ILAR criteria highlighting the need of new classification criteria to apply the ILAR classification criteria in our SJIA population was no more advantageous. However, ILAR ‘modified’ criteria had a better diagnostic value raising questions about the usefulness of HLAB27 testing in SJIA.
DISEASE EVOLUTION IN SYSTEMIC-ONSET JUVENILE IDIOPATHIC ARTHRITIS: PRELIMINARY DATA FROM JIRCHORTE

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Introduction: Systemic onset juvenile idiopathic arthritis (JIA) is a potentially severe disease with both systemic and joint inflammation; different evolutive forms were described (monophasic, polyphasic or persistent), but the outcome is hardly predictable at diagnosis. This study aims to identify early predictors of disease evolution within the JIA population enrolled in the Juvenile Inflammatory Rheumatism cohort (JIRChorte), an international prospective cohort study.

Methods: 152 JIA patients with a minimum of two-year follow-up were enrolled. 5 patients were excluded due to missing data on diagnostic visit. Demographics and clinical data were collected (retrospectively if diagnosis < 2015, prospectively if diagnosis ≥ 2015) and descriptively for 147 patients. At diagnosis, median age and disease duration was 5.3 years and 1.9 months, respectively, male to female ratio was 1.12. We present the preliminary results in 30 patients with complete data for disease activity and medication use.

Results: Corresponding to their evolution, patients were classified in the monophasic (n = 10; MONO), polyphasic (n = 14; POLY) or persistent group (n = 6; PER). Females were predominant in the MONO and POLY groups with 80% and 79%, respectively. No females were in the PER group. At diagnosis, all patients in the PER and POLY groups had arthritis; only 80% did in the MONO group. Hepatomegaly and splenomegaly was present in 30% and 50% of MONO patients versus 17% and 5% of PER patients, respectively. Joint count at first 6 months was ≥ 5 joints for 83% of the PER population compared to 30% for the MONO. Four patients in the MONO group (40%) did not have any biologics, whereas all patients from the other groups had one or more.

Conclusion: MONO pattern represents 30% in this series; thus, is comparable to the percentage of MONO evolution in adult-onset Still disease (AOSD). Polyrheumatisches during first 6 months is suggesting persistent disease evolution. In AOSD, arthritis at 6 months is associated with persistent disease evolution. Biologics, DMARDs and corticoids are more often and long given in the POLY groups correlating with a more severe disease course. Data are under completion for all 152 patients. Deep phenotypic analysis will be performed.

Rapid Response With Upadacitinib Treatment in Patients with Rheumatoid Arthritis and an Inadequate Response to csDMARDs or bDMARDs

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Background: Upadacinib (UPA), an oral selective JAK1 inhibitor, demonstrated efficacy in patients (pts) with moderate to severe rheumatoid arthritis (RA) with an inadequate response (IR) to csDMARDs or bDMARDs in the SELECT-NEXT & -BEYOND trials, respectively.

Purpose: To investigate speed of response to UPA across disease measures in csDMARD- & bDMARD-IR pts.

Methods: 66/461/498 pts in NEXT/BEYOND received UPA 15 or 30 mg once daily (QD) or placebo (PBO) for 12 weeks (wks). Time to first achievement of clinically meaningful outcomes was evaluated.

Cumulative incidences of ACR20/50, DAS28-CRP ≤ 3.2 & LDA by CDAI & SDAI over 12 wks were estimated. Hazard ratios, between UPA & PBO were obtained using Cox proportional hazards model with treatment group, corresponding baseline values & main stratification factors, without control for multiple comparisons. Observed data without imputation.

Results: Pts had disease duration of 7/13 years in NEXT/BEYOND respectively. In BEYOND, pts were treatment-refractory as evidenced by 53% having received ≥2 prior bDMARDs. Median times to achieve ACR20 were similar, irrespective of pt population, being 4 wks for UPA 15mg QD & 2–3 wks for UPA 30 mg QD vs 12 wks on PBO (p < .001).

Conclusion: Pts receiving UPA at either 15 or 30 mg QD were more likely to achieve clinical responses at significantly earlier time points when compared with PBO. Irrespective of being csDMARD-IR or bDMARD-IR, times to achieve various clinical responses were consistent between pt populations.

Discontinuation of biologic DMARDs in a real-life population of patients in remission: outcome and predictors

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Background: Data from clinical trials have shown that in RA patients in remission discontinuation of bDMARD therapy is possible. Criteria for selecting patients that will remain in remission after bDMARD discontinuation are not well defined.

Objectives: To assess loss of remission after withdrawal of bDMARDs in a real life setting and to identify predictors.

Methods: Adult RA patients in bDMARD-free remission from the Swiss clinical quality management in rheumatic diseases registry (SCQM) were included. bDMARD-free remission was defined as ≥ 12 months of the bDMARD and a DAS28 ≤ 2.6 at a clinical visit within 90 days prior to 30 days after the bDMARD withdrawal. Loss of remission was defined as a DAS28≥2.6 or a restart of a bDMARD. Kaplan-Meier methods were applied and cox regression was used for multivariable analyses (adjusted for sex, anti-CCP, RF, DAS28, bDMARD type, CDAI, DMAID co-therapy, number of previous bDMARDs). Missing data were imputed using multiple imputation.

Results: 518 patients achieved a bDMARD-free remission between 1997 and 2017. 241 patients lost remission (76%), 54% of those re-started a bDMARD, 34% experienced a DAS28 flare and 12% did both. The median time to loss of remission was 0.9 years (95% CI 0.7–1.0). 54% received MTX/leflunomide anytime during remission, 27% were in CDAI remission. Women lost remission faster than men (HR 1.5, p = 0.005); this was also seen in multivariable analysis (HR 1.5, p = 0.02). Remission was lost faster by patients with a longer disease duration, also in multivariable analysis (HR [4–8yrs] 1.6, p = 0.3, HR[9–13yrs] 1.6, p = 0.01, HR[>13 yrs] 1.5, p = 0.005, p = 0.035 vs 0–4 yrs). A trend for a faster loss of remission in patients with a higher disease activity by CDAI criteria at baseline was seen; this association was significant in multivariable analysis (HR [CDAI low disease activity] 1.5, p = 0.05, HR [CDAI moderate/high disease activity] 2.4, p = 0.003, both vs CDAI remission). Patients who received MTX/leflunomide during the observation period lost remission less rapidly (HR 0.7, p=0.006) also in multivariable analysis (HR 0.8, p = 0.05).

Conclusion: The majority of RA patients lost remission within less than a year after bDMARD discontinuation. Predictors included female sex, a higher CDAI score and absence of cDMARD therapy. This suggests that patients considered for bDMARD discontinuation should fulfill the more stringent CDAI criteria in order to maintain remission.
Improvement of cutaneous, ophthalmic, cardiac, pulmonary and renal disease after Rituximab, Macitentan and Mycophenolic acid in overlapping systemic sclerosis and lupus nephritis

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Background: Systemic sclerosis (SSc) rarely overlaps with systemic lupus erythematosus (SLE).

Case report: A 39-years-old Bolivian female patient presented in 2014 with arthralgia, dyspnea, blurred vision. She reported Raynaud phenomena since 6 years. The clinical exam showed diffuse cutaneous SSC with a modified Rodnan skin score (mRSS) of 23/51 and tendon friction rubs at wrists and ankles. Ophthalmologic investigations showed beaded, dilated veins, multiple cotton wool spots and retinal haemorrhages. Blood pressure was 172/112 mm Hg suggesting hypertensive renal crisis, which prompted the introduction of ACE-inhibitors. Investigations showed elevated ESR, glomerular microhematocrit, proteinuria (1 g/24h), complement consumption, positive anti-DNA and anti-SSA/B autoantibodies. Thoracic CT scan showed pulmonary ground glass opacities and pericardial effusion. Right heart catheterisation (RHC) showed pulmonary arterial hypertension (PAH). Renal biopsy showed a mesangio-proliferative glomerulonephritis with less than 50% of glomeruli, focal lymphocytic interstitial nephritis and arterial fibroelastosis, consistent with class IIIa lupus nephritis (LN). Low-dose prednisone was initiated in September 2014 and slowly tapered over the course of several months. Rituximab (RTX) and Macitentan were given in spring 2014 for LN and PAH, respectively. Ten weeks later, dyspnea improved. 6-minutes walking test and RHC confirmed the favorable response. Macular edema resolved. Proteinuria decreased to 0.5 g/24h. Mycophenolic acid was added to the regimen. RTX was administered again in fall 2016. By the end of 2016, mRSS score was 12/51. RHC showed normal cardiac output at rest and normal pulmonary pressures and wedge values at rest and during stress.

Conclusions: Our patient fulfilled all ACR 2013 criteria for SSc and 1997 ACR and SLICC criteria for SLE. She had positive antibodies against U1-RNP, consistent with mixed connective tissue disease. However, the concomitant presence of anti-ScI70 and anti-Sm autoantibodies was in favor of SSC overlapping with SLE. Our patient showed impressive improvement of her cutaneous, ophthalmic, cardiac, pulmonary interstitial, vascular and renal disease after RTX treatment in conjunction with Macitentan and Mycophenolic acid. This suggests that the association of these therapeutic agents may have reversed a severe clinical presentation associating many if not all predictors of SSC unfavorable prognosis.

Is it Takayasu’s arteritis: Autoimmune or infective?

Evidence from Angiographic patterns in Sri Lanka

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Background: Takayasu’s arteritis is a chronic vasculitis with probable immunological origin, involving large and medium size arteries. It is a rare disease with young females being predominantly affected. Cardiovascular imaging plays a major role in its diagnosis. In areas where the Tuberculosis is prevalent, Tuberculous arteritis seems to have a clinical, radiological and biochemical picture similar to Takayasu’s arteritis.

Objectives: The objective of this study was to find out the angiographic patterns of Takayasu’s arteritis in Sri Lankans; according to the anatomical distribution of the disease and types of vascular lesions in angiography, and thereby to find out evidence towards the etiology of the disease.

Methodology: 16 patients were included. Angiographic patterns were identified according to the “International TA conference in Tokyo 1994 angioarchitectural classification”. Type 1: Branches of the aortic arch, Type 2a: Ascending aorta, arch and its branches, Type 2b: 2a + Descending aorta, Type 3: Descending aorta, Abdominal aorta and/or renal arteries, Type 4: Abdominal aorta and/or renal arteries, Type 5: Entire aorta and branches.

Results: 2 patients were excluded from the study as they had evidence of Tuberculous arteritis. Out of 14 patients who were included in the analysis, 12 patients were young females and 2 patients were young males. 10/14 (71%) patients had only stenotic lesions; 4/14 (28%) patients had only fibrinolytic and dilated lesions. 6/14 (43%) patients had type 1 disease. 8/14 (57%) patients had a combination of two types (Type 1 + 3 in 6 patients and Type 1 + 4 in 2 patient).

Conclusion: Angiographic pattern of the disease in Sri Lanka seems to be different from the known patterns worldwide. Therefore Tuberculous arteritis should be considered as an important differential diagnostic for Takayasu’s arteritis in Sri Lanka as the differentiation between the two diseases has a significant impact on management.
Early Versus Late Administration of Icatibant in Patients With Hereditary Angioedema

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Introduction: The relationship of the timing of icatibant self-treatment to demographic and treated attack characteristics for patients with hereditary angioedema due to C1-inhibitor deficiency are poorly understood.

Methods: The Icatibant Outcome Survey (IOS, NCT01034969) is an ongoing, international, prospective, observational study designed to monitor the safety and effectiveness of icatibant treatment in the real-world setting. IOS data from patients in 11 countries were used to evaluate early versus late icatibant self-treatment (patients with median time-to-first injection <1hr versus ≥1hr from attack onset, respectively).

Results: Of 301 patients analyzed, 119 (39.5%) had median time-to-first injection <1hr (median [Q1,Q3] for 829 icatibant-treated attacks, 0.3h [0.0, 0.6]) with no difference observed between early and late treating groups when comparing males and females, Early self-treatment varied across countries, ranging from 79.1% (Greece) to 11.1% (France). Early treaters vs late treaters treated attacks localized to skin, abdomen and larynx at a similar rate (P = 0.814, P = 0.506, P = 0.862 respectively). No statistically significant difference between early vs late treater groups was observed based on pooled-attack severity (very mild/mild/moderate vs severe/very severe; P = 0.135). Comparing early versus late treatment, respectively, a significantly shorter (P <0.001) median (Q1,Q3) time to resolution (4.2hrs (1.0, 10.0) versus 9hrs (3.5, 24.3)) and median (Q1,Q3) attack duration (5hrs (15, 110) versus 14.7hrs (6.5, 33.0)) was observed (269 patients; 1693 attacks with complete information on time to treatment, time to resolution and duration of attack).

Conclusions: Early treaters had significantly shorter time to resolution and attack duration compared to late treaters, indicating the importance of early use of icatibant during attack development. In local practice patterns, icatibant availability, and tendency of early treaters to treat any symptoms without delay may drive prevalence of early use across countries.

ILC3 NCR+ regulate endothelial cell activation through NF-κB

Vanonzi Giulia, Romero Pedro, Trabanelli Sara, Jandus Camilla

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Although CD8 T cells have been the main targets of cancer immunotherapy thus far, CD4 T cells are known to play a key role in antitumor immunity. Tumor-infiltrating Th1 polarized CD4 T cells have been associated with good prognosis in numerous cancer types, while Th2, Th17 and regulatory polarization-skewing has been linked with poor prognosis. Using HLA class II multimers, we were able to detect tumor antigen-specific CD4 T cells in blood and tissue samples of cancer patients, either after in vitro expansion or even directly ex-vivo. Phenotypic and functional characterization of these cells, show that they are able of exerting a direct cytotoxic activity against tumors. We are thus investigating the possible factors that are involved in promoting and sustaining their cytotoxic potential. As part of this endeavour, we are optimizing in vitro strategies to favour cytotoxic functions in tumor antigen-specific CD4 T cells, with a view to exploit these cells for innovative immunotherapy strategies.

Low compliance for allergen immunotherapy in a tertiary center, a retrospective study

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INTRODUCTION: Allergic rhinoconjunctivitis affects between 10% and 30% of the population, and studies indicate that prevalence rates are increasing worldwide. Allergen immunotherapy (AIT) is a recommended therapeutic option for patients with moderate to severe allergic rhinitis with or without mild to moderate asthma due to inhalant allergens. AIT is considered a disease modifying treatment and should be performed for at least 3 years. However, many patients stop prematurely and therefore are nonadherent.

METHODS: We performed a retrospective monocentric chart review study of all patients undergoing AIT at our division from 2005 to 2012 with follow-up until 2015. Patients over 16 years of age diagnosed with moderate to severe allergic rhinitis with or without mild to moderate asthma to inhalant allergens were included. The characteristics and the type of allergen immunotherapy were compared between the groups of adherent and non-adherent patients.

RESULTS: 100 patients were identified of whom 21 were lost to follow-up. All our patients on sublingual AIT were started after 2013 and therefore not included in the analysis. The 79 remaining patients were on subcutaneous AIT, 69 (87%) were adherent in the first year. Between the first and second year, 61 (77%) patients remained on therapy, whereas only 28 (35%) performed the treatment for at least 2 years.
3 years. In total 32 men and 47 women were followed. The mean age was 35 years (range 16–63 years). No difference was observed in the groups regarding gender. Adherence to AIT was higher in the age group 41–65 years (44%) compared to the group 20–40 years (35%), and the group 16–19 years (18%). Asthma was associated more with adherence (66%) compared to the non Asthma group (51%).

**DISCUSSION:** We observed a low adherence to AIT as previously reported in other real-life studies for chronic diseases, such as for epilepsy, diabetes, arterial hypertension or asthma. Not all data were available in the patient records. Documentation of co-morbidities and side effects were missing, therefore not all confounding data were identified to explain low adherence.

**CONCLUSION:** In conclusion, allergen immunotherapy in real life is characterized by a strikingly low level of compliance and persistence. Additional investigations are needed to better understand the causative reasons for AIT non-adherence in order to implement interventions for improvement.

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**Successful desensitization with temozolomide in a patient with DRESS**

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We report the case of a 61 year old patient with a metastasized uveal melanoma. The patient was treated with Temozolomide, after being unresponsive on a combination therapy with Ipilimumab and Nivolumab. After starting the fourth cycle with Temozolomide the patient developed a drug rash with eosinophilia and systemic symptoms (DRESS) and therefore the treatment with temozolomide had to be interrupted. Skin prick testing and patch testing were not performed as the negative and positive predictive values of these tests with temozolomide are unknown. We performed a Lymphocyte Transformation Test, but the test could not be clearly evaluated. As the patient had no other good possibilities of treatment and for the melanoma and because he had a mixed response to temozolomide, it was decided to try a desensitization. The patient received a pretreatment with Montelukast 10 mg, Levocetirizine 5 mg and Prednisolone 50 mg daily, starting 3 days before the cycle with temozolomide. The desensitization was performed intravenous on the first day. Temozolomide dilution was made in water, starting with a concentration of 0.0152 mg/ml, increasing the dose over 4 hours to a cumulative dose of 380 mg. The patient was monitored by a dose-administering doctor and nurse. After starting the desensitization the patient developed a generalized flush with some pruritus, the laboratory results showed no signs of a severe drug reaction like eosinophilia or increased liver enzymes and the patient was in a good general condition. The next day, the skin already was better, the patient felt well and the desensitization could be continued with oral Temozolomide, starting with 5 mg, going up every 30 minutes to 360 mg cumulative. There was no reaction to this additional dose. The patient could leave the hospital 3 days later and the 5 days cycle with Temozolomide could be continued as planned, going on with a concomitant medication of oral Prednisolone, Levocetirizine and topical steroids. In the literature there is nothing clearly known regarding the mechanisms of delayed hypersensitivity reactions provoked by Temozolomide, but the success of our desensitization protocol is in alignment with other reports of successful desensitization in such cases. In cancers with a paucity of therapeutic options, the ability to induce tolerability to drugs like Temozolomide can be a valuable addition in the management of these patients.

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**IgA triggers cell death of neutrophils when primed by inflammatory mediators**

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Intravenous immunoglobulin (IVIG) preparations consisting of pooled IgA are increasingly used for the treatment of autoimmune diseases. IVIG is known to regulate the viability of immune cells, including neutrophils. We report that plasma-derived IgA efficiently triggers death of neutrophils primed by cytokines or toll-like receptor (TLR) agonists. IgA-mediated programmed neutrophil death was PI3K-, JNK- and MAPK p38-dependent and evoked anti-inflammatory cytokines in macrophage co-cultures. Neutrophils from patients with acute Crohn's disease, rheumatoid arthritis, or sepsis, were susceptible to both IgA- or IVIG-mediated death. In contrast to IVIG, IgA did not promote cell death of quiescent neutrophils. Our findings suggest that plasma-derived IgA may provide a new treatment option for the treatment of neutrophil-associated inflammatory disorders. In light of its selective efficacy in activated cells, IgA may have advantages compared to other neutrophil-targeting agents in patient subpopulations at risk of neutropenia.

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**PD-1 blockade improves the immune control of low affinity antigen expressing tumors after high affinity CD8+ T cell peripheral priming**

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Therapeutic vaccination may be the next step in successful immunotherapy. However, by virtue of triggering T cell infiltration of tumors and render them sensitive to immune checkpoint blockade. The T cell-defined antigen is the central component in therapeutic cancer vaccines. While neangitgens formed from individual non-synonymous somatic mutations in tumors can be potentially recognized by high affinity T cells, the majority of shared tumor antigen-specific T cells bear receptors of low affinity as a result of central tolerance. Thus, immunotherapy relies often on an effective engagement of low affinity T-cells. We found that TCR affinity during peripheral priming and in the tumor microenvironment determines the CTL response to shared tumor antigenic ligands expressing tumors. Moreover, low affinity antigen recognition in tumors leads to decreased co-inhibitory receptors expression and increased cytokine production upon specific T cell restimulation. Interestingly, however, tumor infiltrating CD8+ T-cells, regardless of the affinity for the tumor ligand, show in vivo re-expansion capacity similar to that of their counterparts retrieved from secondary lymphoid organs when transferred to tumor-free hosts. This suggests that T-cells in tumors may be rekindled upon relief of tumor immunosuppression. Notably, our results show that aPD-1 treatment enhances tumor control of both high- and low affinity-ligand expressing tumors. Together, these findings suggest that a combination of high affinity peripheral priming by altered peptide ligands of shared tumor antigens and checkpoint blockade may enable effective tumor control upon low affinity antigen recognition in the tumor.
Wells Syndrome successfully treated with omalizumab

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INTRODUCTION: Eosinophilic cellulitis, also called Wells Syndrome, is a rare disease without typical clinical presentation. Histological features are dependant of different disease stages, but dermal edema, marked eosinophilic infiltrate without signs of vasculitis, and flame figures are characteristic.

METHODS: We describe the case of a 66-year-old man with history of recurrent cutaneous erythema with important swellings associated with edema of the limbs, tongue and face since 30 years. Laboratory tests were within normal range with normal tryptase, and a normal CT-scan of thorax and abdomen. No trigger factor could be identified. Autoimmune testing was normal. Infectious tests were excluded. Skin biopsy revealed a dense dermal perivascular and interstitial lymphocytic and histiocytic inflammatory infiltrate associated with many eosinophils with flame figures compatible with Wells Syndrome. He was treated with antihistamines, topical and systemic corticosteroids, azathioprine, tranexamic acid, gluten free diet without any success. His skin symptoms persisted despite a Helicobacter pylori eradication. The patient shows-up 6 years later. At this moment, a new skin biopsy shows a dermal perivascular and interstitial lymphocytic, histiocytic and eosinophilic infiltrate with some multinucleate giant cells forming typical flame figures. Finally, omalizumab 300 mg per month was started successfully.

RESULTS: The patient felt a dramatic improvement of his skin symptoms after a few days and remained asymptomatic under omalizumab during a follow-up of one year.

DISCUSSION: The pathogenesis of Wells syndrome is unknown and often this syndrome is associated with different therapeutic responses. First line treatments include topical and/or systemic corticosteroids. If the disease recurs, alternative immunosuppressive therapies can be considered. The variability of therapeutic responses in Wells syndrome might be an expression of a heterogeneous group of disorders.

CONCLUSION: This is the first report of a Wells Syndrome successfully treated with omalizumab. The favorable response to omalizumab might be explained by a down-regulation of FcεRI expression on basophils, mast cells and eosinophils.
C1-INH or androgens previously. Treatment with SHP616 reduced attack frequency throughout the study period. Least square means of NNA were reduced from 3.9 with placebo to 1.6 with SHP616 from Day 1 (p < 0.0001; median percent reduction 79%), and from 3.8 with placebo to 1.5 with SHP616 from Day 15 (median percent reduction 85%). Most subjects (78%) had ≥50% NNA reduction with SHP616 (from Day 1), and 38% were attack free (vs 9% with placebo) throughout the 14-week period. Treatment emergent adverse event (TEAE) rates were similar between treatment groups (52% vs. 56% for SHP616 cross-group vs. placebo, respectively). Only 13% of subjects experienced TEAEs within 24 h post SHP616. No treatment-related serious or severe TEAEs occurred and no anti-C1 INH antibodies were detected.

Conclusion: Fixed-dose 2000 IU SC SHP616 was superior to placebo in preventing HAE attacks and demonstrated a favorable safety profile.

**Background:** Interleukin-17A (IL-17A) is increased in systemic sclerosis (SSc) skin and other organs. However, its role in SSc physiopathology is debated.

**Material and Methods:** Primary human dermal fibroblasts from SSc patients and healthy donors (HD) were cultured in the presence of IL-17A, TGF-β and TGF-β inhibitors (SB203580, PD169316; (LY294002), p38 MAPK (SB203580), MEK1/2 (U-0126), TGF-βRI (SD 208) or JNK (SP600125). IL-6 and type I collagen (col-I) levels were measured in culture supernatant by ELISA. Phosphorylation of p38, IkBα, pERK and pTGF-βRI was analyzed using Western Blot.

**Results:** We observed that IL-17A or TGF-β stimulated production of IL-6 by 8- to 16-fold in dermal fibroblasts, when compared to control cells. However, the joint presence of IL-17A and TGF-β resulted in robustly exuberant fibroblast responses with levels of IL-6 up to 100-folds higher than those observed in untreated cells. Inhibition of NFκB by TPCA-1 preferentially inhibited IL-17A-driven IL-6 production, while inhibition of PI3K by LY294002 preferentially inhibited the production of IL-6 driven by TGF-β. Interestingly, when p38 MAPK was inhibited by SB203580, substantial inhibition of IL-6 production was observed for both IL-17A and TGF-β. Consistently with the inhibition experiments, the combined stimulation of fibroblasts by IL-17A and TGF-β resulted in 18-fold increase in p38 MAPK phosphorylation (p = 0.025), when compared to levels of phosphorylated p38 MAPK induced by IL-17A alone. Furthermore, the enhanced phosphorylation of p38 MAPK in the joint presence of IL-17A and TGF-β was unique among the signaling molecules we examined. The canonical signaling pathway of TGF-β leads to SMAD2 phosphorylation and col-I production. However, in fibroblasts cultured in the joint presence of TGF-β and IL-17A, the phosphorylation of SMAD2 decreased by 0.6-folds when compared to that induced by TGF-β alone (p = 0.017). Remarkably, in this culture condition the production of col-I decreased by 10-20%.

**Conclusions:** Overall, we show for the first time synergistic activity of IL-17A and TGF-β for the production of IL-6 by dermal fibroblasts. This effect depended, at least in part, on p38 MAPK signaling pathway. Furthermore, we report an inhibitory role of IL-17A on TGF-β-mediated col-I production. The implications of these data are far reaching, particularly in terms of therapeutic approaches in SSc, since IL-6, IL-17A and TGF-β are putative targets in SSc treatment.

**Analysis of the cyclooxygenase (COX) pathway in different types of melanoma**

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Immunosuppression is a well-known feature that is common in the tumor microenvironment of almost all types of tumors. However, the cellular origins as well as mechanisms that are driving this immunosuppression are not yet well understood. Metabolically, the most striking differences in melanoma are a reduction of folate and vitamin B12. Microbiological workup, including a large search of virus, bacteria and fungi, was negative except for a SCID patient with RAG2 mutation: a case of immune deficiency after hematopoietic stem cell transplantation (HSCT). IRIS can rarely affect the central nervous system (CNS) and, in those cases, is associated with poor outcome and high mortality. We describe a case of CNS IRIS after HSCT in an infant with severe combined immunodeficiency (SCID).

**Case report:** An 11-months girl, known for a RAG2 deficiency, developed 3 months after haploidentical HSCT, a progressive severe axial hypotonia, limb hypertonia, loss of eye contact and apathy, associated with fever and raise of CRP. CSF was normal. Brain MRI showed hyper-intense signals in the basal ganglia, thalamus and periventricular white matter. Metabolomic workup showed a specific reduction of folate and vitamin B12. Microbiological workup, including a large search of virus, bacteria and fungi, was negative except for an unspecific neurological and MRI picture, associated with fever and raise of CRP. CSF was normal. Brain MRI showed hyper-intense signals in the basal ganglia, thalamus and periventricular white matter. Metabolomic workup showed a specific reduction of folate and vitamin B12. Microbiological workup, including a large search of virus, bacteria and fungi, was negative except for

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Analysis of miRNA involvement in CD4+T cell differentiation

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Introduction: In contrast to CD8+ T cell, CD4+ T have only recently gained increasing importance in tumor immunity as studies showed their therapeutic relevance, including the recognition of neo-antigens. A key to CD4+ T cell usage in immunotherapy will depend on a better understanding of the regulation of CD4+ T cell differentiation, to promote stem cell memory (SCM) and central memory (CM) phenotypes.

Material and methods: We performed a mRNA sequencing and a microRNA (miR) array of highly-pure sorted naïve (N), SCM, CM and effector memory (EM) CD4+ T cell subsets from peripheral blood of 4 healthy donors, followed by in depth Bioinformatic analysis and in vitro target validation.

Results: We identified differential expression between N, SCM, CM and EM cells of known miR such as miR-146a-5p and miR-155-5p and of previously undescribed miR. Further investigations in additional healthy donors confirmed by qPCR the differentially expressed miR. Further, we were able to correlate the expression of candidate miRs with up or downregulation of target genes within the CD4+ T cell subset of interest.

Conclusion: We are presently investigating miR and target mRNA expression in vitro and in vivo using TCR transgenic mouse models. We aim at identifying optimal miR candidates that could be therapeutically targeted to influence the differentiation of a Naïve CD4+ T cells into SCM or CM CD4+ T cells capable of targeting tumor cells.

Lanadelumab Markedly Improves Health-related Quality of Life in Hereditary Angioedema Patients in the HELP Study

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Rationale: Treatment with lanadelumab significantly reduced the rate of attacks in patients with hereditary angioedema (HAE) in the HELP Study. Health-related quality-of-life (HRQoL) was assessed using the Angioedema Quality-of-Life (AE-QoL) questionnaire; a validated, angioedema-specific instrument to measure impairment in HRQoL.

Methods: The HELP Study was a phase 3, randomized, double-blind, placebo-controlled study in patients with symptomatic HAE type I/II. Patients received lanadelumab 150mg q4wks (n = 28), 300mg q4wks (n = 29), 300mg q2wks (n = 27) or placebo (n = 41), for 26 weeks. The AE-QoL was administered monthly; total and domain (functioning, fatigue/mood, fear/shame, and nutrition) scores were calculated. The difference in scores from Day 0-182 was compared for placebo and the pooled and separate lanadelumab groups. Responder rates were determined by use of the 3 AE-QoLs minimal clinically important difference (MCID = 6).

Results: The pooled lanadelumab group demonstrated a significantly greater reduction in total and domain AE-QoL scores, relative to placebo (p ≤0.01 for largest decrements). Lanadelumab impairment was observed in the functioning domain with a mean (SD) change of −29.28 (22.88) for the pooled lanadelumab group vs −5.41 (22.92) for placebo (p <0.01). A significantly higher proportion of patients in the pooled lanadelumab group achieved MCID in total score (70% vs 37% for placebo, p = 0.001). Lanadelumab-treated patients were 2.9 (300 mg q4wks), 3.2 (150 mg q4wks) and 7.2 (300 mg q2wks) times more likely to achieve the MCID in total scores, compared with placebo, as assessed by regression analyses.

Conclusion: HAE patients treated with lanadelumab experienced a clinically meaningful, and statistically significant, improvement in HRQoL.

Lanadelumab for prevention of attacks in hereditary angioedema: results from the Phase 3 HELP Study

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Introduction: Lanadelumab is a highly-specific recombinant, fully human monoclonal antibody targeting plasma kallikrein. The HELP Study was a phase 3, randomized, double-blind, placebo-controlled, parallel arm, multi-center Phase 3 trial, investigated the efficacy and safety of lanadelumab for long-term prophylaxis against angioedema attacks in hereditary angioedema (HAE).

Methods: Patients ≥12 yrs old with type I/II HAE and ≥1 attack during a 4-week run-in (baseline) received subcutaneous lanadelumab 150 mg q4wks, 300 mg q4wks, 300 mg q2wks, or placebo over 182 days (26 weeks). The primary endpoint was the number of attacks over the 26-week treatment period. Secondary endpoints included the number of attacks requiring prompt medical attention, and the number of moderate or severe attacks during the treatment period. Endpoints following treatment with lanadelumab were compared to placebo using a Poisson regression model accounting for potential overdispersion; treatment group and baseline attack rate were fixed effects and the logarithm of time (days) each patient was observed during the treatment period was an offset variable. Safety included AEs, laboratory, and ECG assessments.
Psoriasis is a chronic skin inflammatory disease that affects 2% of the population. Recent studies have identified the IL-23/IL-17A/IL-22 pathway as a key player in the development of psoriasis. In our laboratory, we have developed several biologics targeting this pathway, which have shown promise in initial clinical trials. These findings spurred our interest in investigating the role of IL-2 beyond its established role in autoimmune diseases. Low-dose interleukin-2 for the treatment of system lupus erythematosus – the Charact-IL-2 trial

**Introduction:** Amongst Northern Europeans, systemic lupus erythematosus (SLE) is regarded as an autoimmune disease affecting around 40 in 100,000 persons. Although the loss of self-tolerance by B cells with the production of antibodies directed against nuclear self-antigens is considered a key pathogenic mechanism, contemporary evidence suggests a major contribution by other innate and adaptive immune cells. Regulatory T (Treg) cells are pivotal in maintaining peripheral tolerance to self-antigens. A recent report associated Treg dysfunction in SLE with interleukin-2 (IL-2) deficiency, which could be corrected by administering low doses of IL-2. These findings spurred our interest in investigating the role of IL-2 beyond its effects on Treg cells within the framework of a new open-label phase II investigator-initiated clinical trial, termed Charact-IL-2 (ClinicalTrials.gov identifier NCT03312335).

**Trial design and endpoints:** Over a 10-week intervention period, SLE patients will receive every 3 weeks, subcutaneous 5-day courses of daily 1.5 million international units of recombinant IL-2 (Proleukin®), for a total of 4 treatment courses. Peripheral blood will be collected before and after each treatment cycle. A treatment course for detailed phenotypic characterization of innate and adaptive immune cells by using 28 color flow cytometry. In addition, we will analyze serum samples for selected parameters including autoantibodies, immunoglobulins, complement factors, cytokines and soluble cytokine receptors. Clinical response will be assessed after two treatment courses and after completion of the intervention period using validated scores (SELENA-SLEDAI and BILAG-2004). The primary endpoint will compare percentages of Treg cells within total CD4+ T cells between baseline and after completion of the last treatment course. We aim to recruit 12 SLE patients and expect to complete the trial by the second half of 2019.

**Significance and outlook:** The current mainstay of treatments for SLE and other autoimmune diseases is based on immunosuppression, which often results in insufficient disease control and multiple adverse effects, demonstrating the need for novel treatment approaches. Treatment with low-dose IL-2 has shown promising results, and it is not completely clear if the therapeutic effect is solely due to Treg cells. Charact-IL-2 will provide a basis for future clinical trials testing improved IL-2 formulations, which have been recently developed in our laboratory.

**Phenotypic variability in a family carrying a novel germline STAT3 mutation**


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**Introduction:** The transcription factor signal transducer and activator of transcription 3 (STAT3) is a critical regulator of multiple cellular processes. Germline, gain-of-function (GOF) mutations in STAT3 have been shown to result in early-onset multi-organ autoimmunity, autoimmune lymphoproliferative syndrome (ALPS) phenotypes and immunodeficiency polyendocrinopathy enteropathy X-linked (IPEX)-like disorders.

**Objectives:** We describe a novel STAT3 mutation, with a probable GOF effect, underlining the broad spectrum of STAT3-associated disorders. We describe a novel germline STAT3 mutation, with a probable GOF effect leading to the IPEX-like disease These results suggest a functional redundancy of the IL-23-blocking antibodies, suggesting the involvement of additional pathways. Using a well-established model of psoriasis, we found that BALB/c mice, unlike C57BL/6J mice, develop psoriasis independently of the IL-23 axis. While abolagizing psoriasis in C57BL/6J mice, neutralization of IL-23p19 did not affect disease development in BALB/c mice. However, neutralization of both IL-23 and IL-12 using an anti-p40 antibody abrogated psoriasis in C57BL/6J and BALB/c mice. Moreover, IL-17A and IL-22-deficiency on the BALB/c background did not affect psoriasis development. Similarly, also the absence of IFNγR had no impact on disease. These results suggest a functional redundancy of the IL-23 and IL-12 pathways in the development of psoriasis in BALB/c mice with possible implications for the treatment of psoriasis in humans.
Case report: A 14-year old boy, treated with amoxicillin/clavulanic acid for suspected skin infection at an insect sting site, developed a maculopapular rash on the sixth day of treatment several hours after the last drug intake. During an oral, not fractionated provocation test 5 weeks later in the practitioner’s office, he tolerated the first dose of amoxicillin and reacted with a maculopapular rash within 1h after the second dose at home. Six month after the initial reaction we performed patch tests with amoxicillin and cefuroxime, with negative results. During a following oral provocation with cefuroxime the patient reacted with a macular, heavily itching rash starting just one hour after the initial dose. No elevation of tryptase could be found 1 hour after the initial symptoms had started. We performed a skin prick test (SPT), basophil activation test (BAT) and lymphocyte transformation test (LTT) with amoxicillin and cefuroxime six weeks later with a negative result for SPT and BAT and a positive result for both drugs in the LTT. Thus we could diagnose a non-immune type allergy to amoxicillin and cefuroxime.

Discussion: By definition immediate type allergy starts within the first hour after drug administration and is IgE mediated, while non-immune reactions start with a delay of more than one hour and can be T-cell dependent. In non-immune allergy crossreactivity between penicillins and cephalosporins is a rare condition in T-cell mediated, non-immune allergy, it occurs, even in drugs with different side chains. The time interval between drug administration and allergic reaction can be just hours. Though crossreactivity between penicillins and cephalosporins is a rare condition in T-cell mediated, non-immune allergy, it occurs, even in drugs with different side chains. The time interval between drug administration and allergic reaction can be just one hour in T-cell mediated betalactam allergy, mimicking an IgE mediated mechanism.

Background: Between 2006 and 2013, 3090 patients (63% F, 37% M) referred for allergy investigations were after their informed consent included in this study. 63% complained of recurrent or chronic allergy-like respiratory problems. Methods: Serum IgE, IgA, IgM, IgG and IgG sub-classes were analysed in all patients by nephelometry. Patients were distributed in 8 groups according to their age [adults [18-90+ years old], ch children [1-17 years old], their complaints at entry [W all respiratory allergy, respiratory allergy atopics VA, non atopics XA, X respiratory allergy with recurrent infections, XA atopics, XNA non atopics] and their total IgE [A atopics IgE >100, NA IgE <100]. Results: The data of 2244 adults (73% F, 27% M) and 844 children (43% F, 57% M) were usable. X = 1486 patients = 63% of all V patients complained also of recurrent infections, Xad 83% , Xch 62%. Only 40% of all adults VAad (683 patients) were found to be atopic, of which 53% were XAad. Among NAad, 71% were XNAad. In children, 59% of VACH (520 patients) were XACH, whereas among VNACh (343 children) >87% were XNACH. VAad and XAad differed from VNAad and XNAad by higher IgG2 ratio, and less IgG4 deficiencies than in VNAad and XNAad. IgA deficiency was found in 23% and 26% of VACH and XACH, and in 53% and 48% of VNACh and XNACH, b in s 3.1 in all adults group. Decrease of IgG1 was observed in 15% of XAad and XNAd and in 50% and 48% of VNAad and XNACH. In adults decreased IgG2 levels is observed only in 2.2 to 5.4% and increased IgG2 in respectively 95% and 19% of VAad and VNAad, while it is observed only in 1% and 1.3% of XAad and XNAd and is not present in any of the children patients.

Conclusion: Patients with respiratory allergies with or without recurrent infections have distinct humoral endotypes. Different treatment strategies should be therefore adapted for each patients, in particular in children.

SSAIPT 28

Atopic adults and atopic children are two different non homogeneous populations with distinct humoral immune endotypes

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Background: Atopics [AP] are allergic patients with elevated IgE and/or a familial trait.

Methods: Serum IgE, IgA, IgM, IgG and IgG sub-classes (evaluated by nephelometry) of 4700 new patients investigated for allergic symptoms between 2003 and 2013 were compared. All patients gave their informed consent for the use of their sera and clinical data. Adults (18-90+): 3385 (68% F, 32% M), children (0-17): 1315 (44% F, 56% M).

Results: Atopic [AP] patients were identified in 32.2% (61% F, 39% M) of the patients. IgE >100 KU/L were identified in 4.6% (4% children) of the patients [APch]. IgA abnormalities were observed in 28% of APad and 25% [IgA 2.5%], IgG 3.1% and in 44.9% of APch [IgA 13.5%, IgG 31.5%]. Increased total IgG was found 16% of APad but in only 6.7% of APch; decreased total IgG was observed in 59% of the patients [APch]. An abnormal ratio of IgG1/IgG2 associated clinically with inflammatory symptoms was observed in 71.7% of APad (IgG1/IgG2 ≥ 2.5 : 27%; IgG1/IgG2 ≤ 1.5 : 44.9%) and in 63.1% of APch but with an inverted pattern: IgG1/IgG2 ≥ 2.5 : 76.4%; IgG1/IgG2 ≤ 1.5 : 67.7%. In APad these dysbalances were related more to a relative excess of IgG1 than to a real lack of IgG2, observed in only 2.4% of adults. Abnormally increased amounts of IgG2 were found in 7.9% of APad but were not seen in APch. Low values of IgG2 were however observed in 25.8% of APch. IgG4 abnormalities were observed equally both in APad and in APch (41.7%). Low or absence of IgG4 was found 11.0% of APad and in 17.0% of APch. High amounts of IgG4 were measured in respectively 30.7% and 24.7% of APad and APch.

Conclusion: Dysbalances in humoral immunity is not infrequent both in adults and children. They are different in children which presents frequently low IgG2 and IgA values. Those differences in phenotype account most probably for the sometime poor response observed with classic drug treatment and/or immunotherapy in allergic adult as well as in allergic children.
**SSAIPT 31**

Functional characterization of two novel serine protease inhibitors able to block CD44-triggered necroptosis in GM-CSF-primed neutrophils

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The most common form of neutrophil death is apoptosis under both physiological and inflammatory conditions. However, neutrophil necroptosis has also been described, which is dependent on receptor-interacting protein kinase-3 (RIPK3) and mixed lineage kinase-like (MLKL) activities. The mode of cell death has consequences on the surrounding environment and inflammatory responses. This is especially relevant for neutrophils, which contain granules filled with reactive chemicals and enzymes. Clearly, a necrotic neutrophil death may induce inflammatory responses by the immediate release of danger-associated molecular patterns (DAMPs) but also by causing tissue damage. In this report, we investigated the effect of newly synthesized serine protease inhibitors on neutrophil death in vitro. Two inhibitors were identified that are able to inhibit CD44-induced necroptosis in GM-CSF-primed neutrophils. In contrast, FAS receptor-mediated apoptosis was not blocked. Interestingly, these two serine protease inhibitors could inhibit PI3K and NADPH oxidase activation in CD44-induced necroptosis. Therefore, several serine proteases (NSPs) appear to initiate CD44-induced reactive oxygen species (ROS) production and subsequent neutrophil necroptosis. In the future work, we will focus on identifying these NSPs, which could be the potential targets in neutrophil-associated disorders for therapeutic modulation in infectious, inflammatory and autoimmune diseases.

**SASS 33**

IL-17E expression is dysregulated in scleroderma epidermis and modulates keratinocyte-dependent activation of fibroblasts

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Background: Fibrosis of skin and internal organs is a hallmark of systemic sclerosis (SSc) likely resulting from altered immune-inflammatory events. The potential role of keratinocytes in regulating fibroblast responses has received little attention in SSc, although it may play a role in extracellular matrix deposition. IL-17E is a member of the IL-17 family with the lowest structure homology compared to IL-17A and with different cellular sources and potential functions. Furthermore, we have previously demonstrated an increased frequency of IL-17E positive cells in SSc dermis.

Objective: To investigate the expression of IL-17E in SSc epidermis and its role in the regulation of keratinocyte-fibroblast crosstalk.

Methods: Skin biopsies were obtained from 11 SSc and 10 healthy donors (HD). IL-17E was visualized by immunofluorescence and quantified by automated imaging analysis. Primary keratinocytes were generated from 8 HD and primed in vitro with IL-17E. Their conditioned medium was used to activate fibroblasts. IL-6, IL-8, MMP-1 and type-I collagen (col-I) production was assessed by ELISA.

Results: SSc epidermis expressed high levels of IL-17E, which was differentially distributed when compared to HD. The supernatant of HD keratinocytes enhanced the production of IL-6, IL-8, MMP-1 but not of col-I when applied to HD fibroblasts. The priming of HD keratinocytes by IL-17E further and potently enhanced the production of these mediators. This effect was not due to IL-17E carryover, nor to their direct keratinocyte responses. Neutralization experiments indicated that IL-1 and TNF produced by keratinocytes were, at least in part, involved in fibroblast activation.

Conclusion: Our results data demonstrate any increase in the expression of IL-17E in SSc epidermis. We further confirm that keratinocytes selectively enhance dermal fibroblasts responses, and for the first time show that IL-17E potently modulates this activity, switching fibroblasts from anti-inflammatory to pro-inflammatory phenotypes. Investigation are planned to better elucidate the role of IL-17E using SSc keratinocytes in 3D culture conditions.

**SASS 34**

Exploring the role of mTOR on ILC subsets during physiological conditions vs tumor microenvironment

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Innate lymphoid cells (ILCs) were recently recognized as a distinct and new family of immune cells belonging to the lymphoid lineage, yet not expressing somatically rearranged antigen specific receptor genes. ILCs are operationally defined as lineage negative lymphocytes expressing the IL-7 receptor (Lin-CD127+). They can be grouped into at least 3 distinct subsets based on both their cytokine secretion profiles and the requirement of master transcription factors: Group 1 ILCs (ILC1) producers of IFNγ and dependent on T-bet; Group 2 ILCs (ILC2) producers of IL-4, IL-5, IL-9 and IL-15 and dependent on GATA3 and finally, Group 3 ILCs, including the lymphoid tissue inducer cells (LTI) and ILC3, producers of IL-17 and/or IL-22, dependent on RORγt expression. Based on recent evidence it has become clear that lymphocytes fate determination and stability is not inflexible. The first observations pointing to plasticity were made on ILC1 and ILC3 subsets with the observation of increasing T-bet gradient was described. Some data suggests that this gradient is reversible and that it might be a true bi-directional plasticity that changes RORγt and Tbet. Moreover, LTI-like CCR6+ILC3 can upregulate Tbet when exposed to Notch stimulus in vitro and there is also evidence of transcription factor modulation on ILC2 expressing T-bet and becoming INFγproducing under the influence of IL-12. However, little is known about the mechanisms and is important to understand the molecular basis of this plasticity. In the past few years several data indicates that metabolism regulation is also an important factor in the tumor microenvironment, affecting both, tumor and immune cells. Recently mTOR signaling, one of the central regulators of mammalian metabolism, has been reported as important for NK activation and anti-tumor activity; nevertheless, little has been described for the other ILC subsets. Using the Rictor and Raptor I12-CreERT2mouse models we are studying the impact of this pathway on ILC subsets distribution and activation in physiological or inflammatory vs tumor microenvironment. Our first results shows, that at least in part, mTORC1 could be regulating the plasticity among ILC subsets.
**Non-apoptotic TRAIL function modulates NK cell activity during viral infection**

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The role of death receptor signaling for pathogen control and infection-associated pathogenesis is multifaceted and controversial. Here, we show that during viral infection, tumor necrosis factor-related apoptosis-inducing ligand (TRAIL) modulates NK cell activity independently of its pro-apoptotic function. In mice infected with lymphocytic choriomeningitis virus (LCMV), TRAIL-deficiency led to improved specific CD8+ T cell responses, resulting in faster pathogen clearance and reduced liver pathology. Depletion experiments indicated that this effect was mediated by NK cells. Mechanistically, TRAIL restricts NK1.1-triggered IFNγ production by NK cells. In addition, TRAIL expressed by immune cells positively and dose-dependently modulates IL-15 signaling-induced granzyme B production in NK cells, leading to enhanced NK cell-mediated T cell killing. TRAIL also regulates the signaling downstream of IL-15 receptor in human NK cells. The function of TRAIL on immune cells was so far confined to the induction of apoptosis on target cells. Our study reveals a hitherto unappreciated immunoregulatory role of TRAIL signaling on NK cells for the granzyme B-dependent elimination of antiviral T cells.

**Neurons under T cell attack coordinate phagocyte-mediated synaptic stripping**

Di Liberto Giovanni1,2, Pantelyushin Stanislav1, Kreutzfeldt Marie1, Page Nicolas1, Musardo Stefano2, Coras Roland3, Steinbach Karin2, Vincenti Ileana4, Klimek Bogna5, Lingner Thomas6, Salinas Gabriela7, Rasmussen’s encephalitis patients. In this devastating CD8+ T cell-mediated encephalitis caused by CD8+ T cells targeting antigenic neurons. Neuronal STAT1 profiled the neuronal translatome in a murine model of encephalitis accompanied by synaptic loss for which phagocytic microglia and inflammatory disorders of the central nervous system are frequently caused by CD8+ T cell-mediated neuronal damage. Here, we profiled the neuronal translantome in a murine model of encephalitis caused by CD8+ T cells targeting antigenic neurons. Neuronal STAT1 signaling and downstream CCL2 expression were essential for recruitment of phagocytes, ensuing synaptic loss and neurological disease. Analogous observations were made in brains of Rasmussen’s encephalitis patients. In this devastating CD8+ T cell attack coordinate phagocyte-mediated synaptic stripping.
cell-driven autoimmune disease, neuronal STAT1 phosphorylation and CCL2 expression co-clustered with infiltrating CD8+ T cells, as well as phagocytes. Taken together our findings uncover an active role of neurons in coordinating phagocyte-mediated synaptic loss and highlight neuronal STAT1 and CCL2 as critical steps in this process, which are amenable to pharmacological interventions.

Role of ER stress and lipid metabolism in Tumor-associated macrophages

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The presence of Tumor-associated macrophages (TAMs) in several solid tumors is associated with poor prognosis and decreased overall survival. TAMs are mainly trapped in the hypoxic area where they exert either immunosuppressive functions or proangiogenic functions, by promoting vessel formation and metastatic dissemination. These protumoral TAMs show a M2-like phenotype, Re-education of TAMs towards an anti-tumoral M1-like phenotype has been proposed as potential immunotherapy, alone or in combination with checkpoint blockade inhibitors. Unraveling the cause of the M2-like switch of macrophages in the tumor microenvironment represents a big challenge and a key point in order to design specific therapy that allow the re-education of TAMs. Here we show that lipids released by cancer cells play an important role in skewing macrophages towards an immunosuppressive M2-like phenotype. Uptake of cancer cell-derived lipids by macrophages induces an XBP1-mediated ER stress response that directly affects the regulation of important proangiogenic and immunosuppressive genes. In vitro, pharmacological or genetic inhibition of ER stress could rescue the M2-like switch caused by cancer cell-derived lipids. These data open new therapeutic possibilities by either modulating lipid metabolism in cancer cells or by inhibiting ER stress in TAMs.

Impact of the tumor microenvironment on lymphatic phenotype and function

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The lymphatic system comprises a network of lymphoid tissues and vessels that drains the extracellular compartment of most tissues. During tumor development, lymphatic endothelial cells (LECs), which express VEGF-R3, substantially expand in response to VEGF-C produced in the tumor microenvironment, a process called lymphangiogenesis. The ability of a tumor to induce and activate lymphatic growth has been strongly correlated with metastasis. However, to date very few investigations have addressed the role of tumor-associated lymphatics on primary tumor growth and tumor immune inactivity. In our study, we evaluate how the tumor microenvironment affects LEC phenotype and functions to modulate subsequently anti-tumor immune inactivity. In mice, we performed comparative transcriptome profiling on LECs purified from B16 F10 OVA+VC solid tumors (B16-F10 melanoma tumors expressing both OVA and high levels of VEGF-C), tumor draining lymph nodes (LN) and steady-state LN. Significant number of genes are differentially regulated in tumor associated (TA)-LECs compared to LN-LECs, suggesting that tumor microenvironment affects LEC features and function in vivo. Based on our RNAseq data, we have more specifically divided into two categories the genes impacted in LECs by the tumor microenvironment: (1) regulation of lymphangiogenesis and (2) modulation of anti-tumoral immunity. We have already validated by qPCR several genes differentially expressed by TA-LECs compared to LN-LECs. These preliminary data indicate that the tumor microenvironment modifies the expression of several genes in LECs, which could subsequently affect different aspects of anti-tumoral T cell responses, such as migration, homeostasis and activation. Genes identified to be regulated in LECs by the tumor microenvironment will be tested in two other murine cancer models: Non-small cell lung carcinoma (NSCLC) and colorectal cancer (CRC) mouse models. Tumor growth in mice with LECs deficient (Prox1CreERT2) for candidate genes (Flox genes) will be assessed in melanoma, NSCLC and CRC murine cancer models.
mitochondrial uncoupling in the regulation of T lymphocyte function

**SSAIPeF 7**

**Mitochondrial uncoupling in the regulation of T lymphocyte function**

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The uncoupling proteins (UCPs) act as ionophores across the inner mitochondrial membrane to control the mitochondrial membrane potential, ROS production and metabolic fluxes. Whereas UCP1 and UCP3 are specific for adipocytes and muscle tissue, UCP2 is expressed by diverse cell types, including immune cells. UCP2 expression is strongly induced upon T cell activation; however, its physiological relevance for T lymphocyte function remains unclear. In this project, we examine the impact of UCP2 on T cell biology using mice with a conditional deletion of UCP2 in T lymphocytes (UCP2^−/−). Removal of UCP2 did not affect the populations of conventional CD4+ and CD8+ T cells, but resulted in significantly increased frequencies of Foxp3^+CD4+ regulatory T (Treg) cells in naive UCP2^−/− mice. In particular, UCP2-deficient Treg cells exhibited a marked competitive advantage over wild type Treg cells in mixed BM chimeras. Furthermore, our studies indicate that UCP2 modulates both the cytokine response and the co-inhibitory receptor profile of Treg cells. In conclusion, we found UCP2 to influence the mitochondrial membrane potential and metabolism of effector and memory CD8+ T cells. Taken together, these findings implicate physiological mitochondrial uncoupling in the maintenance and functionality of distinct T cell subsets. We are further investigating the molecular mechanisms linking UCP2 to specific T cell effector functions and cellular metabolic programs.

**SSAIPeF 6**

**Correlation between auto-antibody positivity and disease activity in systemic lupus erythematosus**


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**Background:** Autoantibodies are antibodies directed against host molecules that are pathogenic in inflammatory diseases, such as systemic lupus erythematosus (SLE). Importantly, these antibodies correlate strongly with markers of biological activity, particularly those that are associated with disease activity or cardiovascular events (CVE). In SLE, the presence of autoantibodies against specific antigens has been linked to a higher risk of CVE. In the current study, we aimed to evaluate the correlation between autoantibody positivity and disease activity or CVE.

**Methods:** Three-hundred fifty-four biological samples and study visits from 176 individuals were obtained from the SLE cohort study (SSCS). Clinical characteristics, anamnestic CVE and therapy details were recorded. Disease activity was prospectively captured by the SELENA-SLEDAI score, which is a validated tool for measuring disease activity in SLE. The presence of autoantibodies was determined using commercial assays and confirmed by confirmatory tests. The association between autoantibody positivity and disease activity or CVE was analyzed using statistical methods.

**Results:** In this study, we analyzed the association between autoantibody positivity and disease activity or CVE in 176 individuals with SLE. We found that the presence of specific autoantibodies, such as anti-dsDNA IgG, anti-cardiolipin IgG, anti-beta2 glycoprotein 1 (anti-b2GP1) IgG, and anti-phospholipid antibodies, was significantly associated with disease activity or CVE. In particular, the presence of anti-dsDNA IgG was strongly associated with CVE, including cardiovascular events.

**Conclusions:** The findings of this study highlight the importance of autoantibody positivity in the risk of CVE in SLE. These results suggest that screening for specific autoantibodies may be useful in identifying individuals at higher risk of CVE. Further studies are needed to validate these findings and to determine the clinical relevance of autoantibody positivity in SLE.

**SSAIPeF 5**

**Infusion Parameters and Adverse Events in Patients With Primary Immunodeficiency Diseases Who Switched to Subcutaneous Human Immune Globulin 20% (IgG20GlY) From Intravenous or Subcutaneous Immune Globulin**


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**Rationale:** IgG20GlY (CivitA) is a new subcutaneous human immune globulin (IgG) 20% preparation for the treatment of primary immunodeficiency diseases. To evaluate whether the previous route of Ig administration affects the tolerability or infusion characteristics of
IS protocols however mainly control T-cell activation and differentiation acute rejection has allowed solid organ transplantation (Tx) to become The use of potent immunosuppressive (IS) drugs that can prevent complications in association with the laboratory finding evoked a presence of autoantibodies such as ANA and anti-SSA. The neurologic manifestations. She developed during the sixth month of treatment a autoimmune autonomic ganglionopathy (AAG). The cerebral spinal fluid protein level was 1.07 g/L, and the CSF analysis revealed a high level of protein and an autoimmune autonomic ganglionopathy (AAG). The cerebral MRT revealed an enhancement of the mandibular branch of the trigeminal nerve. The lumbar puncture showed a high level of protein and pleiocytosis, with negative cultures, compatible with an aseptic meningitis. Blood tests revealed an important inflammatory syndrome, a hemolytic anemia, an elevation of the total IgG level and the presence of autoantibodies such as ANA and anti-SSA. The neurological complications in association with the laboratory finding evoked a possible Sjögren syndrome. Investigations were completed with a biopsy of the salivary glands that confirmed the clinical suspicion, with a Chisholm and Mann score of 3. Despite "upfront" treatment with 4 pulses of steroids and 5 days of intravenous immunoglobulins, the clinical evolution was not favorable. We decided to introduce a single dose of cyclophosphamide 15 mg/kg in association with oral prednisone, followed by 4 cures of rituximab at 375 mg/m² according to the GFEV (Groupe Français d’Etude des Vascularités) recommendations, with a favorable outcome for the time being.

Identification of peripheral blood mononuclear cells signatures associated with rejection and graft outcome after kidney transplantation, a longitudinal prospective study

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The use of potent immunosuppressive (IS) drugs that can prevent acute rejection has allowed solid organ transplantation (TX) to become the therapy of choice for end-stage renal diseases. Current available IS protocols however mainly control T-cell activation and differentiation with a poor effect on pre-existing memory T-cells and B-cell responses, which are responsible for chronic rejection and allograft loss. Moreover, some of the IS drugs used in the clinic have a deleterious effect on the homeostasis of donor-specific regulatory T-cells (Treg). Therefore, while acute allograft rejection can be prevented or treated in most cases in the current era, optimal long-term patient and graft survival still remains a problem. This is even a greater challenge for HLA-sensitized patients. In our study we aimed to characterize the role of T- and B-cell subsets in the immunological responses promoting allograft rejection or long-term graft survival organ acceptance after kidney Tx. We could benefit from the Swiss Transplant Cohort Study (STCS) to retrieve prospective clinical data and biological samples. This allowed us to follow the immune repertoire of each recipient of HLA-mismatched graft, from the day of kidney Tx onwards. Using standard flow cytometry as well as CyTOF technology, we first analyzed the effect of current IS drugs on in vitro activated PBMC subsets. We observed a reduction of activated CD4 T-cells (mainly Th1 subset), but with a negative effect on Treg survival. The IS drugs tested were is was less efficient pronounced on memory CD4 and activated CD8 T-cells effector function. We are now studying longitudinally PBMC subsets dynamics during the first year after kidney Tx. In preliminary experiments, we were able to detect differences between the pre- and post-Tx sera, compared to patients under long-term dialysis patients with acute rejection, patients with acute rejection, as well as between sensitized and non-sensitized recipients. These initial data are promising and we are now starting to analyze in further detail the association between PBMC signatures and cellular vs. antibody-mediated rejection, controlling for relevant confounding factors.

Comparing the diagnostic efficacy of manual and automated screening assays for the detection of antinuclear antibodies in routine diagnostics of systemic autoimmune rheumatic diseases

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Detection of antinuclear antibodies (ANA) is part of routine diagnostic work-up of patients presenting with symptoms of systemic autoimmune rheumatic diseases (SARD). Various methods for the detection of ANA are available – each with individual advantages and drawbacks. Our aim was to evaluate different laboratory test methods to improve the detection efficacy of ANA in serum samples for routine diagnostics of SARD. For this purpose, we compared two automated ANA screening assays: 1) Elia® CTD Screen (Fluorescence Enzyme Immunoassay (FEIA), Thermo Fischer) for the detection of a defined spectrum of antinuclear antibodies (ANA); and 2) an automated indirect immunofluorescence (IFA) method NOVA Lite® HEP-2 interpreted by (digital microscope system) NovaView® (Inova Diagnostics) with our currently used, manual IIF method on NOVA Lite® HEP-2 ANA substrate (Inova Diagnostics). The assays were performed on consecutive routine clinical laboratory requests that were sent to the Medical Immunology Laboratory of the University Hospital Basel for measurement of ANA during a period of two months (n = 353). Using cut-offs recommended by the manufacturers for the automated assays and our established in-house cut-off for the manual IIF, the specificities were (92.2%), (80.2%) and (74.4%), for FEIA, automated IIF, and manual IIF, respectively. Direct comparison of the manual IIF versus automated IIF for ANA screening showed an equally good performance of both methods at identical sample dilution, with identical specificities (85.4%). The specificity of the screening increased to 99.1% for double positivity of IIF and FEIA. In conclusion, our results indicate that there are slight differences in the performance of the individual test assays and that the highest diagnostic accuracy for ANA screening as part of the diagnostic work-up of potential SARD patients can be reached by a combination of IIF and FEIA.
type 2 diabetes mellitus (T2DM) patients and has been associated with the progression of the disease. As aggregates are considered to be a key factor in β cell death, we aim at developing a vaccine targeting these pathogenic aggregates to prevent and/or reverse accumulation and enhancing β cell survival. To study this, a transgenic mouse model expressing human IAPP (hIAPP) was used. The vaccines were designed using different amylin peptide sequences chemically cross-linked to virus like particles (VLPs). The induced antibodies response against each peptide, was analyzed by ELISA assay with serum obtained from immunized C57BL/6 mice. The peptides coupled to the VLPs inducing the highest IgG titers against IAPP where then tested in a transgenic mouse model developing spontaneously T2DM. Interestingly, mice immunized with vaccine showed symptoms of T2DM at a later point compared to the control ones, which received only the VLPs. Besides the active immunization, a separate group of mice was immunized with monoclonal antibodies against the same peptide of amylin used in the active immunization. Preliminary results showed that T2DM appeared in the passive immunized mice at a later onset. In addition, based on recent data suggesting that hIAPP interacts with immune cells present in the islets promoting the synthesis of IL-1β via activation of the inflammasome NLRP3; we wanted to assess whether the IgG against IAPP can decrease inflammasome activation and the secretion of IL-1β. For this purpose bone marrow derived dendritic cells (BMDC) were obtained after stimulation with the granulocyte-macrophage colony-stimulating factor (GM-CSF) from BMDC from E8.2L cells to induce the transcription of pro-IL-1β, and later either with hIAPP or rat IAPP (nIAPP) for inflammasome activation and secretion of mature IL-1β. As expected, only hIAPP could induce the activation of the inflammasome after priming; and, as hypothesized, the anti-hIAPP IgG prevented the release of IL-1β in a dose-dependent manner. A mechanistic approach is now under investigation.

**Risk factors for severe systemic sting reactions in wasp and honeybee venom allergic patients**

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**Background:** Hymenoptera stings are a major cause of anaphylaxis. Various risk factors are discussed in literature.

**Objective:** This study aims to investigate potential risk factors for severe sting reactions in wasp and honeybee venom allergic patients and analyses the correlation between diagnostic test results and the severity of the allergic reaction.

**Methods:** 480 patients suffering from wasp or honeybee venom allergy were included in this retrospective case series. The severity of their systemic reaction was evaluated with regard to the amount of specific IgE antibodies to whole venom extracts and to major allergens of honeybee respectively wasp venom. Furthermore, the following potential risk factors for severe sting reactions were examined: age, sex, latency time, skin symptoms, baseline serum tryptase levels and the concentration of venom inducing a positive intracutaneous test.

**Results:** The two following indicators for severe systemic sting reactions in honeybee and wasp venom allergic patients have been identified: a short latency time and the absence of skin symptoms. The patient’s age and baseline serum tryptase levels have been found to positively correlate with the grade of the sting reaction only in individuals allergic to wasp venom. No correlation could be found between the degree of sensitisation and the severity of the allergic reaction. Neither the amount of specific IgE antibodies to whole venom extracts nor to major allergens were significantly associated with the severity of the sting reaction.

**Conclusion:** The clinical history is essential for the allergological workup and therapeutic decision on Hymenoptera venom allergies. A short latency time and the absence of skin symptoms are indicators for severe systemic sting reactions, followed by the patient’s age and baseline serum tryptase levels.

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**Severe asthma in Switzerland: Overview of the population and treatments by specialists**

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**Introduction:** Although the majority of asthma patients can be effectively treated with currently available medications, 5–10% of them develop a severe asthma. No recent national data are currently available, we therefore developed a survey to investigate how severe asthma is currently diagnosed and treated in Switzerland.

**Methods:** The survey covered the habits and approaches of Swiss specialists regarding the diagnosis, evaluation and treatment of their severe asthmatic patients. The survey consisted of 19 questions and was distributed to Swiss pulmonologists and allergists (including pediatricians) from 01/2017 to 04/2018. Completion of the questionnaire was made on a voluntary basis, without any counterpart or fee.

**Results:** 37 specialists answered to the survey. 51% of the physicians felt very confident in diagnosing severe asthma. Overall, they estimated that 54% of their asthmatic patients have a respiratory allergy and that 24% of them are polymorbid. The most frequently mentioned comorbidities are cardiovascular diseases (66%) and psychological disorders (24%). Inhalastim corticosteroid/long-acting beta-agonist combinations and monoclonal antibodies (mAbs) were considered by more than 80% of specialists as potential background therapy whereas oral corticosteroids (OCS) were mentioned by 68% of them and leukotriene receptor antagonists by 73%. Although no long-acting muscarinic antagonist is currently approved for the treatment of asthma in Switzerland, it was considered as a potential treatment by more than half of the physicians. 56% of physicians reported using OCS in their severe asthma patients, which may be linked to the fact that the majority (65%) reported limited experience with the clinical use of biologics.

**Conclusion:** These results support the idea that diagnosis and treatment of severe asthma is not obvious and that a resourceful healthcare system. In contradiction with the GINA guidelines, the majority of Swiss specialists still mentioned OCS before mAbs in their own asthma treatment algorithm. Furthermore, this survey highlights the need of more studies regarding management of polymorbid severe asthma patients which consist a quarter of the population.

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**Lanadelumab is highly efficacious at steady-state in hereditary angioedema (HAE): results of the phase 3 HELP Study**

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**Introduction:** Lanadelumab is a fully human monoclonal antibody targeting plasma kallikrein that demonstrated sustained protection against HAE attacks and the largest proportion of attack-free periods in the HELP Study. With a half-life of ~14 days, lanadelumab is expected to reach steady-state at ~70 days. Here, we report the efficacy profiles of lanadelumab through the steady-state period (days 70–182, 16 weeks).

**Methods:** The HELP Study was a phase 3, randomized, double-blind, placebo-controlled study in patients ≥12 years old with HAE type I/II. Patients were randomized (2:2:2:3) to lanadelumab 150 mg q4wks, 300 mg q4wks, 300 mg q2wks, or placebo. Ad hoc analyses were performed on the number of investigator-confirmed attacks (primary endpoint) and the severity of attacks during the steady-state period.

**Results:** 125 patients were treated, of which 120 reached day 70 and were included in this analysis (150 mg q4wks: n = 28; 300 mg q4wks: n = 29; 300 mg q2wks: n = 26; placebo: n = 37). During the steady-state period, least squares mean monthly attack rate was significantly reduced with all lanadelumab regimens (150 mg q4wks: 0.42 [−77.6% vs placebo]; 300 mg q4wks: 0.37 [−80.6%]; 300 mg q2wks: 0.16 [−91.5%] compared with placebo (1.88; unadjusted P < 0.001 for all). The proportions of attack-free patients were markedly higher with lanadelumab (150 mg q4wks: 53.6%; 300 mg q4wks: 44.8%; 300 mg q2wks: 76.9%) than with placebo (2.7%). The number of severe attacks was lower with lanadelumab (150 mg q4wks: 1; 300 mg q4wks: 2; 300 mg q2wks: 1) versus placebo (31).

**Conclusions:** The benefit of lanadelumab treatment was optimal during the steady-state period; the 300 mg q2wks group had the greatest attack rate reduction, the largest proportion in attack-free patients, and only 1 severe attack. These results further support the primary efficacy analyses during the complete treatment period in the HELP Study.
Objectives: To depict the real-world experience on the efficacy and adverse events of dupilumab treatment of severe AD at the Department of Dermatology Zurich, Switzerland.

Methods: We assessed the efficacy and adverse events of dupilumab treatment in patients with severe AD, seen at the specialized AD outpatient clinic of the Department of Dermatology Zurich, Switzerland. Dupilumab is ordered within a compassionate use program, inclusion criteria are (i) adult age, (ii) severe AD with a scoring atopic dermatitis (SCORAD) > 50, (iii) candidate for systemic treatment, (iv) not adequately controlled under conventional therapies. Patients received dupilumab 300 mg subcutaneously every 2 weeks, continued emollients and topical steroids on demand.

Results: Since September 2017, 12 patients started dupilumab treatment (9 males, 3 females; median age 43.5 years); 9 patients (75%) were adult with AD, 3 patients (25%) were children with AD. Median SCORAD before treatment was 66.1, decreasing to median 50.7 (p = .002) after 2 weeks of treatment (n = 12 patients), to median 26.1 (p < .001) after 6 weeks (n = 9), to median 22.3 after 12 weeks (n = 3). Regarding side effects, 6 patients (50%) reported ocular symptoms starting in median 6 weeks after onset of treatment. Three of these patients (50%) had mild conjunctivitis with ophthalmitis, resolving with moisturizing eye drops and avoidance of mechanical irritation (e.g. glasses instead of contact lenses); 2 patients (33%) had a moderate conjunctivitis that resolved with topical steroids; 1 patient (17%) stopped dupilumab treatment due to severe conjunctivitis. Other side effects were mild-to-moderate nasopharyngitis in 4 patients (33%), delayed wound healing in 1 patient (8.3%) and mild redness and swelling at the injection site in 1 patient (8.3%).

Conclusion: Dupilumab is an efficient treatment for severe AD in real-life, starting to be efficacious already after the first injection and increasingly efficacious after 6 weeks. Most common side effect is allergic conjunctivitis, which may be more frequently observed in real-life than in clinical studies and may need early care by ophthalmologists.

Patient education for adults and children with atopic dermatitis in Switzerland

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Background: Atopic dermatitis (AD) is a chronic inflammatory skin disease. Recent studies corroborated the importance of patient education for treatment adherence and the improvement of AD severity. However, AD patients in Switzerland rarely undergo patient education because it is rarely offered and not covered by insurances.

Objective: To assess the feasibility of patient education and its acceptance by children and adults with AD in Switzerland.

Methods: Education for AD patients is performed in three centers: Since 2014 at the Department of Dermatology, University Hospital of Zurich and since 2016 at the Department of Dermatology, University Hospital of Lausanne. Patients received a personalized education for 50 minutes with an health care professional AD expert, covering topics such as topical treatment, itch management or coping strategies. Patients or their parents received a questionnaire to assess the organization of the education, satisfaction with trained staff, patient’s feelings concerning the consultation, the relevance and practicability of information, adherence to recommendations, and health-related quality of life.

Results: Between 2014 and 2017, 416 patients underwent education. Of these, 141 (33.9%) returned a questionnaire. Most patients (n = 65, 46.1%) underwent education at the University Hospital of Lausanne, followed by the University Hospital of Zürich (n = 61, 43.3%) and the Children’s Hospital of Zurich (n = 15, 10.6%). Most patients were children with AD together with their parents (n = 96, 68%), while 42 individuals (30%) were adults with AD. Three individuals (2%) did not report their age. The number of patients undergoing education increased from 38 in 2014 (9.1%) and 20 in 2015 (8.8%) to 153 in 2016 (36.8%) and 205 (49.3%) in 2017. The overall satisfaction with the education was high in 118 patients (84.3%), but low in only 5 patients (3.6%). Of importance, most patients (n = 137, 98.6%) would recommend this education to other AD patients.

Conclusions: Patient education for AD patients is feasible in Switzerland. A clear majority of AD patients is very satisfied with education. The interest of AD patients in patient education is increasing. While the common AD patient undergoing education is a child with its parents, also adults with AD should be motivated to undergo education.

Delayed- type allergy to cobalt – comparison of a flow cytometric lymphocyte proliferation test with patch testing

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Background: Patch test is considered the standard test to diagnose delayed-type sensitizations. If patch test is contra-indicated, flow cytometric lymphocyte proliferation test (LPT), which allows to determine the number and type of cells responding to a specific antigen in vitro, might be considered as an alternative.

Objectives: Our aim was to establish a flow cytometric lymphocyte proliferation test (LPT) for the detection of delayed-type allergic reactions to cobalt and to determine the magnitude of correlation between stimulation indices (SI) in LPT and grade of patch test reactions. With patch test as diagnostic reference, we furthermore assessed sensitivity and specificity of LPT.

Methods: Fifty-four patients with any indication for patch test (baseline series including cobalt (CoCl2)) were additionally tested by flow cytometric LPT in response to CoCl2.

Results: There was significant correlation between the results of both tests: r = 0.43; p = 0.001. LPT with CoCl2 showed a sensitivity of 52.6% and a specificity of 65.7%. Underlying low sensitivity of the LPT, high likelihood ratios for a positive patch test were reached only in case of strong lymphocyte proliferation (SI ≥ 10).

Conclusions: In case of clearly increased SIs, flow cytometric LPT with CoCl2 gives relevant diagnostic information and represents a valuable alternative to patch test.

Glycan-Checkpoint Inhibitor Unleashing CD8+ T cells against Cancer

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In the past few years, the role of cytotoxic T lymphocytes (CTL) in the fight against cancer has been put into light and is playing a growing importance into the development of checkpoint inhibitor therapies. Siglec-9 are inhibitory receptors recognizing sialic acid containing ligands and are able to trigger inhibitory functions. The ligands of Siglec receptors have been shown to be highly upregulated in various types of tumors. We hypothesized that Siglec-9 expressed on CD8+ T cells might be used by sialic acid containing tumor cells to hide from the immune system, and therefore escape elimination. Thus, we investigated the Siglec-9 + CD8+ T cell pool characteristics of healthy donors as well as in tissues of patients with melanoma. Cells were screened for various membrane receptor expression, cytokine production, proliferation capacity and fundamental tissue quantification to overview the Siglec-9 + CD8+ T cell pool characteristics. Moreover, functional assays measuring the cytotoxic potential towards tumors were also performed, as well as

References: 

RNA levels of various proteins linked to Siglec-9 and its ligands. Our study shows an increased Siglec-9+ CD8+ T cell pool presence in the Tumor Infiltrating Lymphocytes (TILs) isolated from patients with melanoma compared to healthy donors. The Siglec-9+ CD8+ T cell pool represents a more differentiated, more cytotoxic and more proliferative subpopulation than CD8+ T cells, indicating that the RNA and protein levels of PD-1 and Siglec-9 appeared to behave similarly in patients with melanoma. Finally, we demonstrated that the ligands of Siglec-9 are highly upregulated on tumor surface of patients with melanoma. Ultimately, we demonstrated that blocking siglec-9 interaction with its Ligands on tumor increased the cytotoxic potential of the Siglec-9+ pool towards the tumor cells. Adding anti-PD-1, our data suggest a synergistic effect of both treatments on tumor cell elimination. Taken together, our data suggest that Siglec-9 on CD8+ T cells may represent a novel potential therapeutic targets for immune check-point therapy of malignancies with high expression of sialoglycans, such as melanoma. Moreover, our results suggest that and anti-Siglec-9 treatment could enhance the efficiency of famous already-existing anti-tumor treatments targeting check-point inhibitors, opening the door to potential co-treatments with a higher impact and lower side effects.

Cell death induction upon IVIg treatment in mature neutrophils is increased compared to immature neutrophils

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POSTERS SSAI

IL-17A as pro-inflammatory and anti-fibrotic cytokine in systemic sclerosis skin

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BACKGROUND: Increased levels of IL-17A have been reported in systemic sclerosis (SSc). Furthermore, epithelial cells are preferential targets of IL-17A and recent findings suggest that keratinocytes may participate in dynamic extracellular matrix homeostasis. We aimed to investigate the interactions between epithelium and dermis in the presence of IL-17A, taking into perspective the fibrotic process.

METHODS: Primary human keratinocytes were primed with IL-17A and/or TGF-β and conditioned media were used to stimulate healthy donors (HD) and SSC fibroblasts. Alternatively, organotypic cultures of HD full skin human were challenged with these cytokines. Responses were assessed by quantifying inflammatory mediators and type I collagen (Col-I) levels. The factors produced by keratinocytes were identified by a proteomic approach and their contribution was evaluated by neutralization assays. Changes in gene expression in full human skin after treatment with IL-17A and TGF-β were analysed by RNA sequencing (RNA-seq). MicroRNA expression was examined by qMParaflo® technology platform.

RESULTS: Unstimulated HD- and SSC-derived keratinocyte-conditioned media (KCM) promoted collagen production by fibroblasts. Cytokine array analysis and neutralizing assays showed that TGF-β was, at least in part, responsible for the pro-fibrotic effect of KCM. Priming of keratinocytes with IL-17A directly decreased Col-I production and significantly reduced Col-I induced by TGF-β both in SSC and HD fibroblasts. In full human skin, IL-17A promoted pro-inflammatory responses by inducing 2- to 4-fold increase of IL-8, IL-6, MCP-1 and MMP-1 levels, while showing direct anti-fibrotic effects, as well as decreasing by 2-fold Col-I production triggered by TGF-β (p = 0.02). RNA-seq revealed that TGF-β induced the expression of many collagen genes, while this was not the case for IL-17A. However, IL-17A promoted a pro-inflammatory signature in the skin. The combined injection of IL-17A and TGF-β in the full human skin resulted in a non-parallel pattern of expression results compared to injection of TGF-β, indicating that IL-17A could enhance the efficiency of already-existing anti-fibrotic treatments targeting check-point inhibitors, opening the door to potential co-treatments with a higher impact and lower side effects.

Stem cell-like memory CD8 T cells establish early in the acute response to Yellow Fever vaccination

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The live-attenuated Yellow Fever virus vaccine (YF-17D) is well recognised to induce robust and remarkably durable CD8 T cell responses. YF-17D vaccination research has been particularly intensified in the last decade, being viewed as one of the best models to fully apprehend how optimal CD8 T cell responses are induced in humans, including the study of human CD8 T cell differentiation (Miller et al., 2008; Puthanakit et al., 2013). This is also relevant for tumour immunologists since it is now well established that strong cytotoxic CD8 T cell responses correlate with better prognosis and checkpoint blockade immunotherapies have defeated various types of metastatic cancers with unprecedented success (Friedman et al., 2018). Our research is focused on clinical studies on YF-17D vaccination as a model of optimal immunogenicity in humans. We first discovered that the YF-17D vaccine induces a potent stem cell-like memory (SCM) CD8 T cell population that lasts for at least 25 years (Sci. Trans. Med. 2015). Currently, we study human samples from three different protocols, including one cross-sectional (n = 41, up to 35 years after vaccination), one longitudinal (n = 16, up to 6 months after vaccination), and one anatomical (bone marrow and blood, recruiting). Recent longitudinal analyses have revealed that SCM CD8 T cells are detectable very early in the acute response. In fact, SCM CD8 T cells appear and are activated in parallel to the other differentiation subsets. While effectors (CCR7-) rapidly downregulate T cell factor-1 (TCF1), SCM cells preserve high TCF1 levels throughout, consistent with the role of TCF1 in memory establishment (Jean et al., 2010) as well as with the epigenetic control of stemness that sustains CCR7 and TCF1 expression and precludes effector differentiation (Pace et al., 2018). By performing multi-dimensional reduction and unsupervised clustering of flow cytometry data, we reveal the dynamics of the early CD8 T cell response to YF-17D vaccination: the SCM cells stay closely related to the baseline Naïve cells, while effectors burst out of baseline and gradually return as they contract after the activation peak. Our human data argue in favour of CD8 T cell memory differentiation models where long-term memory is established by the early decision to preserve stemness as opposed to models where memory develops ad after the effector, and perhaps, cannot.
Blood basophils show low susceptibility to apoptosis under allergic conditions

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Background: Basophils are a multifaceted type of leukocyte, which participate in allergic reactions such as allergic asthma. Mouse models of asthma suggest that basophils not only act as effector but also as immunoregulatory cells that aggravate allergic asthma. It has not yet been conclusively clarified whether human basophils play a similar role. We previously published that an allergic milieu, which we mimicked through addition of IL-3 or induction of FceRI cross-linking, caused resistance to apoptosis induced by IFN-α, death-receptor ligands (Fasl, TRAIL) and inhibitors of anti-apoptotic Bcl-2 proteins (BH3-mimetics) in human basophils isolated from healthy volunteers. We thus suspect that inefficient induction of apoptosis of human basophils may contribute to maintaining chronic allergic airway inflammation.

Aim: We aim at elucidating the underlying mechanisms regulating apoptosis in basophils of allergic patients compared to healthy individuals.

Methods: To evaluate sensitivity towards induction of apoptosis, we isolated peripheral blood basophils from allergic patients and stimulated them with IFN-α, TRAIL, BH3-mimetics, IL-3 and combination thereof. Survival of basophils was determined by flow cytometry and anti-apoptotic proteins were detected by flow cytometry or by western blot analysis.

Results: Our results demonstrate that blood basophils of allergic patients are relatively insensitive towards induction of apoptosis by IFN-α and TRAIL. Apart from that, preliminary data show that blood basophils from allergic donors have a tendency to exhibit higher levels of anti-apoptotic proteins Bcl-2, Bcl-xL and Mcl-1 compared to non-allergic donors. Tallying with this, our data show that IL-3 upregulates Bcl-2, Bcl-xL and Mcl-1 in a dose-dependent manner.

Surprisingly, even minimal amounts of IL-3 produced by basophils themselves in response to cross-linking of FceRI resulted in significant increase of Bcl-xL and Mcl-1 and consequently lower susceptibility to apoptosis.

Outlook: Our findings show that stimuli present in the allergic environment delay induction of apoptosis in human basophils and may therefore favor prolonged allergic inflammation as shown in several animal studies. In order to strengthen our preliminary data and determine whether allergic inflammation impedes induction of apoptosis, we continue our study by analyzing respiratory cell samples such as induced sputum.

The effect of anti-IgE antibodies on IgE binding to CD23

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The biological activity of anti-IgE antibodies has been shown to be very diverse with some of them having anti-inflammatory and others having pro-inflammatory effects. However, the impact of anti-IgE antibodies on the low-affinity IgE receptor CD23 expressed mostly in B cells and immature DCs is poorly understood. CD23 is known to regulate serum IgE levels and IgE-facilitated antigen presentation and is therefore an important regulatory player in allergy. We have previously generated two monoclonal anti-IgE antibodies. Le27, targeting the Cc4 domain of IgE causes anaphylaxis of IgE-sensitized basophils while BSW17 targeting the Cc3 is non-anaphylactogenic in IgE-sensitized basophils. Here, we aimed at assessing the impact of the anti-IgE antibodies on IgE binding to CD23. Hence, we isolated primary human B cells and monocytes and induced a high CD23 expression in the two cell types by incubating B cells with IL-4/CD40L and monocytes with IL-4/GM-CSF causing differentiation to monocyte-derived dendritic cells (mDCs). We used a Fel d I-specific monoclonal human IgE and investigated binding of BSW17-IgE and Le27-IgE complexes to the cells. We further compared binding of IgE-Fel d 1 complexes to the anti-IgE antibodies. We show that Le27 and BSW17 have opposite effects on IgE binding to CD23. Le27 inhibited binding of IgE to CD23 whereas BSW17 enhanced binding to CD23. This phenomenon was observed in CD23 expressing primary B cells as well as mDCs. In comparison, IgE-Fel d 1 complexes strongly increased IgE binding to CD23. In conclusion, we showed that depending on the recognized epitope of IgE, anti-IgE antibodies can inhibit or enhance IgE binding to CD23. These results may be relevant to consider for the improvement of anti-IgE strategies in allergic disease.

The role of the p73-ATG5 axis in regulating autophagy in atopic dermatitis and psoriasis

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The molecular mechanism of inflammation has been the subject of research in recent years, though many aspects have not yet been elucidated. It is believed that autophagy secures cell survival under stress conditions. We hypothesize that autophagy must be particularly important for the cellular response under pathological conditions such as inflammation. We propose to investigate how autophagy is regulated in epithelial cells in atopic dermatitis and psoriasis patients. Particularly, we are interested in exploring how the p73-ATG5 axis maintains cell functions under conditions of cell stress. Autophagy is a lysosomal degradation pathway that is essential for cellular survival, differentiation, and homeostasis. Autophagy principally serves as an adaptive process to protect organisms against diverse pathologies, but its regulation can become critical for the whole organism, for example, in neurodegenerative diseases and cancer. p73 belongs to the p53 family, a group of transcription factors, which play key roles in the regulation of many cellular processes, such as apoptosis, cell cycle and senescence, especially following DNA damage. Based on the previous observations that p73 is responsible for inducing ATG5 expression and regulates autophagy in hepatocytes, we hypothesize that this mechanism may also play an important role in atopic dermatitis and psoriasis. By applying immunofluorescence techniques, we observed an increased expression of p73 in keratinocytes in skin samples of patients suffering from atopic dermatitis and psoriasis compared to normal controls. While under normal conditions, only cells of the basal layer expressed p73 in their nuclei, we observed additional strong expression of p73 in the stratum spinosum under inflammatory conditions. Until now the role of p73 and autophagy in inflammatory skin diseases has not been studied yet. We are investigating the expression and interaction of p73 and ATG5 in atopic dermatitis and psoriasis. The preliminary results indicate that reducing p73 expression by shRNA, reduces ATG5 expression in keratinocyte cell line (HaCaT) and primary keratinocytes (NHEK). Presently it is known that autophagy has a role in inflammation, investigating this process in atopic dermatitis and psoriasis may lead to new insights and a better understanding of the pathophysiology of these diseases, which may result in identifying new drug targets.

Characterization of CD56bright NK cells which inversely correlate with survival of melanoma patients

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The roles of NK cells in human melanoma remain only partially understood. We characterized NK cells from PBMC and found that their frequencies were similar between stage III/IV melanoma patients and normal controls. We studied the expression of the early activation marker CD56 in these NK cells and showed that CD56bright NK cells inversely correlated with survival of melanoma patients. These findings suggest a potential role of CD56bright NK cells as therapeutic targets in melanoma.
and healthy donors. Interestingly, overall survival was significantly reduced in the patients who had high frequencies of CD56bright NK cells. The production of IFNγ, granzyme B, perforin and CCL4 by the CD56bright NK cells from patients was equal to healthy controls. In contrast, we found lower production of TNFα, GMCSF and CCL3, suggesting that the CD56bright NK cells might be less capable to fight against tumors. Furthermore, the increased expression of CD11a and CD38 may be associated with enhanced inhibition of T cells. Thus, the activation status of CD56bright NK cells may contribute to poor clinical outcome by both reduced anti-tumor activity and increased T cell inhibition. Our results highlight the significance of CD56bright NK cells in patient prognosis, emphasizing the potential of NK cells for biomarker discovery and future therapeutic targeting.

**SSAIPF 28**

**The architecture of the IgG anti-carbohydrate repertoire in primary antibody deficiencies (PADs)**


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Immune system failure in primary antibody deficiencies (PADs) has been linked to recurrent infections, autoimmunity and cancer, yet clinical judgment is often based on the reactivity to a restricted panel of antigens. Previously, we demonstrated that the human repertoire of carbohydrate-specific IgG exhibits modular organization associated with glycan structure. The current study compares the glycan-specific IgG repertoires among different PAD entities. Despite their heterogeneity, a similar repertoire architecture with extensive glycan-recognition defects characterized by the dominant loss of Galα- and GaINAc-reactivity, was observed, in addition to disease-specific recognition of microbial, self-antigens and tumor-associated carbohydrate antigens. Antibody repertoire analysis may provide a useful tool to elucidate the dimension and clinical implications of the immune system failure in individual patients.

**SSAIPF 29**

**Characterizing the role of NFAT5 in tumor specific CD8 T cells**

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Cytotoxic CD8 T cells can efficiently eliminate malignant cells. However, tumor cells and their microenvironment produce several inhibitory signals (via e.g. PD1, LAG3, IDO) that lead to a dysfunctional state in lymphocytes called “exhaustion”. Previous transcriptomic screening performed in our laboratory highlighted the higher expression levels of NFAT5 in Melan-A specific CD8 T cells from melanoma patients. Our hypothesis is that the immunosuppressive tumor microenvironment and chronic TCR stimulation induces the expression of NFAT5 that contributes to T cell exhaustion. In this project, we aim at characterizing the role of NFAT5 during the anti-tumor response of tumor specific CD8 T lymphocytes. Therefore, we bred CD4Cre+/− NFAT5fl/fl and CD8Cre−/− NFAT5fl/fl mice to analyze CD4 and CD8 T cell responses. In vitro, CD3/CD28-stimulated polyclonal NFAT5 KO CD8 T cells displayed similar exhaustion marker levels. Nevertheless, B16-GP33 bearing mice transferred with P14 NFAT5 KO CD8 T lymphocytes displayed significantly decreased tumor growth compared to mice transferred with P14 NFAT5 WT lymphocytes. P14 NFAT5 KO CD8 T cells expressed more CD44, less PD1 and more IFNγ upon restimulation with GP33 peptide than their NFAT5 WT counterparts. Together, our findings point to a novel role for NFAT5 in the regulation of T cell dysfunction and may lead to the development of new therapies that enhance the resistance of T lymphocytes to exhaustion.

**SSAIPF 30**

**Improved quality of life in nut allergic children after sequential oral food challenges to nuts**

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**Introduction:** Food allergy has increased in recent decades and has a major impact on patients’ quality of life. Nut allergies are particularly problematic due to their high prevalence in children and slow resolution rate. The Pronuts study was performed to find out whether children who are allergic to one or more nuts (defined as peanuts and all tree nuts) are allergic to tolerate other nuts by performing sequential oral food challenges (OCFs) to nuts. One of the aims of the study was to determine whether performing these OCFs and introducing tolerated nuts improves the overall quality of life of both children and parents.

**Methods:** Nut-allergic children 1 to 16 years of age were recruited in 3 European centers; Geneva, London, and Valencia. Health related quality of life (HRQL) assessment was performed using the validated food allergy quality of life (FAQLQ-PF) and the validated FAQLQ child form (FAQLQ-CF) in children 7 to 12 years both before the sequential OCFs and after 1 year. Data was analyzed using a two-tailed Wilcoxon signed-rank test for paired samples and a Wilcoxon rank-sum test for independent samples. At this time we present data for the Geneva and London centers.

**Results:** Sixty-two parents and 11 children filled out the HRQL questionnaires before the OCFs and after 1 year. Median age of children at inclusion was 8 years. There was a significant improvement in the mean FAQLQ-PF subscale score reflecting social and dietary limitations (2.89, 95% CI [2.50–3.29] to 2.39, 95% CI [2.09–2.69], p = 0.001). However, there was no statistically significant difference in mean FAQLQ-CF total score (2.67, 95% CI [2.34–3.00] to 2.44, 95% CI [2.16–2.71]; p = 0.089). On the other hand, the mean FAQLQ-CF total score was significantly improved during the same period (4.11, 95% CI [3.39–4.83] to 2.97, 95% CI [2.55–3.39], p = 0.0034). In addition, 3 out of 4 subscales of the child FAQLQ including allergy avoidance, risk of accidental exposure, and dietary restrictions were significantly improved (p <0.05). No statistically significant differences were found between the Geneva and London cohorts.

**Discussion:** Sequential OCFs to individual nuts improved quality of life pertaining to social and dietary limitations in both parents and children but did not significantly improve total parent FAQLQ score. Total FAQLQ-CF score was significantly improved in children, although interpretation in this group is limited by a small sample size.

**SSAIPF 31**

**PPARγ is essential for development of splenic red pulp macrophages and independent of the Bacti-Spi-C pathway**

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Tissue resident macrophages are derived from erythroid myeloid progenitors (EMPs) from the fetal yolk sac. They play important roles in innate immune response and tissue homeostasis. These phagocytic cells populate every organ and display a unique gene signature, which is essential for development and function. The regulation of macrophage development in the spleen is a complex process influenced by the regulation of T cell dysfunction and may lead to the development of new therapies that enhance the resistance of T lymphocytes to exhaustion.
monocytes, demonstrating a cell intrinsic requirement of PPARγ. Previously, it has been shown that development of RPM and VCA1+ BMM depends on the transcription factor Spi-C, which is activated when heme binds to its transcriptional repressor Bach1. We found that the heme induced Spi-C expression occurs independently of PPARγ. Interestingly, IL-12 and IL-18 are not required for PPARγ-induced RPM development, in contrast to AM. Taken together, these data suggest that (at least) two transcription factors, PPARγ and Spi-C, induced by distinct environmental triggers, are essential and non-redundant in RPM and VCA1+ BMM development.

**Association between cannabis allergy and anaphylactic reactions to banana: a case report**
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**RATIONALE:** IgE-mediated allergy seems to be on the rise. The clinical manifestations of IgE-mediated cannabis allergies can vary from respiratory, gastrointestinal to systemic anaphylactic reactions related to the route of exposure. It includes secondary crossreactivities mostly to plant-derived food designated as the cannabis-fruit/vegetable syndrome, but also involves other crossreactivities to latex and tobacco.

**PATIENT CONCERNS:** We present a case of a 20-year-old woman who experienced, on January and March 2018, a stage III anaphylactic reaction (malaise, urticaria, angioedema and dyspnea) after banana consumption. She initially developed from October 2017 a new-onset rhinoconjunctivitis after cannabis handling and smoking, without any previous history of pollen or latex allergy.

**DIAGNOSIS:** Diagnosis of banana allergy was established by positive prick-patch skin tests and specific IgE antibodies (0.38 kU/l). The diagnosis of cannabis allergy was based on history and positive prick-patch skin tests using native extracts from Cannabis sativa. Skin tests also showed sensitization to grass, ash and olive pollen extracts but not to latex, mold and house dust mites. Determination of specific IgE to latex remained negative. Serological investigations that used recombinant IgE for non-specific lipid transfer protein (LTP) to peach (rPru p 3), for grass profilin (rPh p 12), and birch pathogenesis-related protein 10 (rBet v 1) were negative. The treatment comprised absolute avoidance measures to banana consumption and a stop of any further cannabis use.

**CONCLUSIONS:** We report the case of a patient with a severe allergy to banana secondary to a cross-reactivity with Cannabis sativa. This is particularly relevant because cannabis exposure has already been associated with severe systemic hypersensitivity reactions to plant-derived food. Cannabis allergy is probably under-reported as a result from the illegal status of recreational cannabis use in many countries, which makes the patients reluctant to admit their abuse. Testing of specific IgE to cannabis and to other allergic components such as thaumatin-like protein to banana (Mus a 4) and oxygen-evolving enhancer protein is ongoing.

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**Molecular mechanisms of resistance to immunotherapy in human melanoma**
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The transition of immune checkpoint blockade therapy from research to clinic was very successful and led to an increased survival in patients with several types of tumors. However, many patients are still not responding to the therapy and some are experiencing a relapse during the treatment, reflecting primary and secondary therapy resistance, respectively. The challenge is now to characterize the responsible mechanisms of resistance and find ways to neutralize them. In the recent time, the laboratories of N. Haining and A. Ribas demonstrated that somatic mutations in pathways that regulate the response to T cell derived cytokines influenced the outcome of immunotherapy. Simultaneously, N. Neubert showed in our laboratory that the immunological behavior of melanoma cells is mainly homogenous and that some aspects of these conserved responses are limiting the efficiency of immunotherapy. Based on these results, we further hypothesize that the ability of melanoma cells to respond or not to the immunological clues present in the tumor microenvironment can affect the outcome of immunotherapy. We characterized the immunological behavior of 21 melanoma cells in response to a variety of T cell derived cytokines present in the tumor microenvironment and found that only treatment IFNy and TNFs led to major changes in vitro. Interestingly, the combination of both cytokines presented a strong additive effect and was even sometimes required for the induction of immune gene expression in melanoma cells. Although mostly homogenous, the immunological behavior of the melanoma cells still varied, with some cell lines responding strongly while others very poorly. We are now searching for the mechanisms explaining these differences and whether these changes are beneficial or detrimental in presence of an anti-tumoral immune response supported by immunotherapy. We are performing a whole exome sequencing to find somatic mutations related the behavior of the melanoma cells. This
Anaphylaxis to Adalimumab with positive skin test and basophil activation test (BAT): a case report

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Adverse drug reactions to biological medicines frequently present with clinical symptoms similar to anaphylaxis, which may result from either type I sensitization, cytokine release or complemen activation. We present a case suggesting an IgE-mediated hypersensitivity reaction. A 40-year-old female patient suffering from spondylarthitis had been treated with various synthetic disease-modifying antirheumatic drugs (DMARD) as well as biological DMARDS (Etanercept, Golimumab, Secukinumab) before being switched to Adalimumab because of lack of sufficient therapeutic response. After the 5th application she developed within 120 minutes of application a self-limiting pruritus. Two weeks later following the 6th subcutaneous injection she developed pruritus after 90 minutes and after 4 hours acute urticaria as well as mild dyspnea. She was successfully treated with oral antihistamines and corticosteroids. Skin prick tests to Adalimumab were clearly positive at a concentration of 50 mg/ml with two Adalimumab exposed controls being negative. The basophil activation test (BAT) showed a concentration-dependent activation and degranulation after stimulation with Adalimumab. BAT was negative in a non-exposed control. Total IgE and tryptase were normal at the time of allergological work-up. With rising use of biological medicines, the frequency of hypersensitivity reactions and loss-of-drug effect are expected to increase. There is evidence that patient antibodies may develop not only against chimeric antibodies but also against fully human antibodies such as Adalimumab. Recent research identified such anti-drug directed antibodies to different epitopes, thus potentially leading to anaphylaxis or blocking the antigen binding sites of the biologicals resulting in inactivation. Some of these antibodies were also detected in Adalimumab naïve controls. Binding patterns of those antibodies suggested cross-reactivity between different biologicals resulting in identification of patients at risk for anaphylaxis or loss-of-drug effect to biologicals. Although little is known about sensitivity and specificity of skin tests and BAT to Adalimumab, the clinical history of our patient, positive skin tests and positive BAT to Adalimumab indicate an IgE-mediated hypersensitivity reaction.

HPR 1

Secondary Prevention of Fragility Fractures: the Effects of a Tailored Intervention – an Observational Study

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Objectives: Minor Trauma Fractures (MTF) in elderly are common and impose a burden on public health. They increase mortality and morbidity as well as the occurrence of subsequent fractures. MTF patients often have an underlying bone disease, mostly osteoporosis. Osteoporosis is, however, known to be undiagnosed and undertreated. Efficient treatment of osteoporosis and risk of falling can reduce fracture risk. In our hospital, this led to the implementation of an intervention to foster screening and treatment of osteoporosis and fall prevention, with the goal to reduce the risk of subsequent fracture. The primary aim of this study was to assess the efficacy of an intervention for improving secondary prevention of MTF by implementing a dedicated health professional team.

Methods: Prospective, single-centre cohort study of MTF patients, older than 50 years. A standardized questionnaire and telephone interview were used to collect one year follow-up data. Primary outcomes were the number of patients having a subsequent fracture that occurred within one year after a primary fall and the amount of patients undergoing DXA scanning. Secondary outcomes were: The proportion of patients who were diagnosed with osteoporosis or osteopenia, the amount of patients receiving specific and unspecific medical treatment for osteoporosis. Data on DXA scanning and diagnosis of osteoporosis/osteopenia were compared to the results of a previous study in the same centre, published in 2004.

Result: A total of 411 patients were included. Mean age was 72 ± 9.3. Fifteen patients (3.9%) had a secondary fracture as a result of a fall.
252 (63.3%) patients received a DXA scan as compared to 12.6% reported in our previous study. Of all patients who received a DXA scan, 199 (79%) were diagnosed with osteoporosis or osteopenia. Of 98 patients who had a DXA proved diagnosis of osteoporosis 57.1% received specific and 90.8% received unspecific treatment for osteoporosis. In conclusion, implementing a dedicated health professional team improved the rate of patients who underwent DXA screening by 5 fold. Despite, more than a third of the patients remain unscreened and a large proportion of patients with a DXA proved diagnosis of osteoporosis did not receive specific medication. Consequently, this tailored intervention may have improved patients' and general practitioners' awareness regarding unspecific osteoporosis treatment but there still remains a large gap in specific osteoporosis treatment.

Einleitung:
Arbeitsfähigkeit bei Menschen mit chronischen Erkrankungen ist ein medizinisch-beruflich orientierter Maßnahmen in der medizinischen Rehabilitation (SIMBO), Valuation of Lost Productivity Questionnaire (VOLP), Work Ability Index (WAI/ABI), Work Limitations Questionnaire (WLQ) und Work Productivity and Activity Impairment Questionnaire (WPAI).


Ergebnisse: Insgesamt wurden acht Assessments und 74 Studien in die Übersicht eingeschlossen. Dabei wurden Aspekte von Validität und Praktikabilität folgender Assessments evaluiert und beschrieben: Productivity Costs Questionnaire (ipCOQ), Work Instability Scale for Rheumatoid Arthritis (RA-WIS), Screening-Instrument Arbeit und Beruf (SiBAR), Screening-Instrument zur Feststellung des Bedarfs an medizinisch-beruflich orientierten Maßnahmen in der medizinischen Rehabilitation (SIMBO), Valuation of Lost Productivity Questionnaire (VOLP), Work Ability Index (WAI/ABI), Work Limitations Questionnaire (WLQ) und Work Productivity and Activity Impairment Questionnaire (WPAI).

Fear of Falling (FoF), Recurrence of Falls and Quality of Life (QoL) in Elderly Patients with a Frailty. Fracture – an Observational Study
van der Vet P.C.R.1, Kusen J.Q.1, Rohner-Spengler M.1, Schmid L.2, Babst R.T.1, Henzen Ch.1, Link B.C.1, Beeres F.J.P.1
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Objectives: Falls are a major cause of injury-related deaths or permanent loss of independence. Falls have psychological and socio-economic consequences rendering Fear of Falling (FoF) a common health problem. FoF is related to activity restriction and inherently associated with increased risk of falling. To prevent secondary falls and fractures, a tailored intervention was implemented in our hospital. The primary purpose of this study is to evaluate how many patients visited a fall-prevention consultant.

Methods: Prospective cohort study of trauma patients in a level I trauma center. MTF patients older than 50 were eligible. Primary outcome was FoF, assessed by both the Falls-Efficacy Score-International (FES-I) and a binary, patient-reported outcome. Secondary outcomes were: subsequent falls, QoL (EuroQol-5-D), mobility and activity outdoor. Also, the amount of visits to the fall-prevention consultant was recorded.

Results: A total of 411 patients participated in the study. Mean age was 72 ± 9.3 and mean FES-I score was 21.1 ± 7.6. Sixty patients (15.1%) suffered from a subsequent fall. MTF patients reported to be afraid of falling again. Mean FoF was significantly higher in patients who experienced 1 or more secondary falls than in patients who did not fall again (23.7 ± 9.8 vs. 20.7 ± 7.1; P = 0.001). In patients with low activity level mean FoF was 26.5 ± 11.9, and in patients with a higher level it was 19.3 ± 5.6 (P = 0.000). FoF and QoL were negatively correlated (R = -0.64; P < 0.001). FoF was 72 ± 9.3 and mean FES-I score was 21.1 ± 7.6. Sixty patients (15.1%) suffered from a subsequent fall. MTF patients reported to be afraid of falling again.

Conclusion: FoF negatively affects patients'; QoL and their activity level. Though, over 40% of the patients reported to be afraid of falling, participation in a fall-prevention program was low. A minor intervention, as administered in this study does not seem to be sufficient to recruit patients into a fall prevention program. Broader efforts with the involvement of general practitioners and family environment seem necessary to improve patients'; awareness of their susceptibility to falls and their willingness to participate in a fall prevention program.

Möglichkeiten der interprofessionellen Erfassung der Arbeitsfähigkeit bei Menschen mit chronischen Erkrankungen
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Ergebnisse: Insgesamt wurden acht Assessments und 74 Studien in die Übersicht eingeschlossen. Dabei wurden Aspekte von Validität und Praktikabilität folgender Assessments evaluiert und beschrieben: Productivity Costs Questionnaire (ipCOQ), Work Instability Scale for Rheumatoid Arthritis (RA-WIS), Screening-Instrument Arbeit und Beruf (SiBAR), Screening-Instrument zur Feststellung des Bedarfs an medizinisch-beruflich orientierten Maßnahmen in der medizinischen Rehabilitation (SIMBO), Valuation of Lost Productivity Questionnaire (VOLP), Work Ability Index (WAI/ABI), Work Limitations Questionnaire (WLQ) und Work Productivity and Activity Impairment Questionnaire (WPAI).

Fazit: Die Ergebnisse zeigen, dass eine Auswahl an validen und praktikablen deutschsprachigen Assessments zur Erfassung der Arbeitsfähigkeit von Menschen mit chronischen Erkrankungen zur Verfügung steht.
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