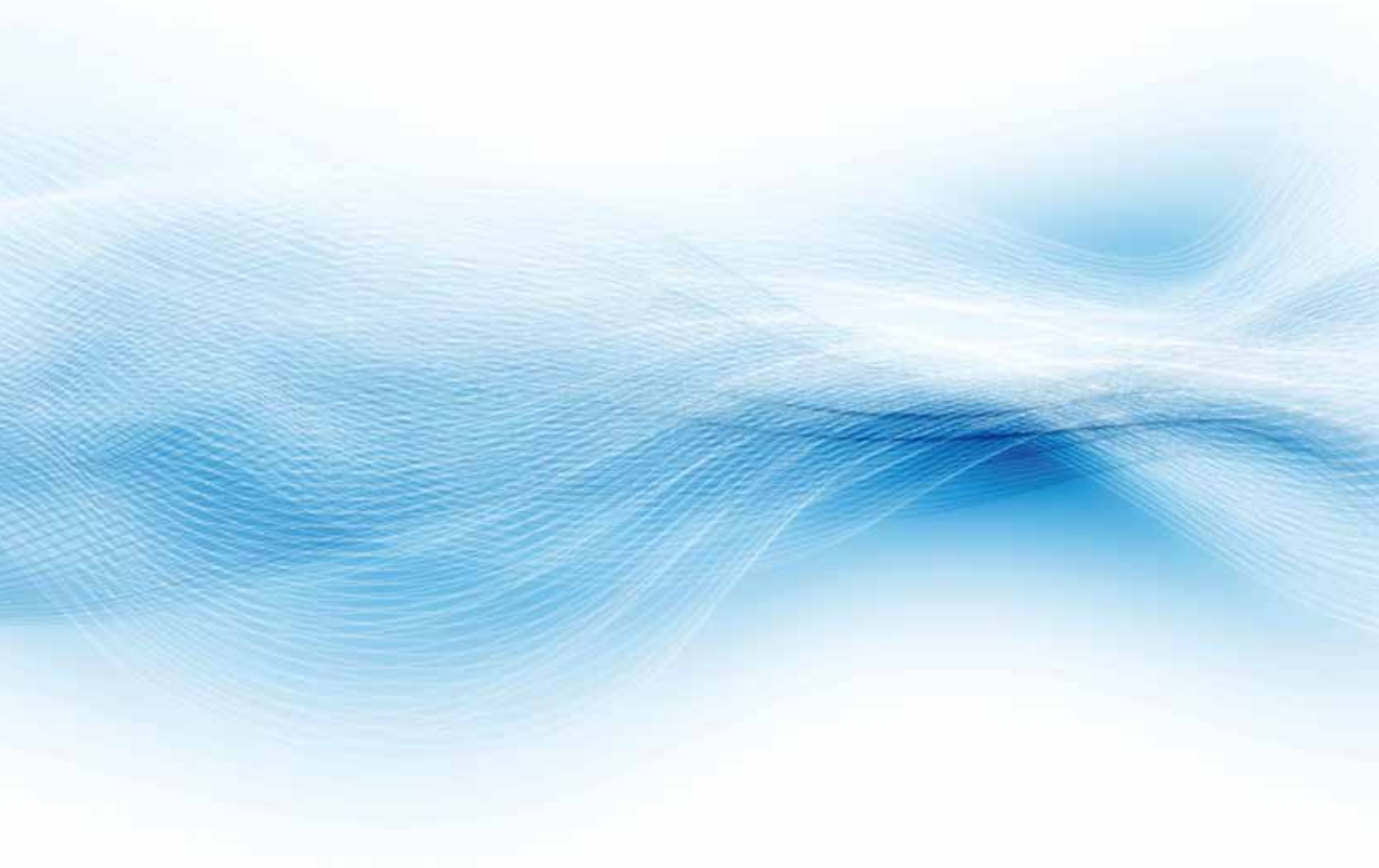
SVENSKA LÄKARESÄLLSKAPETS RIKSSTÄMMA 2010

PROGRAM REUMATOLOGI



Programmet genomförs med stöd av Abbott, Bristol Myers-Squibb, Medac, MSD, Pfizer, Roche och UCB

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Onsdag 1/12

8.30–10.00
Arbetsgruppsmöten
Professorskollegium
Studiegruppsmöten

Allmänt möte 10.00–12.15

11.30–12.30
Lunch

12.30–14.00
Allmänt sympsium
Psoriatic arthritis – clinical and epidemiologic aspects
Moderator: Ulla Lindqvist
Medverkande: Philip Helliwell, Leeds, UK m.fl.

14.30–16.00
Allmänt symposium
New concepts in the management of psoriatic arthritis
Moderator: Ulla Lindqvist
Medverkande: Ian Bruce, Manchester, UK m.fl.

16.30–18.00
Svensk Reumatologisk Förenings Årsmöte
Med utdelning av MSDs reumatologistipendium

Torsdag 2/12

8.30–10.00
Sektionssymposium
Co-morbiditet vid reumatisk sjukdom – muntlig presentation av utvalda abstract

1. Nordmark G et al. Variationer i genen för komplementfaktor 3 (C3) är associerade med lymfom vid primärt Sjögrens syndrom.
2. Erlandsson M et al. S100A4 is a novel regulator of bone formation and potential target in patients with osteoporosis.
3. Engdahl C et al. Östrogen skyddar mot artrit och inflammationsmedierad benförlust via östrogen receptor alfa.
4. Klingberg E et al. Impaired back mobility and syndesmophyte formation in ankylosing spondylitis are associated with low trabecular bone mineral density in both axial and peripheral skeleton.
5. Bremander A et al. Increased Rate of Cardiovascular Diseases in Patients with Ankylosing Spondylitis.
6. Nordin A et al. Patients with Systemic Sclerosis and Anti-Centromere Antibodies are affected with accelerated atherosclerosis.
7. Ljung L et al. Risk för akuta koronara syndrom i relation till TNF-hämning vid tidig reumatoid artrit.
8. Jakobsson K et al. Lower Body Mass Index is Associated with an Increased Risk of Giant Cell Arteritis.

10.00–12.00
Postersession

12.00–13.00
Lunch

13.00–14.00
Årets Nanna Svartzföreläsning
Eric Matteson, Rochester, MN, USA
Lessons from Vasculitis History; A Name, A No-Name, A New Name

14.30–16.00
Prisbelönt reumatologisk forskning

Pfizers Stora Forskningsstipendium inom Reumatologi – med föredrag av stipendiaten

Pfizers Stipendium till Yngre Forskare inom Reumatologi

Bästa abstract till riksstämman inom basal reumatologisk respektive klinisk reumatologisk forskning

16.15–18.00
Future Faculty Rheumatology
Med presentation av utvalda abstract
Gunnel Nordmark, Mattias Magnusson,
Meliha Kapetanovic

Verksamhetschefsmöte

Fredag 3/12

8.30–10.00
Allmänt symposium
Socioekonomiska faktorers betydelse för kronisk sjukdom
Moderator: Ingemar Petersson

10.30–12.00
Allmänt symposium
Nationella riktlinjer för rörelseorganens sjukdomar
Moderator: Richard Wallensten

ABSTRAKT

Psychometric Properties of the Swedish Rheumatic Disease Empowerment Scale, SWE-RES-23

Susann Arvidsson (2), Stefan Bergman (1), Barbro Arvidsson (5), Bengt Fridlund (3), Pia Tingström (4)
FoU Centrum, Spenshult Halmstad (1). FoU Centrum, Spenshult Halmstad och Hälsohögskolan, Jönköping (2). Hälsohögskolan, Jönköping (3). Linköpings universitet (4). Sektionen för Hälsa och Samhälle, Högskolan Halmstad och Gjøvik University College, Gjøvik, Norge (5).

Empowerment is a central concept in a patient-focused rheumatology care. WHO describes empowerment as a process in which the person receives more control over decisions and actions that affect the own life and health. Today there is no Swedish empowerment instrument for rheumatic diseases created or transl

The already existing questionnaire, Swedish Diabetes Empowerment Scale (SWE-DES-23), was adapted for use in patients with rheumatic diseases by exchanging the word diabetes with rheumatic disease in all the questions. No items were added or removed. The adapted questionnaire was called SWE-RES-23. In 2009, 260 patients with rheumatic diseases from a rheumatology unit in the southwest of Sweden completed the questionnaire.

In order to establish discriminant validity, a question about self-perceived health from SF-36 was used in addition to SWE-RES-23.

Construct validity was tested by using exploratory factor analysis. In order to determine unidimensionality of the empowerment subscales, inter-item correlations were calculated. Internal consistency reliability was tested by the use of the Cronbach-α coefficient.

The exploratory factor analysis resulted in five factors (empowerment subscales) with Eigenvalues >1 explaining 64.1% of the variance. The five empowerment subscales were: Goal achievement and overcoming barriers to goal achievement, Self-awareness, Managing stress, Assessing dissatisfaction and readiness to change, and Support for caring. The Cronbach-α values ranged from 0.59 to 0.91 and for the total score 0.92. All inter-item correlations were significant. Patients with very good and good self-reported health scored significantly higher on three empowerment subscales (Goal achievement, Self-awareness and Managing stress). The same patterns were seen in the other two empowerment subscales (Readiness to change and Support for change), but did not reach significance.

The SWE-RES-23 was a first step in developing a questionnaire for assessment of empowerment of patients with rheumatic diseases. The questionnaire possesses acceptable validity and reliability. To fully validate the SWE-RES-23 further studies are needed, but the instrument is even now possible to use in empowerment education programmes for patients with rheumatic diseases.

Patient reported events preceding the onset of rheumatoid arthritis – possible clues to etiology?

Maria Söderlin (3), Ulrika Bergsten (2), Björn Svensson (1)
Institutionen för rörelseorganens sjukdomar, Lunds Universitet (1). Spenshults Fou centrum (2). Spenshults reumatikersjukhus, Oskarström (3).

Little is known about the patients' own beliefs of the cause of RA. The aim of the study was to assess patients' beliefs of the cause of RA and outcome.

Between 1996 and 2004, 1,787 patients were included in the BARFOT early RA study in Sweden. The causes of RA were recorded at baseline. The number of swollen and tender joints, CRP, ESR, HAQ and VAS scales for pain and general health and DAS28 were registered at inclusion and at 3, 6 and 12 months. The EULAR Response Criteria were applied.

Data for the causes of RA according to the patients' explanation were available for 1,627 patients (92%). 70% of the patients could think of no cause of his/her RA. 16 % thought opinion that infection had caused their RA, 4.4% psychological trauma, 4.1% physical trauma, 2.8% surgery, 1.5% pregnancy and 1.2% vaccination. Younger patients associated infection as the cause of their RA more often than older patients. There were no differences in EULAR response and remission rates up to 1 year between patients reporting some event or infection and patients reporting no event. The patients who thought that RA was caused by infection showed a seasonal trend in the month of onset of RA. Women experienced RA more often as caused by infection and psychological trauma than men.

70% of the patients had no idea of the cause of their RA and 16% thought that infection was the cause. Our data supports the idea of multifactorial etiology in RA.

Factors promoting health-related quality of life in patients with rheumatic diseases 12 months after rehabilitation

Susann Arvidsson (2), Barbro Arvidsson (4), Bengt Fridlund (3), Stefan Bergman (1)
FoU Centrum, Spenshult Halmstad (1). FoU Centrum, Spenshult Halmstad och Hälsohögskolan, Jönköping (2). Hälsohögskolan, Jönköping (3). Sektionen för Hälsa och Samhälle, Högskolan i Halmstad (4).

Rheumatic diseases have significant adverse impact on the individual from physical, mental and social aspects, resulting in a low estimation of health-related quality of life (HRQL). Patients with rheumatoid arthritis who receive a multi-disciplinary team-based care in a rheumatology clinic could get improved HRQL. Several factors can be supposed to promote health in patients with rheumatic diseases and in health-promoting work within the clinical practice it would be valuable to identify health factors that affect HRQL in a positive direction.

This is a longitudinal cohort study in 185 patients with rheumatic diseases with test one week and 12 months after rehabilitation on a Swedish rheumatology clinic. HRQL was assessed by SF-36 together with suggested health factors (chronic musculoskeletal pain, sleep quality, food habits, exercise habits, leisure habits, sexual lust, sense of coherence (SOC), social support and socio-demographic variables). The association between SF-36 subscales and suggested health factors were estimated by OR and 95 % CI calculated by multivariable logistic regressions.

Factors predicting better outcome in HRQL in one or several SF-36 subscales were being of younger ages or middle-ages, feeling painless, having good sleep structure, feeling rested after sleep, doing low effort of exercise more than twice a week, having strong SOC, having emotional support and practical assistance, having higher educational level, and having working capacity. The most important factors were having strong SOC, feeling rested after sleep, having working capacity, being of younger ages or middle-ages, and having no/small problem with sleep structure.

The most important factors promoting HRQL in patients with rheumatic diseases 12 months after rehabilitation were having strong SOC, feeling rested after sleep, having working capacity, being of younger ages or middle-ages, and having no/small problem with sleep structure. These health factors are important to address in clinical work with rheumatic diseases to optimise treatment strategies.

Impaired "window of opportunity" in smokers. Data from BARFOT, a multicenter study of early RA

Maria Söderlin (2), Stefan Bergman (1)
FoU-centrum, Spenshults Reumatikersjukhus, Halmstad (1). Spenshults reumatikersjukhus, Oskarström (2).

We wanted to study outcome in very early RA (disease duration < 12 weeks). We also wanted to study the effect of smoking on very early RA.
Between 1996 and 2004, 1,684 adult patients were included in the BARFOT early RA study in Sweden. DAS28,CRP, HAQ, RF, anti-CCP, general health and pain VAS and drug treatment were registered at inclusion and at 3, 6 and 12 months. Smoking was recorded at inclusion. EULAR Response criteria were measured at 3, 6 and 12 months.
A total of 193 RA (193/1684, 11%) patients had a disease duration < 12 weeks. These patients achieved significantly more often EULAR response at 3 and 12 months than patients recruited in the study later despite having a more aggressive disease (75% EULAR response for patients with a disease duration <12 weeks, 71% 13-24 weeks, 67% 25-52 weeks disease duration at 3 months p=0.039, 12 months 82%, 81% and 75%, respectively, p=0.015). There was a significant correlation between disease duration and EULAR response. The trend for improvement from baseline to 12 months of DAS28 and HAQ was linear up to 9 months from symptom onset after which the improvement trend levelled off. For smokers no such trend could be seen.

This study showed a "window of opportunity" in subjects with short disease duration, with better therapeutic response as measured by DAS28 and HAQ over 12 months for non-smokers, but not for smokers.

The NMDA receptor antagonist ameliorates and delays development of arthritis by enhancing regulatory T cells

Sofia Silfverswärd Lindblad (2), Piotr Mydel (2), Annelie Hellvard (1), Ing-Marie Jonsson (2), Maria Bokarewa (2)
Avdelningen för Reumatologi & Inflammations forsking, Sahlgrenska Akademin vid Göteborgs Universitet (1). Avdelningen för Reumatologi & Inflammationsforskning, Sahlgrenska Akademin vid Göteborgs Universitet (2).

Neurotransmitters are strong regulators of immune responses. Glutamate (Glu) is the most prevalent excitatory neurotransmitter in vertebrates. The Glu-receptor family consists of eight different metabotropic and three ionotropic Glu receptors. The neuroendocrine impact on rheumatoid arthritis is not fully understood. In this study, we assessed the influence of Glu-sensitive receptors on collagen-induced arthritis (CIA) in mice.

CIA was induced in male DBA/1 mice by immunization with chicken collagen type II.

From immunization day 1 mice were exposed to the following Glu-receptor inhibitors: group 1 received the NMDA-receptor antagonist, memantine; group 2 received the metabotropic Glu receptor antagonist, AIDA; and group 3 received the excitatory amino acid antagonist kynurenic acid. Arthritis was evaluated clinically and morphologically. The effect of treatment on B- and T cell populations and levels of anti-CII and anti-CCP antibodies were evaluated.

Memantine treatment significantly improved the course of CIA, diminishing its

frequency (P<0.05) and severity (P<0.05) in comparison to the control group and groups treated with AIDA and kynurenic acid. Memantine reduced the histological arthritis index, including synovitis (P=0.009), erosion (P=0.004) and the levels of bone resorption marker CTX-I (P=0.04). Memantine treatment upregulated expression of Foxp3 in spleen CD4+ T cells followed by an increase in CD4+CD25+ regulatory T cells. Memantine treatment induced accumulation of CD19+ B cells in spleen and up-regulated CD25 on the cell surface. Consequently, levels of anti-CII antibodies in the memantine-trated group were significantly higher (P=0.008) than in control.

These results demonstrate that inhibition of NMDA receptors delays and ameliorates

development of arthritis, potentially by promoting formation of regulatory T lymphocytes. Thus, abrogation of NMDA receptor signalling may be a promising tool in the treatment of rheumatoid arthritis.

Low circulating soluble RAGE levels in juvenile idiopathic arthritis are associated with systemic disease

Chris Pruunsild (1), Karin Uibo (4), Hille Liivamägi (1), Sirje Tarraste (3), Tiina Talvik (1), Rille Pullerits (2)
Children's Clinic, Tartu University Hospital, Estonia (1). Dept. of Rheumatology and Inflammation Research, Sahlgrenska Academy at Göteborg University (2). Tallinn Children's Hospital, Estonia (3). Tallinn Children's Hospital, Estonia (4).

Chronic arthritis occurs in childhood as juvenile idiopathic arthritis (JIA). Activation of membrane-bound RAGE receptor via its pro-inflammatory ligands leads to chronic sustained inflammation whereas soluble RAGE (sRAGE) has been suggested to neutralise RAGE ligands and abrogate inflammation.

The objective of our study was to assess sRAGE levels in children with JIA and to investigate the relationship between sRAGE levels and disease subgroup characteristics, inflammatory / immunological parameters and disease progression.

Soluble RAGE levels in sera from 136 Estonian children (mean age 9.7 ± 0.4 years) with JIA at the disease initiation (mean disease duration 8 ± 1 months) and after 10 years prospective follow up period (n = 21) were analysed using an ELISA technique.

The mean sRAGE levels in the circulation of JIA patients were comparable at the diagnosis and after 10 years follow up (1214 ± 40 vs 1159 ± 82 pg/ml, respectively).

Children with systemic JIA displayed lower sRAGE levels (895 ± 255 pg/ml) as compared to other groups. In contrast, children with enthesitis-related arthritis had highest serum sRAGE (1552 ± 96 pg/ml) whereas sRAGE levels positively correlated with CRP (rho 0.704, $p < 0.05$) and platelet count (rho 0.867, $p < 0.02$) in these patients. A significant positive correlation was found between sRAGE levels at study start and after 10 years follow up in the whole studied group (rho 0.572, $p = 0.006$) and in the subgroups without any radiological damage or ultrasound verified inflammation (rho 0.684 and 0.886, respectively; $p < 0.05$). There was no difference between sRAGE levels in boys and girls (1264 ± 57 pg/ml vs.1177 ± 54 pg/ml, respectively).

Children with severe systemic arthritis display low sRAGE levels, probably reflecting the magnitude of inflammation and consumption of sRAGE due to binding of pro-inflammatory RAGE ligands. In contrast, higher sRAGE level might relate to better radiological outcome.

Role of the Fms-Like tyrosine Kinase 3 ligand induced dendritic cells for development of antigen induced arthritis

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Avdelningen för Reumatologi & Inflammations forsking, Sahlgrenska Akademin vid Göteborgs Universitet (1). Avdelningen för Reumatologi & Inflammationsforskning, Sahlgrenska Akademin vid Göteborgs Universitet (2). Department of Rheumatology and Inflammation Research, Sahlgrenska University Hospital, Göteborg (3).

Dendritic cells (DCs) are a heterogeneous group of antigen presenting cells that helps to maintain peripheral tolerance and to induce adaptive immune responses. Fms-Like tyrosine Kinase 3 (Flt3) is a receptor tyrosine kinase crucial for development of DCs. Flt3 is activated by binding of its ligand (Flt3-L). We have recently shown that Flt3-L is accumulated in synovial fluid of RA patients and has arthritogenic potential. Inhibition of Flt3 by tyrosine kinase inhibitor sunitinib reduces antigen induced antibody formation and alleviates severity of experimental arthritis. In the present study we evaluate the role of Flt3-L induced DCs for development of antigen induced arthritis.

Balb/C (n=20) and As/n (n=18) mice were immunized with mBSA on day 0 and day 7, on day 21 mBSA was injected intra-articular in the knee joint. Balb/C (n=8) and As/n (n=7) mice were treated with soluble Flt3-L (1,5 ug/mouse/day), starting 4 days before the first immunization and continued until the end of experiment on day 28. Severity of arthritis was evaluated morphologically. Levels of antibodies (mBSA and anti-CCP), Flt3-L, MMP-3, Ctx and Rank-ligand levels in serum were measured using ELISA. IL-6 levels in serum were measured by bioassay. Plasmacytoid and conventional DC populations were analyzed in spleen, lymph nodes and synovia using flow cytometry.

Treatment with Flt3-L resulted in a significant increase of CD11c+ spleen cells in both Balb/c and As/n mice strains. Analysis of DC subpopulations in spleen showed increased numbers of CD11c+/CD8+/CD11b- cells in treated mice whereas other DC subpopulations were decreased compared to controls. Similar pattern was found in synovia and lymph nodes from treated Balb/c mice. Flt3-L levels in serum were significantly increased in treated As/n mice compared to As/n controls, though there was no difference in serum levels of MMP-3, CTX and RANK-L. Morphological evaluation showed no change in synovitis in Flt3-L treated As/n and Balb/c mice compared to controls. Results on the development of erosions were inconclusive and need further assessment.

We show that low levels of soluble Flt3-L are sufficient to induce formation of DCs in vivo. Treatment with Flt3-L also seems to cause a shift in DC subpopulations, but increased numbers of DCs do not affect synovitis mBSA induced arthritis. Continuing experiments are carried out to further evaluate role of Flt3-L induced DCs for antigen presenting function.

Germinal center (GC) formation in salivary gland biopsies is a new and strong predictor of Non-Hodgkin's lymphoma (NHL) in primary Sjögren's Syndrome (pSS)

Elke Theander (2), Lilian Vasaitis (4), Eva Baecklund (4), Gunnel Nordmark (4), Rolf Liedholm (3), Gunnar Warfvinge (5), Roland Jonsson (1), Malin Jonsson (1)
Broegelmann Research laboratory, the Gade institute, Bergens universitet (1). Kliniken för Reumatologi, Skånes Universitetssjukhus, Lund Universitet (2). Käkkirurgiska kliniken, Skånes Universitetssjukhus, Lund Universitet (3). Reumatologkliniken, Inst. för medicinska vetenskaper, Uppsala universitet (4). Tandvårdshögskolan i Malmö, Lund Universitet (5).

Due to increased risk of NHL in pSS the identification of better markers for lymphoma development is crucial. Objective: Does GC formation in salivary gland biopsies from the time point of pSS diagnosis predict NHL? Does GC formation correlate with other markers of NHL?

174 pSS minor salivary gland biopsies from the Swedish SS centers in Malmö and Uppsala underwent blind and independent reevaluation by light-microscopy at the Broegelmann Research Laboratory, Bergen, Norway for the presence of GC-like structures. These were determined by a densely packed dark zone and a light zone in biopsies with classical focal infiltration within otherwise normal salivary glands. The presence of NHL was determined by linkage of the local SS registries to the Swedish cancer registry. Observation time was defined as time from salivary gland biopsy until lymphoma diagnosis, death or end of follow-up. The median (IQ range) time between diagnosing pSS and biopsy was 1 week (0-16). The total observation time was 1859 patient years at risk (range:1 month - 26 yrs). Time between salivary gland biopsy and NHL diagnosis was in median 8 yrs (range: 2 yrs and 4 months -12 yrs and 7 months). Risk of developing NHL in patients with or without GC formation was compared by Cox regression analysis and Kaplan Meier statistics/log rank test. Associations between GC formation and other risk variables were determined by Chi2 statistics.

In total 136 biopsies showed focal sialadenitis (focus score >1) at reevaluation. In 43 (32%) of the biopsies with focal sialadenits GC like structures were detected. Seven patients had developed NHL. Six of the 7 NHL patients (86%) had GC like structures at the time of diagnosing pSS. Patients with GC-like structures had 15 times increased risk of developing NHL compared to those without. Hazard Ratio (HR) 15.4, 95%CI: 1.85-128, p=0.01. Log-rank test: p=0.001. Positive predictive value 16%, negative predictive value 99%.

GC positivity correlated with autoantibodies to SSA/SSB, lymphadenopathy, systemic disease activity, high-risk type of SS (all $p<0.05$).

The presence of GC-like structures in the diagnostic salivary gland biopsies in pSS is highly predictive of lymphoma development. This marker shows a stronger association with NHL occurrence than earlier risk markers and is an important new prognostic factor in the care of pSS patients. It may be included in guidelines for selection of pSS patients for biological B-cell directed treatment.

Circulating Immune Complexes in Patients with Severe Extra-articular RA Induce Tumour Necrosis Factor Production by Peripheral Blood Mononuclear Cells

Carl Turesson (3), Linda Mathsson (1), Lennart Jacobsson (3), Gunnar Sturfelt (2), Johan Rönnelid (1)
Enheten för Klinisk Immunologi, Uppsala Universitet (1). Reumatologiska kliniken, Skånes Universitetssjukhus, Lund (2). Reumatologiska kliniken, Skånes Universitetssjukhus, Malmö (3).

A subset of patients with rheumatoid arthritis (RA) develop severe extra-articular disease manifestations. Autoantibodies and immune complexes (IC) have been implicated in the pathogenesis, but their role in systemic inflammation in RA remains to be defined. Our aim was to study circulating IC and their influence on cytokine production by peripheral blood mononuclear cells (PBMC) in patients with active, severe extra-articular RA (ExRA) compared to RA controls with no extra-articular manifestations.

Thirty-five consecutive patients with RA and severe ExRA manifestations according to predefined criteria (pericarditis, pleuritis, major cutaneous vasculitis, Felty's syndrome, glomerulonephritis, vasculitis related neuropathy, scleritis, episcleritis or other major organ vasculitis) were studied. Seventy controls with RA but no ExRA manifestations, individually matched for age, sex and disease duration, served as the comparison group. Blood was drawn directly after ExRA was diagnosed and before any new treatment was started, and samples were stored at −70°C until investigated. IC prepared as serum polyethylene glycol (PEG) precipitates were added to serum-free PBMC cultures and tumour necrosis factor (TNF) levels were measured after 20 hours using ELISA. Circulating C1q-binding IC and anti-CCP antibodies were determined using ELISA. RF was detected using nephelometry.

Circulating IC levels were higher among patients with ExRA compared to RA controls [median 8.52 μgEq/mL; interquartile range (IQR) 3.63-24.27 vs median 4.51 μgEq/mL; IQR 1.81-10.45 ($p=0.005$)]. TNF induction from PBMC was greater after adding

serum PEG precipitates from ExRA patients [mean 17.7 pg/mL; SD 12.1 vs mean 12.9; SD 7.6; for RA controls (p=0.02)], and levels of C1q-binding IC correlated with IC-induced levels of TNF among ExRA patients (r=0.40; p=0.02) as well as among RA controls (r=0.35; p=0.004). There was a strong association between circulating IC levels and RF among patients with ExRA (r=0.62; p<0.001), in particular in the subset with major cutaneous vasculitis (n=9; r=0.76; p=0.03). Anti-CCP antibodies did not correlate with circulating IC levels in patients with ExRA.

Patients with severe ExRA manifestations were characterized by high levels of circulating IC, and IC from ExRA patients were stronger inducers of TNF production from PBMC compared to IC from RA controls. These results suggest that circulating IC enhance RF production and systemic inflammation in severe ExRA.

S100A4 deficiency prevents joint destruction in septic arthritis by changing the pattern of adhesion molecules

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Staphylococcal infection in the joints accounts for rapidly progressing bone destruction and irreversible loss of joint function. We have recently demonstrated that S100A4 deficiency is associated with efficient bacterial clearance in septic arthritis. The aim of our study is to investigate the impact of S100A4 deficiency in staphylococcal arthritis.
S.aureus was introduced intra-articularly by a single injection in the knee joints of healthy S100A4KO (n=6) and WT mice (n=10) (LS-1 strain, 1x104 cfu/knee). Four days after inoculation, morphological changes in infected joints were evaluated with regard to synovitis and bone erosion. Synovia tissues and spleens were processed for flow cytometric analysis of distribution of inflammatory cells and surface adhesion molecules.

Morphological assessment of infected knee joints showed synovitis in 40% of S100A4KO mice compared to 100% of WT mice. The arthritis index in S100A4KO mice was lower as compared to WT mice (p=0.05). Erosions were seen in none of S100A4KO mice and in 83% of WT mice (p=0.02). As expected, the infected mice showed an increased influx of granulocytes (Ly6G+) to synovia (p=0.0002) and to spleen (p=0.0006) as compared to non-infected mice. In spleens, granulocytes (Ly6G+) had high expression of integrins (CD18+ and CD11b+) (p<0.05), while T lymphocytes (CD4+, CD8+) had high expression of L-selectin (p=0.03). S100A4KO mice have higher integrin and lower L-selectin expression on CD4+ T cells both in spleen and synovial tissue compared with WT mice (p=0.05).

S100A4 deficiency prevents joint destruction during staphylococcal infection, potentially by changing the leukocyte pattern of adhesion molecules.

Infliximab dose reduction sustains the clinical treatment effect in ankylosing spondylitis

Rille Pullerits (2), Boel Mörck (1), Mats Geijer (3), Tomas Bremell (2), Helena Forsblad d'Elia (1)
Avdelningen för Reumatologi och Inflammationsforskning, Sahlgrenska Akademin vid Göteborgs Universitet (1). Avdelningen för reumatologi och inflammationsforskning, Sahlgrenska Universitetssjukhuset, Göteborg (2). Radiologi, Universitetssjukhuset Lund (3).

The primary objective of the study was to evaluate the efficacy of infliximab (IFX) (5 mg/kg) treatment on clinical and radiological disease activity and quality of life in patients with active ankylosing spondylitis (AS) at 16 and at 52 weeks. The second aim was to determine whether IFX dose reduction during the second year would retain the treatment effect.

The patients (n = 19) fulfilling the modified New York criteria for definite AS and having active disease (BASDAI score > 4.0) were included and treated with IFX 5 mg/kg at week 0, 2, 6 and thereafter every 6 weeks for totally 52 weeks. The efficacy of therapy was determined at week 16 and 52 by evaluating changes in disease activity (BASDAI, ESR, CRP), functional assessment (BASFI), metrological measure (BASMI), quality of life (SF-36) and MRI of sacroiliac joints. During the second year IFX dose was reduced to 3 mg/kg every 8 weeks and the patients were followed up by inflammatory parameters and BASDAI at 2 years.

18 patients were followed up at 1 year and 15 patients completed the 2-year trial. The primary endpoint of the study defined as < 50% or 2 cm improvement at week 16 from baseline of BASDAI was achieved in 16/19 (84%) patients. Significant reduction in BASDAI index (p = 0.0002), decrease in CRP (p <0.007), ESR (p < 0.002), decrease in BASFI score (p < 0.0004) along with reduction in BASMI score (p < 0.007) was observed at week 16 and 56 in comparison with baseline. A significant improvement in patients' quality of life regarding mental health was observed at week 16 and 56 as compared with baseline. MRI-defined inflammatory changes in the sacroiliac joints were detected at baseline in 15/19 (79%) of patients, decreased significantly (p = 0.0006) after initiation of IFX therapy and disappeared in 11/15 patients (73%) already at 16 weeks. IFX treatment effect was preserved throughout the second year after dose reduction of IFX (median CRP 8 mg/l, SR 8 mm/h, BASDAI 3.2).

IFX treatment (5 mg/kg) reduces disease activity, improves spinal mobility, functional status and patients´ quality of life and decreases MRI-defined inflammatory changes in active AS. More importantly, dose reduction of IFX to 3 mg/kg sustains the treatment effect.

Impaired back mobility and syndesmophyte formation in ankylosing spondylitis are associated with low trabecular bone mineral density in both axial and peripheral skeleton

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Bone mineral density (BMD) can be overestimated when measured in the spine by dual energy x-ray absorptiometry (DXA) in ankylosing spondylitis (AS) patients with advanced disease. Quantitative CT (QCT) of the spine is considered a superior method and offers an opportunity to examine BMD in trabecular bone and cortical bone separately. XtremeCT, a high-resolution 3D peripheral QCT method, enables bone morphology studies of peripheral skeleton. The aims of this study were to compare different techniques of assessing BMD in AS and to study the effects of disease related parameters on trabecular and cortical bone.

69 male patients, randomised from a group 204 AS patients (Modified New York criteria) included in an observational study of osteoporosis in the west of Sweden, underwent BMD assessment with QCT of L1-L4 and XtremeCT of ultradistal radius and tibia. BMD was also measured by DXA in lumbar spine in anteroposterior (ap) and lateral projection, in hip and in forearm. Lateral x-rays of spine were taken to assess vertebral fractures using Genant score and syndesmophyte formation using mSASSS.

Age (median and range) 48 (17-78) years, symptom duration 20 (2-55) years, BASDAI 2.7 (0.2-7.9), ASDAS 2.1 (1.0, 4.4) and BASMI 3.0(1.0-7.2). QCT of lumbar spine revealed significantly more patients with osteoporosis (n=26, 37.7%) and osteopenia (n=21, 30.4%), compared with lumbar spine ap DXA, which showed osteoporosis in 4 patients (5.8%) and osteopenia in 13 (18.8%) (p<0.001). Low trabecular BMD in lumbar spine measured by QCT and low trabecular density in radius and tibia measured by XtremeCT were significantly connected with high mSASSS (rS= -0.41 to -0.62), BASMI (rS= -0.45 to -0.62), BASFI (rS=-0.39 to -0.54) and mean ESR during the last 5 years (rS=-0.24 to -0.42), but only weakly associated with Genant score (rS=-0.25 to -0.28). BMD in total hip and femoral neck measured by DXA were more strongly associated with Genant score (rS= - 0.37; p=0.002). BMD measured with DXA in lumbar spine in ap and lateral projection were not connected with disease parameters.

Impaired back mobility and syndesmophyte formation in AS are closely connected with low trabecular BMD in both axial and peripheral skeleton and associated with deteriorated peripheral bone morphology, demonstrated by the new imaging technique, Xtreme CT. QCT of lumbar spine is more sensitive than DXA in detecting osteoporosis in AS and may be the gold standard method in the future.

Variationer i genen för komplementfaktor 3 (C3) är associerade med lymfom vid primärt Sjögrens syndrom

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Patienter med primärt Sjögrens syndrom (pSS) har 15 gånger ökad risk för lymfom. Riskfaktorer är recidiverande spottkörtelsvullnad, hudvaskulit och lågt komplement. Färska resultat visar att förekomsten av germinalcentra i läppspottkörtelbiopsier predikterar lymfom. Det är inte känt om genetiska faktorer bidrar till lymfomutvecklingen. Målet med denna studie var att analysera singel nukleotid polymorfier (SNPs) i gener med tänkbar betydelse för lymfomutvecklingen.

Vi inkluderade 540 svenska och norska patienter med pSS och 532 friska kontroller. Patienterna uppfyllde gällande diagnoskriterier (AECC 2002) för pSS och alla var kaukasier. SNPs i 12 utvalda gener genotypades med GoldenGate assay från Illumina Inc.,USA. Initialt jämfördes allelfrekvenserna mellan pSS patienter och kontroller i en fall-kontrollstudie, därefter allelfrekvenserna mellan patienter med lymfom (n=21, 3,9%) och patienter utan lymfom (n=519) i en fall-fall associationsanalys. Kliniska och laboratoriedata hämtades ur patienternas journaler.

I fall-kontrollstudien fann vi en association mellan pSS och SNPs i generna C3, C4A, BCL2 och IL5, alla p<0,05. När vi analyserade pSS patienter med lymfom jämfört med pSS patienter utan lymfom fann vi en stark association mellan SNP rs2241394 i C3 och lymfom, med p = 4,8 x 10-4, OR 3,1 (95% CI 1,59-6,02). Ytterligare 4 SNPs i C3 visade association till lymfom med p<0,05. Vi fann en svag association mellan lymfom och SNPs i BCL2 och BCL6 (p<0,05). Patienterna med lymfom hade signifikant högre frekvens ANA, hudvaskulit, spottkörtelsvullnad, lymfadenopati, leukopeni och förekomst av extraglandulära manifestationer totalt, alla p<0,05. Plasmanivåer av C3 fanns uppmätta på 9 patienter med lymfom och 83 patienter utan lymfom. Nivåerna var signifikant lägre hos patienterna med lymfom, 0,78 ± 0,19 g/L versus 0,97 ± 0,19, p=0,03.

Vi fann variationer i genen C3 med stark association till förekomsten av lymfom hos patienter med pSS. Fortsatta studier får utvisa om dessa SNPs har funktionella konsekvenser som kan bidra till förståelsen för lymfomutvecklingen samt om dessa SNPs associerar till specifika typer av lymfom vid pSS.

Long-chain polyunsaturated fatty acid composition in plasma, adipose tissue and diet among patients with ankylosing spondylitis

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Non-steroidal anti-inflammatory drugs (NSAIDs) are the basic treatment of pain and stiffness in patients with ankylosing spondylitis (AS). NSAIDs act by blocking the synthesis of eicosanoids which are derived from 20-carbon long-chained polyunsaturated fatty acids (LCPUFAs). LCPUFAs in the body are obtained from the diet or from endogenous elongation of shorter dietary polyunsaturated fatty acids.

In a cross-sectional design, dietary intake of LCPUFAs, composition of LCPUFAs in plasma and adipose tissues and disease activity were assessed among patients with AS who were not on treatment with biologics. Blood samples and gluteal fat biopsy were drawn from sixty-six patients (51 male, 15 female,mean age 48 years, range 26-65) with AS fulfilling the modified New York criteria. Dietary intake of LCPUFAs were calculated on the basis of a semi-quantitative food frequency questionnaire. Plasma and adipose tissue content of LCPUFAs were assessed using gas chromatography. Disease status was measured with erythrocyte sedimentation rate (ESR, Westergren), high sensitive C-reactive protein (hiCRP) and the Bath Ankylosing Spondylitis Disease Activity Index (BASDAI).

The phospholipid plasma level of Arachodonic Acid (AA) correlated significantly with disease activity according to both the total BASDAI score (Rs=0.39, p<0.01), and five of its six sub-scores. Levels of other long-chained fatty acids in plasma phospholipids such as dihomo gammalinolenic acid and eicosapentaenoic acid did not correlate with BASDAI. Neither did contents of LCPUFAs in gluteal adipose tissue and dietary intake correlate with BASDAI.

The plasma phospholipid content of AA correlated with BASDAI, and may be regarded as a biomarker for disease activity. The lack of correlation between BASDAI and LCPUFAs in diet and adipose tissue, suggests that the endogenous production and incorporation of AA in phospholipids may be involved in the pathogenesis of AS.

The interferon (IFN)-alpha production by plasmacytoid dendritic cells stimulated with RNA-containing immune complexes is promoted by NK cells via soluble factors and cell-cell contact

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In systemic lupus erythematosus (SLE) and other autoimmune diseases an overactivation of the type I interferon (IFN) system has been demonstrated. This is due to IFN production from plasmacytoid dendritic cells (pDC) trigged by endogenous nucleic acid containing immune complexes. We showed earlier that IFN-alpha production by pDC is regulated by NK cells and monocytes. NK cells enhance the IFN-alpha production up to thousand fold, while monocytes inhibit the stimulatory effect of NK cells (1). We investigated the mechanism whereby NK cells promote type I IFN production by pDCs and whether the enhancing capacity of NK cells from SLE patients is altered.

pDCs and NK cells were isolated from PBMC of healthy blood donors or SLE patients and stimulated with RNA-IC consisting of purified U1 snRNP and SLE-IgG. IFN-alpha and 16 other cytokines in cell culture supernatants were determined by immunoassays.

Soluble factors, which enhanced the IFN-alpha production by RNA-IC stimulated pDCs, were produced after RNA-IC or IL-12/IL-18 stimulation of NK cells. We showed that MIP-1β; (CCL4) was partially responsible for the increased IFN production while MIP-1alpha (CCL3), RANTES (CCL5), IFN-γ; or TNF-alpha which were produced after RNA-IC stimulation did not have any stimulatory effects. Further, cell-cell contact via LFA-1 contributed to the NK cell enhanced IFN-alpha production by pDCs. Finally, NK cells from SLE patients and healthy controls were compared for their ability to promote the RNA-IC induced IFN-alpha production by pDCs. SLE-NK cells were less stimulatory compared to control NK cells when stimulated with RNA-IC (p=0,004). However, addition of IL-12/IL-18 made the SLE-NK cells as efficient as healthy control-NK cells in enhancing the IFN production by pDCs

We describe novel mechanisms, involved in the cross-talk between NK cells and pDCs, which regulate the production of IFN-alpha via both soluble factors and cell-cell contact. Further, we showed that the stimulatory function of the NK cells from SLE patients is decreased but can be restored by IL-12/IL-18. Thus, several molecular mechanisms are responsible for the NK cell mediated increase in IFN production by RNA-IC stimulated pDC and suggest that the NK cell/pDC axis could be targeted in autoimmune diseases driven by an increased type I IFN production.

1. Eloranta et al. Arthritis Rheum. 2009:2418-27. Regulation of the IFN-alpha production induced by RNA-containing immune complexes in PDC.

KI-6: a serological biomarker for interstitial lung disease and pulmonary function in patients with polymyositis and dermatomyositis

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Objectives: To investigate whether Caucasian patients with polymyositis (PM) or dermatomyositis (DM) and interstitial lung disease (ILD) have elevated serum levels of KL-6 compared to patients without ILD, and whether KL-6 could be used as a marker for disease activity and prognosis of ILD in PM/DM.
Methods: 30 PM/DM patients (seven with ILD), and 17 age- and gender matched healthy controls were included for a cross-sectional analysis. Twelve patients were followed for longitudinal evaluation. ILD was defined as restrictive lung function impairment with radiographic signs of ILD. KL-6 serum levels were measured using a sandwich enzyme immunoassay kit. Groups were compared by Mann Whitney test.
Results: PM/DM patients with ILD had significantly higher KL-6 serum levels compared to patients without ILD (995, 533-2318 U/ml versus 322, 132-1225 U/ml, p=0.0002). Median serum levels of healthy controls were 225 U/ml (range 136-519). At cut-off level of 549 U/ml (mean ±2.5 SD of controls) the sensitivity and specificity was 82% and 92%, respectively for diagnosis of ILD. KL-6 serum levels inversely correlated with percentage forced expiatory volume in one second (FEV1), vital capacity (VC), total lung capacity (TLC), Forced VC and diffusing capacity of carbon monoxide (DLco). In the longitudinal follow up, this inverse correlation was even higher. The changes of KL-6 serum levels showed a significant inverse correlation with changes of FEV1%, TLC%, DLco% and residual volume.
Conclusions: Serum KL-6 levels may serve as biomarker of ILD in patients with PM/DM, and seem to be useful to assess clinical response to treatment.

Bone mineral density by digital X-ray radiogrammmetry is strongly decreased and associated with joint destruction in established rheumatoid arthritis; hormone replacement therapy reduces hand bone loss

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Rheumatoid arthritis (RA) is characterised by the development of cartilage destruction in the joints, erosions in the subchondral bone at the joint margins and by periarticular osteopenia. In addition, generalised osteoporosis is a well-known phenomenon. Localised bone loss in the hands can be measured by digital X-ray radiogrammmetry (DXR), which gives an estimate of cortical hand bone mineral density (BMD) in the metacarpals two to four. Quantification of the localised periarticular osteoporosis has been proposed to be an outcome measure in early RA and to be able to predict future radiographic joint damage. DXR-BMD may also be used in monitoring treatments. So far, there is limited knowledge of DXR-BMD in established RA and the effect of hormone replacement therapy (HRT) on DXR-BMD has not been assessed in RA. The aims were to explore BMD by DXR in postmenopausal women with established RA in relation to conventional dual x-ray absorptiometry (DXA)-BMD and to joint destruction and to evaluate the effect of HRT on DXR-BMD.

Seventy-five women were randomised to receive vitamin D3 and calcium supplementation with or without HRT (oestradiol plus noretisterone acetate) in a 2-year trial (mean age 57.6±5.2 years, disease duration 15.2±11.5 years).Disease activity, DXA-BMD distal forearm, hip and spine, joint damage by Larsen score and DXR-BMD in metacarpals two to four were assessed at baseline and at 2-year. DXR-BMD was compared to age- and sexmatched references. Associations between baseline values and changes during the trial were investigated with bivariate and multiple linear regression analyses.

DXR-BMD was markedly decreased compared to references ($p<0.001$). In multiple regression analyses Larsen score and BMD forearm were independent determinants of DXR-BMD ($R2=0.79$). Disease duration, ESR and DXR-BMD were independent variables associated with Larsen score ($R2= 0.64$). BMD total hip, lumbar spine and DXR-BMD were principle independent variables connected with DXA-BMD forearm ($R2= 0.76$). DXR-BMD decreased more in erosive disease compared with in non-erosive disease ($p<0.05$). DXR-BMD remained stable by HRT whereas it decreased in controls at 2-year follow-up ($p<0.05$).

DXR-BMD was strongly connected with both Larsen score and DXA-BMD forearm implying that DXR-BMD is a technique that reflects both the erosive process and bone loss adjacent to affected joints. HRT during 2 years stabilized DXR-BMD.

The prevalence of autoantibodies prior to diagnosis in patients with primary Sjögren's syndrome

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Autoantibodies to Ro and La are associated with systemic disease and unfavourable outcome in primary Sjögren's syndrome (pSS). Their pathogenic role is unclear.

Objective: To determine the presence of ANA, RF, and anti-Ro and La in pSS prior to diagnosis and symptom onset.

Register linkage study between Malmö University Hospital pSS research database, Malmö Diet Cancer and Preventive Medicine Study and Microbiology Biobank. From 122 individuals who developed pSS acc to the American-European consensus criteria after inclusion in the above mentioned health registries and 121 controls matched for gender, age, time of sample collection, serum samples were retrieved and analyzed for the presence of ANA, RF, Ro 60, Ro 52, La, Sm, RNP, Scl-70, Jo-1, Ribosome P and Chromatin with Quantaplex SLE profile 8 (multiplex immuno assay).

In total 174 prediagnostic samples from the 122 patients were analyzed. N of prediagnostic samples per patient: 66% 1 sample, 22% 2 samples, 8% 3 samples, 4% > 3 samples. Mean (SD) time between first prediagnostic sample and diagnosis: 6.43 (5.36) yrs, range 0.1 -24. In 38% (n=46) of the patients the prediagnostic samples were from the time before symptom onset, 45% from the time interval between symptom onset and diagnosis, and in 17% symptom onset was not known. Sixteen patients never developed any autoantibodies.

Among patients with samples from the time before first pSS symptom, ANA was present in 63% (88% after diagnosis), RF in 46% (70% after diagnosis) and Ro/La in 37% (63% after diagnosis). One patient had all autoantibodies 18 years before symptom onset. The mean time between autoantibody detection and symptom onset was 6.3 yrs for ANA, 7.3 yrs for RF and 6.5 yrs for Ro/La. Ten patients did not develop any autoantibodies in the pre-symptomatic samples (mean obs. interval 8.2 yrs until symptom onset), but did so later on. Thus in these patients symptoms preceded the occurrence of the classical autoantibodies.

In patients with several prediagnostic samples, titres of Ro/La often increased when approaching the time of diagnosing pSS. Smoking did not influence the prediagnostic prevalence of anti-Ro/La. Presence of other autoantibodies was very rare. Only three controls had low titres of anti-Ro 60.

The classical pSS autoantibodies can be detected years before symptom onset and diagnosis. ANA, RF, anti-Ro/La were equally early detectable, with increasing prevalence close to diagnosis.

A population-based investigation of the autoantibody profile in mothers of children with atrioventricular block

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Congenital heart block without anatomical malformations is a rare disease with an incidence of 1/15, 000-20, 000 in the general population, while the prevalence of complete congenital heart block in pregnancies of women with anti-Ro/SSA antibodies is approximately 2%. These women are commonly diagnosed with SLE or Sjögren's syndrome, but may also be asymptomatic. The fetal atrioventricular (AV) block usually develops during the 18-24th week of gestation after transfer of the maternal antibodies across the placenta. The objective of this study was to investigate prevalence of autoantibodies in mothers of children diagnosed with AV block in a nationwide setting.

Patients with AV block detected before 15 years of age were identified using national registries as well as a network of pediatric and adult cardiologists and rheumatologists at the six university hospitals in Sweden. Patients with gross heart malformations, surgically- or infectiously induced blocks were excluded. Blood samples were obtained from the mothers and maternal autoantibody profile, including the occurrence of antibodies against Ro52, Ro60, La, SmB, SmD, RNP-70k, RNP-A, RNP-C, Cenp-C, Scl-70, Jo-1, ribosomal RNP and histones was all investigated in 154 mothers of children with AV block by immunoblotting and ELISA.

Autoantibody reactivity was detected in 52% (80/154) of the mothers of children with AV block. In autoantibody-positive mothers, the vast majority, 96% (77/80), had antibodies to Ro52, while 61% (49/80) had autoantibodies to Ro60 and 58% (46/80) had autoantibodies to La. Of the autoantibody-positive mothers 11% (9/80) had antibodies to other investigated antigens besides Ro52, Ro60 and La, and of these anti-histone antibodies were most commonly represented, detected in 5% (4/80) of the mothers.

Data from this Swedish population-based study confirm that maternal autoantibodies may be associated with heart block, and was observed in half of the cases. In addition, the presented data also demonstrate the dominant role of Ro52 antibodies in association with development of AV block.

TNF Blockade during Elective Orthopaedic and Hand Surgery in Atrhritis Patients: Friend or Foe?

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Data on the risk for surgical site infections (SSI) in patients with inflammatory arthritis who continue TNF blockade perioperatively, compared to those who stop treatment, is sparse and contradictory. Patients withholding treatment may experience a flare in their arthritis, hampering postoperative mobilisation.

Patients with inflammatory arthritis, admitted to the Dept of Rheumatology in Lund 2003–2009, were evaluated 1-4 weeks preoperatively. Demographic data, previous and current treatment and core set variables of disease activity were recorded. In 2003-2005, infliximab, etanercept and adalimumab were discontinued for 8, 1 and 4 weeks preoperatively and reintroduced 1 week after surgery if there were no infection signs (group A). After Jan 1st, 2006, TNF blockers were continued perioperatively (group B). Patients were followed up for at least 6 months. Infections were recorded according to the Centers for Disease Control 1992 criteria. Procedures were classified as Foot, Hand, Implant or Other.

There were 312 and 515 procedures in group A and B, respectively, 67% had rheumatoid arthritis, and about 5% each had spondyloarthritis including ankylosing spondylitis, psoriatic arthritis and juvenile idiopatic arthritis. 50% were on Prednisolone and 43 and 51% were on Methotrexate, 30 and 37% on biologics and 14 and 21% on biologics + Methotrexate in groups A and B, respectively.

Total SSI rate were 12 (3.8%) in group A and 33 (6.4%) in group B (not statistically significant). There were no significant differences between procedures, except for foot surgery in group B. Total number of infections in the various medication groups were also similar, except for higher rates Methotrexate monotherapy in group B 3.0 vs 8.7%, p=0.027. In a multivariate regression model, correcting for various baseline variables, Methotrexate without biologics was the only predictor of SSI in groups A and B combined (OR 2.66, 95% CI 1.18-6.02).

Overall, there was no increased risk for SSI in patients continuing TNF blockade in the perioperative period in our cohort. SSI rates were higher in foot surgery in group B, perhaps due to extremely low rates in group A. Methotrexate monotherapy unexpectedly had elevated SSI rates, whereas Prednisolone had not. Given the low event rates, this may be due to chance. Our study does not support an increased infection risk when going on with TNF blockers during surgery.

Increased Rate of Cardiovascular Diseases in Patients with Ankylosing Spondylitis

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Mortality due to cardiovascular diseases has been found to be increased in people with ankylosing spondylitis (AS) and a higher prevalence of risk factors such as type II diabetes and hypertension have been reported compared with controls. Comorbidities associated with AS are contributing to the total burden of disease. Epidemiologic studies presenting population-based data on estimates of the increased frequency of cardiovascular disease in AS are scarce. The objective was to study the rate of cardiovascular disease and diabetes mellitus in AS patients compared to the general population.

We studied 1374 subjects (60% men) age >20 years, living in the county of Skåne, Sweden, who were registered with an AS diagnosis (ICD-10 code M45) in the Skåne Health Care Register at least once during 4 calendar years (2004 to 2007). We then recorded the occurrence of physicians' diagnostic codes for a select number of cardiovascular diagnoses: hypertensive diseases (I10-I15), ischemic heart diseases (I20-I25), acute myocardial infarction (I21) and diabetes mellitus (E10-E14). To obtain morbidity rates we calculated the person-time from the day after the first occurrence of the AS diagnosis within the study period until the diagnosis of the disease or another censoring event (death/relocation). We then obtained standardized morbidity ratios (SMRs) by dividing the observed morbidity rate in AS patients by the expected based on the corresponding rate of the disease in the general health care seeking population of the county (761 210 inhabitants aged >20); an SMR >1 equals a higher rate of the disease among AS patients than in the general population of corresponding age and sex distribution.

There was an increased SMR for ischemic heart diseases in subjects with AS compared with the reference population; 1.83 (95% CI 1.53, 2.18). The SMR was also significantly elevated for hypertensive diseases; 1.70 (95% CI 1.51, 1.91) disorders of lipoprotein metabolism 1.34 (95% CI 1.04, 1.71), and diabetes mellitus; 1.34 (95% CI 1.10, 1.62). Within the group of ischemic heart diseases we also evaluated acute myocardial infarction separately and although it is a relatively rare event the SMR was close to be significantly elevated; 1.43 (95% CI 0.97, 2.03).

Although some bias due to increased medical work-up of AS patients is expected, cardiovascular disease seems to be more frequent compared with the general population adding to the total burden of the rheumatic disease.

Kliniska prediktorer för långvarig (5 år)/framgångsrik behandling med biologiskt läkemedel vid reumatisk sjukdom

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Behandling med biologiska läkemedel används idag vid olika kroniska inflammatoriska reumatiska sjukdomar. Om behandlingen tolereras och ger god minskning av sjukdomsaktivitet kan den pågå under lång tid och kan då innebära dramatiskt förbättrad hälsa för patienten. Andelen patienter som kvarstår på behandling över tid anses vara ett mått som ger information om hur väl behandlingen fungerar.

Alla behandlingar med biologiskt läkemedel som givits vid Falu lasarett pga reumatisk sjukdom som kunnat följas upp i minst fem år efter terapistart inkluderades. Behandlingar som avbrutits pga remission (9), graviditet (2) eller svårvärderad anledning (14) exkluderades. 438 behandlingsepisoder (hos 225 patienter) kvarstod för analys. Andelen patienter som fortsätter med sin behandling över tid har beräknats. Subgruppsanalys har gjorts för att se vilka kliniska data som kan prediktera om en biologisk behandling ska fungera över tid.

54% av behandlingarna pågick fortfarande efter 2 år och 37% efter 5 år. Män stod kvar på sin biologiska behandling antytt längre än kvinnor. Vid jämförelse mellan olika diagnoser sågs en tydlig skillnad. I de fall behandlingen gavs pga AS/SPA pågick den fortfarande hos 79% efter 2 år och i 58% efter 5 år jämfört med 54 resp 36% för RA och 52 resp 33% för PsA. Vid analys av enbart patienter med RA försvann skillnaden mellan könen. I de fall CRP var ≥ 30 respektive DAS28 ≥ 5,2 (endast RA gruppen) tenderade behandlingen kvarstå under kortare tid jämfört med dem med lägre aktivitet. Chansen att kvarstå på sitt första biologiska preparat var ngt högre jämfört med "icke första". För rökare/icke rökare sågs ingen skillnad. Vid jämförelse mellan de olika preparaten ses tydliga skillnader. Behandling med Enbrel pågick i 67% efter 2 år och i 54% efter 5 år, Humira i 54 respektive 41%, Remicade i 51 respektive 24% och Kineret

i endast 11% efter 2 år. För övriga preparat har vi ännu inte fem års uppföljning.

Av alla biologiska behandlingar pågår fortfarande 37% efter 5 år med samma preparat. Eftersom klinisk praxis är att avbryta behandlingar som inte tolereras eller ger god inflammationshämning talar detta för att en stor andel av patienter med inflammatoriska reumatisk sjukdom som behandlas med ett biolgiskt läkemedel har god nytta under lång tid. Chansen att en behandling ska kunna pågå framgångsrikt under lång tid kan delvis predikteras utifrån kliniska parametrar där skillnader framförallt ses mellan olika diagnoser och olika preparat.

Methotrexate but not TNF-blockers reduces immune response following pneumococcal vaccination using 7-valent conjugate pneumococcal vaccine (Prevenar®) in adult patients with established arthritis

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Aim. To study the influence of anti-inflammatory treatments including methotrexate (MTX) and TNF-blockers on serological response following pneumococcal vaccination using 7-valent conjugate vaccine (Prevenar®) in adult patients with established arthritis.

Altogether 506 patients with rheumatoid arthritis (RA) or spondylarthropathy (SpA) including psoriatic arthritis were vaccinated. All patients were stratified into 6 prespecified groups based on diagnosis and treatment: 1. RA patients on MTX+ in some cases other DMARDs (n=85; 79 % female; mean age 62 y.); 2. RA on TNF blockers as monotherapy (n=80; 88% female; mean age 60 years); 3. RA on anti-TNF +MTX + possibly other DMARDs (n=89; 78% female; mean age 60 years); 4. SpA patients on anti-TNF drugs as monotherapy (n=83; 34% female; mean age 49 years); 5. SpA on anti-TNF drugs +MTX (n=83; 53% female; mean age 50 years) and 6. SpA patients on NSAIDs and/or analgesics (n=86; 45% female; mean age 52 years). Group 6 served as a control group. All patients received one dose (0,5 ml) Prevenar im. Levels of IgG antibodies against two pneumococcal serotypes (23F and 6B) were measured at vaccination and 4-6 weeks following vaccination using standardised ELISA.

Immune response (IR); i.e ratio between post- and prevaccination antibody levels differed significantly between the groups. Controls had better IR compared to groups treated with MTX or MTX combined with TNF blockers. Patients on TNF-blockers as monotherapy (group 2 and 4) had numerically somewhat lower IR but not significantly different compared to controls for both serotypes. Positive immune response (posIR); was defined as ≥ 2 times increase in antibody levels compared to baseline. Patients with RA exhibited reduced responsiveness (low posIR) compared to patients with SpA in univariate analysis. In multivariate analysis only older age (p=0.024; OR 0.98; 95% CI 0.96-0.99) and MTX treatment (p=0.003; OR 0.48; 95% CI 0.30-0.79) predicted reduced response. Ongoing systemic prednisolone elicited better posIR (p= 0.017; OR ratio 1.99; 95% CI 1.13-3.51).

Higher age and treatment with methotrexate predicted an impaired immune response to the 7-valent conjugate pneumococcal vaccine in this cohort of patients with chronic arthritis. Concomitant prednisolone treatment was associated with better IR. TNF-blockers did not affect the immune responses significantly.
Disclosure. Prevenar® vaccine for this study was provided by Wyeth Pharmaceuticals

Type I IFN-mediated inhibition of anti-mBSA antibody production is regulated by indoleamine 2,3, dioxygenase

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The cytokine interferon alpha (IFN-alpha) can down regulate inflammation in experimental models but the mechanism underlying this is still unclear. A recent study showed the requirement for type I IFN signalling for immunosuppression by indole 2, 3, dioxygenase (IDO). In an attempt to elucidate the possible mechanism of type I IFN-mediated down-regulation of arthritis, our aim is to study the role of the immunosuppressive enzyme IDO on IFN-regulated humoral response towards methylated bovine serum albumin (mBSA), an antigen used to trigger arthritis.

For this study, mice were immunized twice by mBSA with or without 1000U IFN-alpha at week interval followed by intraarticular injection of same antigen at day 21. The humoral response was monitored weekly by analyzing the anti-mBSA total serum IgG by ELISA. The role of IDO was studied by inhibiting the IDO activity by surgically inserting IDO inhibitor pellets (1-MT, 5 mg/day).

IFN-alpha significantly decreased the anti-mBSA total serum IgG level at day 21($p<0.05$) and day 28 ($P<0.001$). When IDO was inhibited by 1-MT, the inhibitory effect IFN-alpha was reversed to significant extent ($p<0.05$ at day 28). However, IFN-alpha was found to be still capable to decrease significantly ($p<0.05$ at day 28) this humoral response against mBSA, irrespectively of IDO inhibition.

It can be concluded that the IFN-alpha mediated down-regulation of humoral response towards the arthritic antigen mBSA is partly regulated by IDO.

EBV promotes differentiation of CD25+ B cells into plasma cells in RA patients

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B cells play a major role in the pathogenesis of rheumatoid arthritis (RA). Epstein-Barr virus (EBV) is a potent activator of B cells being persistent in the bone marrow of a substantial part of RA patients. Carriage of replicating EBV in RA patients is associated with a good response to B cell-targeting treatment. We have recently identified a functionally distinct cell population of CD25+ B cells characterized by low Ig-production, efficient antigen presentation and proliferative responses compared to CD25- B cells.

Objective: The aim was to assess the role of CD25+ B cells for the autoantibody production in patients with RA using stimulation with EBV and CpG.

Peripheral blood mononuclear cells were prepared from the peripheral blood of 17 RA patients and 11 age and sex matched

healthy controls and sorted into subpopulations CD20+CD25+ and CD20+CD25- with FACSAria to a purity >97%. Cells were stimulated with EBV and CpG for 96h. Ig producing cell number was evaluated by Elispot, light chain production and reactivity against citrullinated peptides (aCCP) and rabbit IgG (RF) by Elisa.

Stimulation of CD25+ cells of RA patients with EBV induced 10-fold increase of IgG, IgM and IgA secreting cells as compared to unstimulated cultures ($p<0.001$ for all).

Stimulation with CpG showed that RA patients develop more IgM secreting CD25+ cells than CD25-B cells ($p=0.03$).

CD20+CD25+ cells may be the main Ig producing cell population in RA patients being easily activated by EBV and CpG and differentiated into antibody producing cells.

Gene therapy protects against murine collagen type II induced arthritis

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Collagen type II is abundant in cartilage and has been implicated as one of the main targets in human rheumatoid arthritis (RA). Immunization with collagen type II in adjuvant leads to arthritis in mice, rats and primates, which is strictly dependent on a specific MHC class II haplotype and on the adaptive immune response, i.e. T and B cells. This suggests that the tolerance induction to collagen type II (CII) is limited in susceptible individuals.

We have earlier shown that lentiviral induced expression of the T cell immunodominant epitope of CII, amino acids 259-270 (CII259-270), on MHC class II partly induces tolerance in collagen induced arthritis (CIA) when administered either prophylactic or therapeutically. The aim of this study was to investigate if increased expression of CII259-270 on antigen presenting cells could abolish arthritis development, through increased tolerance induction.

Hematopoietic stem cells from naive mice were harvested and transduced with lentiviral particles encoding CII259-270 or a control peptide. The transduced stem cells were injected into lethally irradiated recipient mice and 10 weeks later CIA was induced. At termination, the CII-specific IgG antibodies was analyzed in serum, the proliferative response to CII-restimulation from lymph node leukocytes was determined, splenocytes were separated into CD4+CD25+ and CD4+CD25- cells and cocultured in different ratios, and the joints evaluated with respect to histopathological changes.

We found that 20% of mice receiving CII259-270 transduced stem cells developed a very mild arthritis, while 100% of the controls developed a severe and destructive arthritis. Interestingly, no antigen specific proliferation in effector T cells could be detected in mice receiving CII259-270 transduced stem cells, which suggests induction of central tolerance.

Furthermore, the treated mice produced significantly lower serum levels of CII specific IgG antibody.

In summary, increased expression of CII259-270 has a beneficial effect on arthritis development, most likely by central tolerance induction, and provides an excellent model for further studies of the topic.

Acute flares of neuropsychiatric systemic lupus erythematosus (NPSLE) are sometimes associated with spikes of interferon-alpha activity in the CSF

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Neuropsychiatric involvement in Systemic Lupus Erythematosus (NPSLE) is a serious manifestation in patients with systemic lupus erythematosus (SLE). Diagnosis and treatment is a challenge as no specific biomarker/investigation for NPSLE is available. Enhanced interferon-alpha (IFN-a) activity is an important ethiopathogenic factor in SLE, and a previous study reported that IFN-a contributes to NPSLE. IFN-a activity in the systemic and intrathecal compartments of patients with acute and chronic symptoms of NPSLE was investigated.

59 NPSLE patients, fulfilling ACR 1982 revised SLE criteria, were evaluated clinically. Lumbar puncture and magnetic resonance imaging (MRI, n=56) was performed. All presented with one or several NPSLE manifestation, as defined by the ACR. The majority (n=49) had chronic symptoms but 10 were investigated during acute NPSLE flares. We colledted paired blood/CSF samples from patients and controls (15 Multiple Sclerosis (MS) patients, 22 patients with other neurological diseases (OND)). IFN-a activity was measured as a score with a functional cell reporter assay. mRNA expression of IFN-a was determined in peripheral blood and CSF mononuclear cells (PBMC, CSF-MC) in 39 patients and in controls (MS=34, OND=24).

On a group level there were no differences between SLE patients and controls with respect to IFN-a activity or IFN-a mRNA expression in PBMCs or CSF-MCs, but IFN-a scores were higher in acute vs. chronic NPSLE cases ($p=0.007$). A few patients, but no controls, had very high levels of IFN-a activity in CSF and blood. 4/10 acute vs. 5/49 chronic NPSLE patients had high (>+2SD) IFN-a activity in the CSF ($p=0.02$). A similar trend was observed in blood where 5/10 with acute vs. 5/49 with chronic NPSLE had high IFN-a scores ($p=0.07$). There was no corresponding increase in mRNA expression in CSF-MCs or PBMCs. Two patients had very high mRNA expression in CSF-MCs. There was no specific NPSLE symptom (mood disorder, headache, cognitive dysfunction, seizures or previous infarction), CSF aberration or MRI finding, which was convincingly associated with high IFN-a activity or high expression of IFN-a mRNA.

We report that IFN-a activity in the CSF is high in some patients with NPSLE and is often associated with acute NPSLE symptoms. As a group, patients with chronic NPSLE had similar IFN-a activity in CSF and blood to controls. IFN-a activity may be of diagnostic potential in patients with SLE who present with acute neurological symptoms.

Kostnadseffektivitet för tocilizumab (TOC) i klinisk praxis

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Att beräkna kostnadseffektivitet för tocilizumab (TOC) hos patienter som inte svarar på standardbehandling med DMARDs,

inkluderande metotrexat (MTX), med hjälp av en modell baserad på RA register data från SSATG (South Swedish Arthritis Treatment Group).

Modellen är baserad på data avseende funktionsförmåga (HAQ), sjukdomsaktivitet (DAS) och hälsorelaterad nytta/livskvalitet (EQ-5D) från SSATG för perioden 1999-2007. Data rörande resurskonsumtion har hämtats från en befolkningsundersökning i södra Sverige (Malmö). TOC jämförs med den nuvarande mixen av TNF-hämmare som första behandling med biologiskt läkemedel, med möjlighet till byte till annat läkemedel senare i behandlingsprocessen. Data rörande effekten av TOC har tagits från en klinisk studie (OPTION) som jämför TOC med placebo, men med MTX som underliggande behandling. Resultaten rapporteras som kostnad per kvalitetsjusterat levnadsår (Euro/QALY), för en uppföljningsperiod av 10 år, i ett samhällsperspektiv (både direkta och indirekta kostnader inkluderade). Kostnader och QALY har diskonterats med 3%.

Strategin med TOC behandling har lägre totala kostnader, 234,000 jämfört med 239,000 Euro och bättre effekt, 4.49 jämfört med 4.19 QALY, jämfört med nuvarande TNF-behandling i klinisk praxis. Resultaten var stabila i sensitivitetsanalyser där bl.a. effekten av TOC (HAQ, DAS, behandlingsavbrott) recuderades.

I vår modell leder behandling med TOC jämfört med nuvarande praxis för TNF-behandling till likartade kostnader, men bättre effekt.

Differences in muscle strength and pain thresholds between postmenopausal women with and without RA

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Muscle weakness, in particular loss of muscle mass, pain and tenderness are common symptoms in rheumatoid arthritis (RA). This seems to be the case even when inflammation is well controlled and may result in increasing disability with increasing age. More pain and increased loss of muscle mass is also found among healthy women at the time of menopause. The aim of our study was to examine differences in muscle strength and pain thresholds between postmenopausal women with and without RA.

Ten postmenopausal women with early (<2 years) RA (median age 57.5, median BMI 24) and ten healthy women (median age 58.5, median BMI 25) were recruited for the study. All women were independent in daily living, had passed menopause and did not use hormone replacement therapy. The median DAS 28 score was 2.7 (range 1.3-4.0) and the median HAQ score was 0.57 (range 0-1) in the RA group.

Measurements of isokinetic muscle strength in knee flexors and extensors, hand grip strength, timed standing, pressure pain thresholds (PPT), supra threshold pressure pain rated as 4/10 and 7/10 respectively on a Borg CR-10 scale, and segmental and plurisegmental endogenous pain inhibitory mechanism during muscle contraction were assessed in all participants.

No significant difference in knee extensor strength was detected between the women with RA and the healthy ones. Participants with RA were significantly weaker in the knee flexors ($p=0.01$), in hand grip strength ($p=0.007$) and they needed more time for the timed standing ($p=0.05$). Compared to the healthy women, those with RA had increased sensitivity to threshold pain ($p=0.007$) and to supra threshold pressure pain at both levels measured ($p=0.001$ and $p=0.004$ respectively). PPTs increased at the contracting muscle as well as at a distant resting muscle during standardized static contractions in both groups alike.

Our results indicate that earlier noted difference in muscular strength between women with and without RA is present in early disease and in patients with low disease activity and seems to remain even after menopause. Further, the women with RA have generalized allodynia and hyperalgesia, but no dysfunction of segmental and plurisegmental pain inhibitory mechanisms. The normal function of endogenous pain inhibitory mechanisms despite chronic pain in women with RA might contribute to the good effects of physical activity in this group of patients.

Variation i typ I IFN-produktion mellan friska blodgivare från Uppsala Bioresurs

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Patienter med olika reumatiska systemsjukdomar har en kontinuerlig aktivering av typ I interferon (IFN)-systemet. Detta är bäst studerat vid systemisk lupus erythematosus (SLE). Polymorfier i flera gener som reglerar typ I IFN-produktion och effekt är associerade till SLE. För att i detalj studera hur de sjukdomsassocierade genvarianterna påverkar typ I IFN-systemets funktion har vi etablerat en bioresurs av genotypade friska blodgivare som kan tillgodose behovet av färska immunceller samt DNA och RNA. I ett pilotprojekt har vi undersökt huruvida produktionen av IFN-alfa varierar mellan olika friska individer och om SLE-associerade polymorfier i IRF5- och STAT4-generna är kopplade till mängden IFN-alfa som produceras vid olika stimuli.

Vi har hittills samlat DNA från 400 friska blodgivare (Blodcentralen Uppsala) och mindre än 1% av blodgivarna avböjer att delta. Dessa har genotypats för singel nukleotid polymorfier (SNPs) i bl.a. IRF5 (rs10954213, rs12539741) och STAT4 (rs7582694, rs3821236). Plasmacytoida dendritiska celler (PDC), NK celler och B lymfocyter har preparerats från 50 blodgivar-buffy coats och stimulerats med RNA-innehållande immunkomplex (RNA-IC), herpes simplex virus (HSV) eller en CpG-innehållande syntetisk oligonukleotid (ODN2216). Produktionen av IFN-alfa i cellkulturerna mättes med en DELFIA immunoassay.

Vi fann att friska blodgivare hade en stor individuell variation (10-100 gångers skillnad) i sin förmåga att producera IFN-alfa med de olika stimulerarna. Kvinnor producerade högre nivåer av IFN-alfa jämfört med män när cellerna stimulerades med HSV ($p=0.01$). Det fanns även en tendens till minskad produktion av IFN-alfa med stigande ålder. Analys pågår om IFN-alfa produktionen påverkas av de olika genpolymorfierna i IRF5 and STAT4.

Den aktuella bioresursen kan användas för att isolera färska genotypade immunceller vid upprepade tillfällen för funktionella studier. De första resultaten visar en stor variation i produktionen av IFN-alfa och hittillsvarande resultat talar för att kvinnor har ett starkare IFN-svar vilket kan bidra till den kvinnliga dominansen vid SLE och många reumatiska systemsjukdomar. För att kunna undersöka flera olika sjukdomsassocierade genvarianternas betydelse för t ex regleringen av typ I IFN-systemet krävs tillgång till ett stort antal genotypade blodgivare vilket vår nyetablerade bioresurs kommer att erbjuda.

Changes in CD3 cell population following B cell depletion using rituximab in patients with rheumatoid arthritis

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Background: B cell depletion therapy is commonly used as treatment of rheumatoid arthritis (RA) patients. We have recently shown that a single course of rituximab treatment as associated with a prolonged disability to form CD27+ memory B cells. Additionally, it has been shown that clinical effect of rituximab is not totally related to the degree of B cell depletion and the regulatory effects on other immunomodulatory cells are suggested.

Objective: The aim of the present study was to characterize changes in the CD3 cell population in blood and bone marrow of RA patients treated with rituximab.

Methods: Blood and bone marrow (BM) samples were obtained from 37 RA patients resistant to previous treatment with methotrexate and TNF inhibitors. Samples were drawn at the day of rituximab treatment and 1 or 3 months after the treatment. All patients obtained rituximab 1000mg x 2. CD3+ cell phenotype was examined by flow cytometry using a combination of surface markers CD27, CD25, CD38, CD95, CD71 and CD10. The analysis was performed by comparing a) changes short-time (1-3 months) after treatment, b) changes in rituximab-naïve patients vs rituximab previously treated, c) clinical responders vs non-responders.

Results: 1-3 months after rituximab treatment peripheral blood CD3+ cells had a reduced expression of CD71 (p=0.016) and higher expression of CD25 (p=0.02). Patients previously treated with rituximab had an increased proportion of CD3+ cells compared to rituximab naïve (p=0.036), additionally these CD3+ cells had lower expression of Fas (CD95) (p=0.036). In BM of previously treated patients, an increase of CD3+CD25-CD27- cell population (p=0.036) was observed. No differences in CD3 cell phenotype were found in relation to clinical response to rituximab treatment.

Conclusions: Rituximab treatment has immediate and long-term effects on CD3+ cell population. Clinical significance of these changes needs further evaluation.

Heptavalent conjugate pneumococcal vaccine (Prevenar®) elicits similar antibody responses as 23-valent polysaccharide vaccine (PPV) in adult patients with established arthritis

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The immunogenicity of 23-valent polysaccharide vaccine (PPV) is debated. Heptavalent conjugate pneumococcal vaccine (Prevenar®) has been shown to elicit better immune responses compared to PPV in children and healthy adults. Corresponding data in patients with established arthritis on immunosuppressive treatments is lacking.

Aim. To study immune response after vaccination with A) Prevenar®; in immunosuppressed patients with rheumatoid arthritis (RA) and patients with spondylarthropathy including psoriatic arthritis (SpA) not receiving immunosuppressive treatment compared to B) immunosuppressed RA patients and healthy controls vaccinated with PPV.

In total, 254 patients with RA on methotrexate (MTX) alone, TNF-blockers as monotherapy or MTX +TNF blockers (80% female, mean age 60 years); and 86 patients with SpA on NSAIDs and/or analgesics (45% female, mean age 52 y.); received a single dose (0.5 ml) of Prevenar®;. Altogether, 149 RA patients receiving corresponding immunosuppressive treatments (72% female, mean age 55 y.); and 47 healthy controls (75% female, mean age 36 y.); were vaccinated with a single dose (0,5 ml) of PPV (ref). Levels of serotype specific IgG to 23 F and 6B were measured at vaccination and 4-6 weeks after vaccination using standard ELISA. Pre- and postvaccination antibody levels for each serotype and immunization response (IR), i.e. ratio between post- and prevaccination antibody levels, were compared between the groups.

Pneumococcal vaccination resulted in significant increase in post-vaccination antibody levels in all groups compared to baseline for both seriotype. RA patients vaccinated with Prevenar®; gained similar postvaccination antibody levels and IR as those receiving PPV. SpA patients not receiving immunosuppressive treatment had better IR for serotype 23F compared to healthy controls who received PPV vaccine (p=0.005; ANCOVA, adjusted for age, sex and prevaccination antibody levels). Among Prevenar vaccinated RA patients, IR was similar in respective treatment modalities as those receiving PPV.

Pneumococcal vaccination using conjugate vaccine elicits similar immune response as 23-valent polysaccharide vaccine in immunosuppressed RA patients. Pneumococcal conjugate vaccine did not give better immune response in general but may be better for some serotype.

Ref. Kapetanovic et al. Rheumatology 2006; 45:110-116

Disclosure: Prevenar®; vaccine for this study was provided by Wyeth Pharmaceuticals

Östrogen skyddar mot artrit och inflammationsmedierad benförlust via östrogen receptor alfa

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Många inflammatoriska sjukdomar, såsom ledgångsreumatism, leder till benförlust. Det kvinnliga könshormonet östrogen har positiva effekter på ben och kan förhindra benförlust, men långtidsbehandling med östrogen är idag inget alternativ pga oönskade bieffekter.

Syftet med denna studie är därför att studera mekanismen bakom östrogens skyddande effekter mot inflammationsmedierad benförlust för att på sikt kunna utveckla nya östrogenliknande preparat som saknar bieffekter.

Vi har använt transgena honmöss som saknar östrogen receptor alfa, men har en intakt östrogenreceptor beta. Mössen kastrerades och en placebo pellet alternativt östrogenpellet (1,5µg/dag) placerades subkutant. 10 dagar efter operationen inducerades artrit (AIA, antigen-induced-arthritis) i ena knäleden genom att injicera metylerat BSA (mBSA), medan den andra knäleden fungerade som kontroll och fick en injektion med fysiologisk koksaltlösning. Vid avslut 14 dagar efter artrit-induktionen sparades knäleder för histologisk utvärdering av lednära benförlust. T lymfocyter i mjälten analyserades med flödescytometri samt proliferationsassay.

I vildtypshonorna skyddade östrogen mot både synovit (-22%, p<0,05) och erosion (-62%, p<0,001), medan ingen skyddande effekt av östrogen kunde detekteras i honorna som saknade östrogen receptor alfa. I vildtypshonornas mjältar såg vi en markant procentuell minskning av T lymfocyterna (-29%, p<0,01) efter östrogen behandling och T cells proliferationen var också kraftigt minskad (-52%, p<0,001) av östrogen, medan ingen effekt fanns i de honor som saknade östrogen receptor alfa.
Denna studie visar, genom att använda en transgen musmodell, att östrogenreceptor alfa krävs för att östrogen ska ha en skyddande effekt mot synovit, lederosivitet och inflammationsmedierad benförlust. T celler är involverade i benmetabolismen och våra resultat kan indikera att dessa celler är involverade i mekanismen bakom östrogenets anti-artritiska och benskyddande effekter.

Predictors of response to methotrexate in early DMARD naïve rheumatoid arthritis. Results from the initial open-label phase of the SWEFOT trial

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To identify predictors of response to methotrexate (MTX) in early rheumatoid arthritis (RA).

In the SWEFOT trial, 487 patients with early RA (symptom duration <1 year) were started on MTX monotherapy (rapidly escalated to 20 mg/weekly) and re-assessed after 3-4 months. Multivariate logistic regression was employed to study the association between baseline characteristics (age, gender, cigarette smoking habits, rheumatoid factor (RF), anti-CCP antibody status, 28-joint disease-activity score (DAS28), health-assessment questionnaire (HAQ) score, concurrent prednisolone and NSAID treatment) and clinical responses using the EULAR response criteria as the primary outcome measure. Secondary outcome measures were the American College of Rheumatology and the clinical disease-activity index (CDAI)-based criteria.

After 3 months of MTX treatment, 34% of patients were EULAR good responders, 41% were EULAR moderate responders and 25% were EULAR non-responders. Parameters associated with decreased likelihood of EULAR response were female gender (adjusted OR=0.50, 95%CI 0.31-0.81), current smoking (adjusted OR=0.35, 95%CI 0.20-0.63), higher HAQ (adjusted OR=0.56, 95%CI 0.40-0.80) and higher DAS28 (adjusted OR=0.64, 95%CI 0.52-0.80). Parameters associated with increased likelihood of EULAR response were higher age (adjusted OR per 10-year increase=1.30, 95%CI 1.11-1.51) and concurrent prednisolone treatment (adjusted OR= 2.84, 95%CI 1.43-5.63). RF or anti-CCP status did not influence response. The findings did not differ between subgroups stratified by gender, anti-CCP or smoking status and were similar when patients on prednisolone were excluded and other response criteria tested.

Younger age, female sex, higher disease activity and current smoking predicts worse response to MTX in patients with new-onset RA.

Östrogenmetaboliten 2-metoxyöstradiol förbättrar artrit och osteoporos i en modell av postmenopasual artrit

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Vid postmenopausal reumatoid artrit (RA) bidrar både den inflammatoriska processen och de minskade östrogennivåerna till utveckling av osteoporos. Hormonbehandling innehållande östradiol både bevarar benet och förbättrar artriten, men detta är inte längre en möjlig långtidsbehandling pga. biverkningar. Vår hypotes var att en metabolit av östradiol, 2-metoxyöstradiol (2me2), kunde vara en effektiv behandling av både osteoporos och artrit. Detta testades i en modell av postmenopausal RA.

Honmöss av typen DBA/1, kastrerades och artrit inducerades genom immunisering med kollagen. Mössen behandlades med 2 doser av 2me2, östradiol eller placebo genom pelletinplantat i en långtidsstudie, eller gavs som injektioner i en korttidsstudie. Kliniska tecken på artrit registrerades under behandlingsperioden och bentäthet utvärderades i slutet av experimentet. Tassar sparades för histologisk utvärdering, benomsättningsmarkörer mättes i serum och reaktiva syreradikaler från mjältceller analyserades. Fenotypisk karakterisering av celler från leder och lymfnoder undersöktes, likaså kollagenantikroppar i serum.

Båda doserna av 2me2 minskade både artitförekomst och svårighetsgrad samt bevarade både trabekulärt och kortikalt ben. Ledförstörelsen minskade, och infiltrationen av makrofager och neutrofiler hade minskat. Behandlingen gav lägre produktion av syreradikaler, medan antikroppssvaret var oförändrat.

I denna väletablerade modell av postmenopausal artrit (kollageninducerad artrit) kunde östrogenmetaboliten 2me2 minska utvecklingen av erosiv artrit och den associerade utvecklingen av osteoporos. Eftersom långtidsterapi med hormoner innehållande östrogen leder till biverkningar visar denna studie att 2me2 kan vara en alternativ adjuvansterapi för postmenopausal RA.

Nordic walking decreases exercise heart rate in women with fibromyalgia

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Fibromyalgia (FM) is characterized by generalized pain and fatigue, and associated with impairments in body functions. The aim of the study was to investigate the effect of Nordic Walking (NW) on exercise heart rate in women with FM.

A randomized controlled trial evaluating the effect of moderate-to-high intensity exercise. The inclusion criteria were: women aged 20-60 years with FM defined (ACR 1990 criteria), to manage a bicycle be test at 50 watt or more, to be interested in exercising outdoors for 15 weeks. Sixty-seven patients were randomized to Nordic walking (NW, n=34, age 48 ±7.8 years) or low-intensity walking (LIW, n=33, age 50±7.6 years). Seven patients used Beta blocks and 45 antidepressants or sedatives.

Heart rate response was measured at a submaximal test on a cycle ergometer. Heart rate was recorded every minute. Perceived exertion was assessed on Borg's Rating of Perceived Exertion (RPE) scale. Blood pressure was measured every second minute. The selected exercise intensity was either 50 or 75 watts, defined

after a structured interview of the physical activity level. Unaltered exercise intensity was applied at post-test. The mean heart value during the fifth and the sixth minute was assessed. Pain was assessed by the Fibromyalgia Impact Questionnaire (FIQ) subscale for pain.

Interventions. NW. Supervised interval exercise for 40-45 minutes twice a week during 15 weeks. The target was to achieve 20 minutes of moderate-to-high intensity of exercise.

LIW. Supervised low-intensity walks for 40-45 minutes once a week during 15 weeks.

Results. Fifty-eight (87%) patients completed the post-test. The median attendance rate was 62% (0-100) in the NW group (n=29) and 50% (0-93%) in the LIW group (n=29).

The baseline exercise heart rate in the NW group was 124.5 (17.1) and 121.1 (12.2) in the LIW. A significant decrease of the heart rate (p=0.02) was found in the NW group (-8.9, SD 12.8) when compared with the LIW group (-3.1, SD 9.6) at the submaximal ergometer test.

Pain rating was 63.9 (21,2) at baseline in the NW group and 71.5 (20.7) in the LIW. Pain tended to slightly decrease in both groups (-4.0; -5.3) but without significant difference (p=0.63) between the two groups.

Conclusion. NW of moderate-to-high intensity appears to be feasible mode of exercise for women with FM, not exacerbating the pain at the group level0. Supervised NW resulted in a significant decrease of exercise heart rate when compared with the control group.

Bone marrow derived dendritic cells with a tolerogenic phenotype in vitro gain inflammatory capacity in vivo and promote the development of collagen type II induced arthritis

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The effect of 1,25-Dihydroxyvitamin D(3) as an immunomodulatory agent inducing specifically myeloid dendritic cells (DCs) to become tolerogenic (tol-DCs) has previously been well characterised. Therapy using tol-DC has the potential to reverse the ongoing destructive immune response in autoimmune conditions e.g. rheumatoid arthritis (RA). However, the vast majority of studies so far have focused on in vitro properties of these tolerogenic tol-DCs. We have previously shown that lentiviral based gene therapy enccoding the immunodominant collagen type II (CII) epitope (amino acids 259-270) induces tolerance in collagen type II induced arthritis (CIA), a mouse model of RA. The aim of this study was to investigated if 1,25-Dihydroxyvitamin D(3) treated tol-DCs transduced with lentiviral particles encoding the CII amino acids 259-270 could be used to induce tolerance in CIA.

To derive DCs, bone marrow cells from DBA/1 mice were cultured in the presence of GM-CSF and with or without 1,25-Dihydroxyvitamin D(3). The cells were further transduced with lentiviral particles.The DC phenotype and the expression of tolerogenic molecules on the cell surface were determined by FACS. Arthritis was induced and DCs were intravenously injected at day 26. At termination serum levels of CII specific IgG antibodies were analyzed and joints evaluated with respect to synovitis and destruction. Splenocytes were re-stimulated with CII and the proliferative response measured.

In this study we demonstrate that in vitro 1,25-Dihydroxyvitamin D(3) treated tol-DCs retain their tolerogenic phenotype after transduction with lentiviral particles encoding CII amino acids 259-270. Both tol-DCs or normal DCs showed similar levels of transgene expression after transduction of with lentiviral particles. However, when tol-DCs or normal DCs expressing CII amino acids 259-270 after lentiviral transduction, were intravenously injected into mice as a treatment for CIA, this resulted in earlier onset of and a significantly more destructive arthritis in the tol-DC treated group. No differences could be detected between the treatment groups with respect to serum levels of IgG anti-CII antibodies or in antigen specific proliferation ex vivo.

To our knowledge, this is first time it is shown, that 1,25-Dihydroxyvitamin D(3)-treated DCs with a tolerogenic phenotype in vitro, aggravates the development of arthritis when administered in vivo. The mechanisms behind these finds are presently being investigated.

Type I IFN downmodulates the humoral response to arthritis-associated antigen mBSA in female, but not male mice

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Interferon-alpha is a cytokine secreted primarily by plasmocytic dendritic cells. It has an ambiguous role in RA. It is known to have a protective role if co-administered with the antigen probably by inhibiting initial immune responses against the antigen. We want to determine the role of gender and timing of IFN-alpha administration on antigen specific antibodies levels in methylated bovine serum albumin-induced arthritis.

Mice were given mBSA challenge with or without IFN-alpha on day 1 and 7. Some mice were treated with IFN-alpha on day 21. Serum anti-mBSA IgG levels were measured by ELISA.

The results show that administration of IFN-alpha along with the immunization with the mBSA significantly suppressed the levels of anti-mBSA IgG in the female mice, but not in male mice. Moreover administering IFN-alpha at a later time point of the experiment (day 21) did not suppress anti-mBSA IgG levels. Female mice showed overall higher anti-mBSA IgG levels than the male mice.

Our results clearly show that IFN-alpha decreased the levels of anti-mBSA antibodies in the initial phase, but not if added in the late phase of the experiment in the female mice. Also, female mice had an overall increased humoral response as compared to male mice. Taken together this indicates two things: 1, That IFN-alpha has no influence on anti-mBSA IgG levels in an already established adaptive immune response and 2, that gender and thereby possibly hormonal factors influence the ability of type I IFN to regulate humoral responses.

Atherosclerosis in SLE; a cross sectional study of 223 patients with 223 individually matched population controls

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Accelerated atherosclerosis is believed to contribute to premature cardiovascular disease (CVD) in patients with Systemic

Lupus Erythematosus (SLE). We investigated the prevalence of subclinical atherosclerosis in SLE patients and controls.

223 SLE patients/ 223 population controls, individually matched for age, sex and region of living were included after overnight fasting. All were investigated clinically including CVD risk factors and inflammatory biomarkers. The same investigator performed B-mode ultrasonography of carotid arteries. Intima media thickness (IMT) and plaques occurrence (local intima-medial thickening >1mm) were tabulated

Mean age was 48,5+/-14,3 years in patients and 48,7+/-14,2 in controls. Manifest CVD (ischemic heart, cerebro- and peripheral vascular disease) was more common in SLE patients (13 % vs. 3 %, p <0.0001). Patients were more likely to smoke, have anti-hypertensive and lipid lowering treatment, lower high density lipoprotein, and higher triglycerides (TG). They had lower low density lipoprotein levels (p<0.05 for all).

Patients had thicker mean IMT than controls (p=0.02), but there was no difference in plaque occurrence, 21% and 17% respectively.

After age adjustment: Manifest CVD was associated with plaques in the SLE group, but not with IMT.

In SLE, IMT was positively associated with systolic blood pressure (sBP, <0.0001), TGs (p=0.008) and hemoglobin levels(p=0.04) and negatively with discoid skin lesions (p=0.03) and leukopenia(p=0.03). Plaques were positively associated with TGs (p=0.01) and systolic blood pressure (p=0.02) and negatively with discoid skin lesions (p=0.04).

In controls, IMT was associated with high CRP levels (p=0.02) and sBP (<0.0001). Smoking (p=0.03) and TG levels (p=0.03) were associated with plaques.

Multivariable adjusted models: In patients age and sBP remained associated with IMT (p<0.001 for both) and plaques (p<0.001 and p=0.01 respectively). In controls age (p<0.001) and sBP (p=0.001) remained associated with IMT and age (p<0.001) and smoking (p=0.03) with plaques.

This is to our knowledge the largest study of subclinical atherosclerosis in SLE patients. Patients had thicker IMT, but we could not confirm the increased prevalence of carotid plaques previously reported. Selection of controls, definition of plaques and possibly ethnicity are possible underlying explanations. Plaques and IMT were mainly associated with traditional CVD risk factors in both patients and controls.

Skilda cytokinmönster hos SLE-patienter med proliferativ resp membranös nefrit, ett steg mot individualiserad behandling?

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Systemisk lupus erythematosus (SLE) är en reumatisk autoimmun sjukdom som kännetecknas av förekomsten av autoantikroppar. B-cellerna som producerar antikropparna har därmed en central roll. Rituximab är ett läkemedel som eliminerar B-cellerna från cirkulationen. Man har tidigare inte kunnat påvisa skillnader i cytokinmönster hos SLE-patienter med eller utan njurpåverkan (nefrit). Syftet med denna studie var att genom karakterisering av nefriterna i proliferativa (PN,WHO III/IV) respektive membranösa (MN, WHO klass V) undersöka om det finns skillnader på cytokinnivå, samt att se hur dessa påverkas av Rituximab-behandling. Detta för att kunna hitta en mer skräddarsydd behandling för dessa patienter.

Patienter med SLE-nefrit (PN, n=13, MN n=8) med bristande behandlingssvar på konventionell terapi, samt friska kontroller (n=10) ingick i studien. Serumprover från start av behandling, efter 2-3 respektive 6 månader analyserades för TGF-ß, IL-6sR, IL-17, IL-21 och IL-23 (ELISA) och IL-2, IL-4, IL-6, IL-10, TNF och IFN-g (Cytometric Bead Array (CBA)), där analysmetoderna anpassats för att detektera de låga nivåerna som återfinns i serum.

Den totala patientgruppen hade vid start av behandling högre nivåer än kontrollgruppen för samtliga cytokiner (statistiskt signifikant för IL-6 (p=0.03) och IL-10 (p=0.0002)), förutom TGF-b som var signifikant lägre (p=0.02). Vid uppdelning i PN och MN hade MN liknande nivåer av IL-6, TNF och IFN-g som de friska kontrollerna, medan dessa cytokiner var förhöjda i PN-gruppen. Nivåerna av IL-17 och IL-23 var något förhöjda för PN jämfört med friska kontroller, medan MN hade högre nivåer än PN. Ingen skillnad noterades av IL-21-nivåerna mellan MN och friska kontroller, medan PN hade lägre nivåer. IL-2 och IL-4 var bara detekterbara hos ett fåtal patienter, ffa PN. 2-3 månader efter behandlingsstart hade de flesta cytokiner minskat i båda grupperna, mest uttalat för IL-23. En stegring av IFN och IL-21 noterades hos flertalet patienter vid 2-3 månader.

B-cellsdepletion hämmar inte bara antikroppsproduktionen, även produktionen av icke B-cellsassocierade cytokiner påverkas. Vid indelningen av nefriter i PN och MN noterades skillnader i cytokinmönstret där PN hade en mer uttalad pro-inflammatorisk profil med högre nivåer av IL-6, TNF och IFN-g medan MN hade en starkare IL-23/IL-17/IL-21-profil. Dessa fynd kan leda till en bättre karakterisering av nefriter, och därmed ha betydelse vid val av läkemedel för individuella patienter.

Anti-cyclic citrullinated peptide antibodies in rheumatoid arthritis patients with lymphoma

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The risk for lymphoma and, in particular, diffuse large B-cell lymphoma (DLBCL), is increased in patients with rheumatoid arthritis (RA). No biomarkers for the development of lymphoma in patients with RA have been identified. The aim of this study was to investigate if anti-CCP antibody levels and subclasses are associated with occurrence of lymphoma in patients with RA.

We identified 37 index patients with RA and subsequent lymphoma from two population-based Swedish case-control studies, one of lymphoma (the SCALE study, 1999-2002) and the other of RA (the EIRA study, 1996-2006). To each index RA-lymphoma case, three pairs of control subjects were matched based upon age at diagnosis of RA or lymphoma (± 5 years) and lymphoma subtype. Controls consisted of 73 patients with RA (EIRA), 73 patients with lymphoma only (SCALE), and 74 individuals with neither disorder (EIRA). Blood samples were collected from

all subjects at either diagnosis of lymphoma (SCALE) or of RA (EIRA). The self-reported RA diagnosis (SCALE) was validated in medical records. Blood samples from all 257 study subjects were analyzed for anti-CCP IgG (ELISA, Eurodiagnostica) and ACPA-isotypes: anti-CCP IgG1-4, IgA, and IgM (Leiden). Anti-CCP IgG levels ≥ 25 U/ml were defined as positive. The chi2 and Wilcoxon rank sum tests were used for statistical analysis.

Similar proportions of patients with RA only (65%) and of patients with RA-lymphoma (65%) had positive anti-CCP IgG levels, as did lymphoma cases (1.4%) and population controls (3%). Similar results were obtained for all anti-CCP subclasses. The median level of anti-CCP IgG in index patients with RA-lymphoma (306 U/ml; min 1- max 5033) was higher than in non-lymphoma RA patients (140 U/ml; min 0-max 5706), but the difference was not statistically significant (p=0.25).

The most common lymphoma subtype among the index cases was DLBCL (37%). The median anti-CCP IgG was numerically higher in RA patients with DLBCL (495 U/ml; min 1-max 5033) compared to patients with RA and other non-Hodgkin lymphoma subtypes (175 U/ml; min 1-max 3626), (p=0.87).

This population-based study with carefully matched controls does not support an association between IgG anti-CCP antibody positivity or levels or ACPA subclasses (IgG, IgG1-4, M or A) and lymphoma occurrence in RA. Further studies are needed to identify other potential biomarkers of lymphoma occurrence in RA.

Changes in health care consumption by RA patients 2006-2008 in southern Sweden

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Patients with rheumatoid arthritis (RA) report better clinical and functional outcomes over the last 2 decades. Screening and monitoring of the new drugs could be expected to increase the number of clinic visits, while the improved situation for patients could be expected to reduce it. There is limited knowledge of changes in health care utilisation of RA patients.

Our objective was to study the frequency and trends of health care utilisation during 2003 to 2008 in patients with RA.

Data from the Skåne Health Care Register (SHCR) covering individual data including diagnostic codes according to ICD-10, date of visit and type of visit were linked through the personal identification number to data from the population register (to only include residents of the county). Adult individuals with a RA diagnosis (M05 and M06) on at least two separate occasions, at least once given by a specialist in rheumatology or internal medicine were included, with start from 1st of January the year when the second diagnosis was given. This open cohort was regarded as stable for the last three years of the observation period.

The cohort comprised 2,903 individuals at start (1st Jan, 2003) and 5,521 at the end of the observation period (31st Dec, 2008) (72% women). During the period the total number of clinic visits/year increased from 12,184 (2003) to 15,885 (2008). The annual mean number of visits per patient during the last three years (2006-2008) to a rheumatologist showed a tendency to decrease from 3.51 (2006) to 2.87 (2008). For the nurse and physiotherapist (PT) the annual total number of visits was fairly stable over the period, while it increased for the occupational therapist (OT) from 295 (2006) to 395 (2008) and decreased for the social worker (SW) from 160 (2006) to 85 (2008). The annual utilisation rate, described as mean per patient – caregiver, was fairly stable 2006 compared to 2008. For the nurse 0.40 compared to 0.38, for the PT 0.59 compared to 0.52, for the OT 0.06 compared to 0.07 and for the SW 0.03 compared to 0.02.

Despite major changes in pharmacological treatment for the most severely ill RA patients there were no major changes in the utilisation of health care for RA patients over 2006-2008.

Cardiovascular event in Systemic Lupus Erythematosus in northern Sweden – Incidence and predictors in a 7-year follow up study

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The incidence of cardiovascular disease (CVD) is generally higher in systemic lupus erythematosus (SLE) patients. The aim of this study was to analyse the standard incidence ration (SIR) for cardiovascular events (CVE), defined as myocardial infarction (MI) and/or stroke, in SLE patients from northern Sweden followed-up after 7 years and to evaluate the predictive values of SLE specific and traditional risk factors.

During one year 277 patients with SLE ≥ 4 ACR criteria) were recruited from the Departments of Rheumatology, Internal medicine, and Dermatology and all GP clinics in the four northern-most counties of Sweden and assessed using SLEDAI, and SLICC/ACR. Laboratory variables, medication, smoking status and history of CVD were recorded. The patients mean (SD) age was 51.2(14.9) years with a mean disease duration 12.5(9.7) years. The median (Q1-Q3) SLEDAI was 2(0-4) and SLICC/ACR index was 2(1-3). 7-year follow-up data concerning MI and stroke was extracted from the registers on hospitalisation, in-patient care and death from National Board of Health in Sweden. The SIR was calculated by comparing the patients with the population of the four counties with data from The National Board of Health and Statistics Sweden. To identify predictors two matched controls from Medical Biobank for each patient were followed up 7 years later by cross-linkage with the same registers. Data were analysed using Cox proportional hazard regression.

The SIR for an event was for both sexes 1.27 (95%CI0.82, 1.87) and for females 40-49 years of 8.0 (95%CI1.65, 23.38). The SIR overall for MI was 2.44 (95%CI1.4, 3.8) for both sexes; for the females overall the SIR was 1.93 (95%CI1.0,3.4) and for the 40-49 years 8.7 (95%CI1.1,31.4). Time to an event was significantly shorter among SLE patients (Log Rank test p<0.001) and predicted by hypertension adjusted for smoking.

A history of previous MI, stroke, disease duration, age, hypertension, higher SLICC and presence of aCL-IgG predicted significantly CVE in unadjusted regression. High SLEDAI and presence of aCL-IgG respectively adjusted for age and previous MI predicted an event in regression models. Diabetes, smoking or sex did not affect the prediction models.

The SIRs for CVE overall and for MI were significantly increased in female patients in particular 40-49 years of age Time to event was significantly shorter in SLE patients. SLICC and aCL-IgG and hypertension and age were associated with development of CVE in SLE patient.

Clinical effect of Abatacept, data from the Swedish Rheumatology Quality Registry

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Abatacept is a biological treatment used in RA both when patients fail on a precedent biological treatment due to lack of efficacy or due to adverse events. The aim of this study was to gain knowledge when abatacept may offer the best clinical effect. Observational data from the Swedish Rheumatology Quality Registry.

411 patients started Abatacept from April 2006 to Febr 2010. 335 patients were diagnosed with RA, 48 % RF-positive, 42 % RF-negative, 10% no data, ACPA status not known. Other diagnosis were: ankylosing spondylitis (4), CREST syndrome (1), dermatomyositis (2) inclusion body myositis (1), juvenile arthritis (37), oligoarthritis (2), polyarthritis (7), polymyositis (1), psoriatic arthritis (18), sarcoidosis (1), SLE (1), spondarthritis (5), systemic sclerosis (2), temporal arteritis (1).

Regarding the RA patients, mean age at abatacept start was 58 years and mean disease duration at abatacept start was 13 years. The mean number of previous biological treatments given was 2.4 and the mean time since first given biological treatment was 4 years. Abatacept was the first biological treatment for 23 patients.

Mean DAS28 before Orencia treatment was 5,57 (N=266) and lowest DAS28 3 - 12 months after Orencia treatment was 4,02 (N=236). A significant clinical effect was recorded for both RA patients who stopped their precedent biological treatment due to adverse events (N=70)

or due to lack of efficacy (N=190). However RA patients who stopped the precedent biological treatment due to adverse event had a significantly lower DAS28 prior to abatacept compared to patients who stopped the precedent biological treatment due to lack of efficacy. DAS28 at 3-12 months was also significantly lower in patients who stopped the precedent biological treatment due to adverse events.

Abatacept has a clinical effect in RA both in patients who stopped their precedent biological treatment due to lack of efficacy and due to adverse events.

Risk för akuta koronara syndrom i relation till TNF-hämning vid tidig reumatoid artrit

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Risken för ischemisk hjärtsjukdom (IHD) är ökad hos patienter med reumatoid artrit (RA) redan tidigt under sjukdomsförloppet. Vid etablerad RA har respons på anti-TNF behandling (anti-TNF) kopplats till en minskad risk för hjärtinfarkt (AMI). I denna studie analyserades risken för akuta koronara syndrom (ACS) i relation till behandling med TNF-hämmare under de första åren av RA-sjukdom.

Alla patienter med tidig RA (dur <12 månader) diagnostiserade 1995-2007, identifierades i Svenska RA registret (n = 8746) och uppgifter om sjukdomsaktivitet och behandling extraherades. Genom länkning till slutenvårds- och dödsorsaksregistret identifierades co-morbiditet och sjukhusvård för ACS (ICD-10: I20-I21). Justerade hazard ratios (HR) jämförande risken för incident ACS relaterat till anti-TNF exposition beräknades med Cox proportional hazards regression hos patienter (n = 6000) inkluderade 1999 eller senare. Vidare analyserades relationen mellan respons på anti-TNF och risk för ACS med konditionell logistisk regression i en nested case-control design; 24 fall med ACS efter start av anti-TNF och 81 matchade kontroller. Patientjournalerna granskades för validering av diagnoser, aktivitetsparametrar, behandling, co-morbiditet, riskfaktorer och extra-artikulär sjukdom.

I kohorten hade 1271 av 6000 patienter exponerats för anti-TNF, motsvarande 4231 anti-TNF-exponerade personår av 21 677 totalt. ACS-incidensen var 9,1/1000 personår (antal ACS = 198). Efter stratifiering för ålder, kön och inklusionsår var HR för ACS efter anti-TNF 0,96 (95% CI 0,61-1,49) och efter ytterligare justering för propensity score var HR 0,81 (95% CI 0,52-1,24).

I fall-kontrollstudien hade 51% respektive 67% av patienterna EULAR respons (god eller måttlig) vid 3 resp. 6 månader efter start av anti-TNF, utan signifikanta skillnader mellan fall och kontroller. Justerat för sjukdomsaktivitet före behandlingstart var EULAR-respons vid 3 eller 6 månader inte associerat med risk för ACS: OR 1,65 (0,54-5,05) respektive 1,48 (0,32-6,88). Inte heller ojusterat eller efter justering för tidigare hjärtkärlsjukdom noterades några signifikanta samband mellan behandlingssvar och risk för ACS.

I denna studie av patienter med tidig RA, kunde inte behandling med, eller respons på anti-TNF kopplas till någon signifikant minskning av risken för akuta koronara event. Huruvida detta beror på faktorer som är specifika för denna kohort eller om TNF-hämning har begränsad skyddande förmåga kan inte avgöras.

Anti B-cell therapy in SLE/ MCTD patients with refractory thrombocytopenia

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To retrospectively evaluate long term clinical and immunological effects of anti B cells treatment in SLE and MCTD patients with autoimmune thrombocytopenia refractory to conventional immunosuppressive treatment with high doses of corticosteroids, DMARDs and/or intravenous immunoglobulin.

Rituximab (RTX) was added to the ongoing treatment in 16 patients (median age 36 years, range 17–84, all female) with treatment resistant autoimmune thrombocytopenia who had SLE (n = 13) and MCTD (n = 3). RTX was given i/v during 4 consecutive weeks at the dose of 375mg/m2. Clinical and laboratory disease activity variables recorded at every visit during the period April 2002 – December 2009 were retrospectively analyzed.

The median duration of the rheumatic disease before RTX-treatment was 9 years (range 0.2–27) and post-treatment follow up time 28 months (range 3–92). 10 patients (63%) were treated repeatedly with RTX either 2 (n = 7), 3 (n = 2) or 4 (n = 1) times during the follow up period. Complete depletion of B cells was achieved in 94% of cases 1 month after RTX treatment. In patients with thrombocytopenia a significant increase ($p = 0.0001$) of platelet counts was seen already after 1 month (median 58x109/ml vs. 110x109/ml) whereas within 3 months platelet counts normalized in 10 patients (median 223x109/ml).

Antibodies of IgM and IgG isotypes were measured in 14 patients before treatment.

A high titers (>10% of antibodies bound to platelets surface) were detected in 7 patients before RTX treatment (IgG - median 15%, range 5-67%; IgM-median 11%, range 5-46%). The autoantibody titers decreased significantly ($p < 0.03$) after RTX treatment in 6 of these patients that also achieved complete remission.

Three patients did not respond to RTX treatment (median platelet count 69x109/ml).

RTX is an additional potent therapeutic treatment option for SLE patients with autoimmune thrombocytopenia refractory to conventional immunosuppressive treatment. Best response may be expected in patients with high titers of anti-thrombocyte antibodies.

Disease activity in juvenile chronic arthritis more than fifteen years after onset

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OBJECTIVE: Juvenile chronic arthritis (JCA) is a heterogeneous disease and there are few longitudinal studies of the disease process in population-based cohorts. Our aim was to study the development of disease activity in children and young adults with JCA during the first fifteen years of the disease.

METHODS: The individuals in this study were recruited from a prospective population-based epidemiological survey of JCA. They were incidence cases identified during the time period January 1, 1984 to December 31, 1986. The EULAR criteria for JCA were used. The disease activity was evaluated by physician's overall assessment according to EULAR: (a) active = increasing number of joints irrespective of drug therapy; (b) stable = stable number of joints but requiring drug therapy; (c) inactive = no evidence of active synovitis and/or active extraarticular features and without drugs for less than two years; (d) remission = no evidence of active synovitis and/or active extraarticular features and without drugs for two years or more. One hundred and twenty eight individuals were examined clinically and with Child-HAQ at median 5.4 years (range 3.0–7.2 years) after onset. Out of these 128 patients 85 (66%) were re-examined at median 16.9 years (range 14.9–19.3 years) after onset. In order to present the disease activity over a time period a disease activity duration score was created specifically for the first five years of disease and calculated as the fraction of active or stable disease as opposed to inactive disease or disease in remission during the observation period.

RESULTS: At 15-year follow-up 2/85 (2%) of the individuals had active disease, 32/85 (38%) had stable disease, 17/85 (20%) inactive disease and 34/85 (40%) had disease in remission. That means that 34/85 (40%) still had active disease (active + stable) and 51/85 (60%) had inactive disease (inactive + remission). Higher disease activity duration score during the first 5 years was associated with active disease at the 15-year follow-up (rho=0.39 p<0.001). More disability displayed by higher Child-HAQ score at 5-year follow-up was associated with active disease at 15-year follow-up (rho=0.44 p<0.001).

CONCLUSION: In a population based JCA cohort 40% of the individuals still had active disease 15 years after disease onset. Active disease after 15 years of disease was associated with active disease during the first five years and functional impairment after five years of disease according to Child-HAQ.

Addition of TNF blockers to DMARDs increases the risk for infections in patients with ankylosing spondylitis

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Treatment with TNF blockers is known to increase the risk for serious infections in rheumatoid arthritis patients. However, post-marketing studies of the infection risk in patients with ankylosing spondylitis (AS) during anti-TNF treatment are missing. 182 AS patients treated at the Rheumatology clinic, Sahlgrenska University hospital were included. All patient-records were retrospectively reviewed regarding documented infections from January 2005 to May 2010. The total followup time was 752,9 patient years. Infection rates in TNF blocker and DMARD only treated patients were calculated and compared using Fischer exact test.

117 patients were treated with TNF blockers (87 infliximab, 16 etanercept and 14 adalimumab), 61 were treated with DMARDs only (21 MTX, 38 Salazopyrine, 2 azathioprin), and 4 patients had only NSAID. Of the TNF blocker treated patients all but 7 patients had TNF blocker in combination with DMARD. The median disease duration was 12 years (range 0,33-50) and the median time with TNF blocker treatment was 36 months (range 1-60 months).

A total of 136 infections were recorded. The incidence rate of all infections (serious and nonserious) was significantly higher in TNF blocker treated patients; 19.7/100 patient years as compared to 14.9/100 patient years in DMARD only treated patients, p=0.0026. The relative risk (RR) for infection in TNF blocker treated patients was 1.59 (95% CI 1.12-2.26).

Twelve serious infections (4 pneumonia, 1 sepsis, 1 tularemia, 3 deep skin/soft tissue infections, and 3 gastroenteritis) defined as requiring hospitalization were recorded. The relative risk for serious infections was not increased in TNF blocker treated patients as compared to DMARD only treated patients, RR 0.75 (95% CI 0.42-1.33). The incidence rates being 1.21/100 patient years and 2.35/100 patient years for TNF blocker and DMARD only treated patients, respectively.

Addition of TNF blocker treatment to DMARDs seemingly increases the overall risk of infections in AS patients. The risk for serious infections was not increased, possibly by lack of power. Further analyses of our data using multivariate logistic regression analyses are ongoing to adjust for known risk factors for infection.

Patients with Systemic Sclerosis and Anti-Centromere Antibodies are affected with accelerated atherosclerosis

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If patients with Systemic Sclerosis(SSc) are affected with accelerated atherosclerosis is an unresolved question as previous studies report divergent results. We know that patients with Anticentromere antibodies have a higher risk for vasculopathy such as pulmonary arterial hypertension (PAH), but we dont know if this subgroup of patients also have more atherosclerosis. We investigated surrogate measures of atherosclerosis in a cohort of well-characterized SSc patients and in populationbased matched controls.

110 consecutive patients who fulfilled the American College of Rheumatology criteria for SSc and 105 controls matched for age, gender and region of living participated.Traditional risk factors for cardiovascular disease(CVD), biomarkers of systemic inflammation and autoantibody patterns were investigated. As surrogate measures of atherosclerosis ankle-brachial index (ABI) and carotid ultrasound was performed.

Mean age was 61,8 ± 12,4 years vs 61,4 ± 12,3 years among patients and controls respectively. There was no difference between patients and controls concerning carotid plaque occurence, intima media thickness (IMT) or ABI on a group level but Sedimentation Rate (p=0,007) and Triglycerides (p=0,03) were higher and BMI (p=0,03) lower in patients than controls. In the patient group, 35(32%) were Anti-centromere Antibody

positive (AcA+) and 75(68%) were Anti-centromere antibody negative(ACA-). Plaque occurred in 65,7% of the AcA+ patients and in 38,7% of the AcA- patients (p=0.008). ABI was 1,0± 0,15 in the AcA+ patients and 1,13 ± 0,09 in the AcA- patients (p=0,05). IMT did not differed between the patient groups. After adjusting for age, Aca+, blood pressure and ever smoked still remained associated with plaque occurrence and Aca+, ever smoked and waist hip ratio remained associated with a low ABI. Lipid levels, blood-pressure, blood glucose, ever smoked, Body Mass Index or markers of systemic inflammation did not differ between AcA+ and AcA- patients.

Independent predictors of plaque were age (p=0,0001),systolic blood pressure(p=0,02), ever smoked(p=0,02) and AcA+ (p=0,02)and for ABI age (p=0,02), ever smoked(p=0,008) and waist-hip ratio(p=0,01)

Atherosclerosis was more prevalent in SSc patients with Anticentromere antibodies than in SSc patients without these antibodies. AcA+ patients already has a higher risk for vasculopathy such as PAH and this subgroup of SSc patients seems to have more atherosclerosis and may thus be at higher risk for CVD.

Daily activities among women with hand osteoarthritis one year after participating in extended Joint Protection Programme

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Hand osteoarthritis (HOA) is the most common joint disease in a grown up population and the prevalence is higher in women than men. The clinical symptoms have been reported to be limiting hand function and treatment options are still inadequate for HOA. My aim was to study Activity of Daily Living (ADL) in detail and how ADL are associated to hand function; pain, stiffness and grip force in women with HOA participating in an extended JP programme (Joint Protection) before intervention and at one year follow up.

Forty two women with HOA in one or both thumb base between 40-76 years of age were consecutively randomized into two groups participated in JP programmers; group sessions with education about joint protection, assistive devices/splints and treatment with paraffin wax bath before exercise. One group participated in the JP programme control group and one group also used splints day/night and performed daily home exercise (SE group). The women were examined regarding ADL and hand function with the self administrated instrument Disability of the Arm, Shoulder and Hand (DASH), the assistive device part of the instrument Evaluation of Daily Activity Questionnaire (EDAQ), the Visual Analogue Scale (VAS) and the Grippit instrument. These instruments were administered before the JP programme one week after and at one year follow up.

At one year follow up thirty-five women, mean age 61 completed the trial, sixteen in the control group and nineteen in the SE group. No statistical differences at baseline evaluations were found between the groups. Both groups showed a significant increased ADL directly after the intervention, but only the SE group showed a significant increased ADL at one year follow up. Comparison on the DASH change scores between the groups before/one year follow up (p-value 0,003) showed a significant increased ADL for the SE group. In all the DASH activities except two, the use of assistive devices and splints was reported to reduce ADL difficulties.

The study showed a greater effect on ADL one year after participating in the extended JP programme than the JP programme alone and we found significant improvements in hand function for pain and stiffness but not in grip force. These results indicate that more analyses about association between ADL and hand function in women with HOA are needed.

Traditionell PR3-ANCA är bättre än högkänsligt test som aktivitetsmarkör vid Wegeners granulomatos

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Denna studie gjordes för att jämföra fyra kommersiella analyskit för 'antineutrofil cytoplasma antikropp' (ANCA) riktad mot 'proteinas 3' (PR3-ANCA) avseende förmåga att avspegla sjukdomsaktivitet hos patienter med känd cANCA-positiv vaskulit. Två sera vardera från 14 patienter med cANCA-positiv småkärlsvaskulit analyserades (13 Wegeners granulomatos; 1 mikroskopisk polyangit enligt "Chapel-Hill kriterierna"). Det ena provet var taget under sjukdomsskov och det andra under remission värderat med "Birmingham Vasculitis Activity Score" (BVAS). Inflammation värderades också med SR och CRP. Frusna sera från friska personer matchade för ålder och kön användes som kontroll. Tinade prover analyserades med IF-mikroskopi och med fyra kommersiella kit för PR3-ANCA: PR3-ELISA och capPR3-ELISA (Wieslab), hsPR3-ANCA (Orgentec) och EliA-PR3 (Phadia). För capPR3 & hsPR3 är den högsta mätbara antikroppskoncentrationen 200 enheter. Högre nivåer noteras >200.

Förekomst av cANCA bekräftades med IF-mikroskopi på samtliga analyserade sera från vaskulitpatienter. För samtliga PR3-ANCA metoder var antikroppsnivån på gruppnivå högre vid skov (p<0,001 för alla med Wilcoxons parade test), men 1-3 patienter (beroende på metod) låg kvar på samma nivå eller högre i remissionsprovet. Spearman rank test visade mycket god korrelation mellan PR3-ELISA & EliA-PR3 (Rho=0,914) och mellan capPR3-ELISA & hsPR3-ELISA (Rho=0,746). PR3-ELISA och EliA-PR3 korrelerade väl med SR (Rho=0,575 resp. 0,565) medan capPR3-ELISA och hsPR3-ELISA var sämre (Rho=0,092 resp. 0,201). Korrelationer till BVAS var överlag lägre för alla fyra tester (Rho 0,3-0,4). Samtliga kontrollsera utföll negativt avseende PR3-ANCA, utom ett strax över cut-off för hsPR3.

Trots att de högkänsliga metoderna för PR3-ANCA (capPR3 resp. hsPR3) är överlägsna vid diagnostik av PR3-ANCA-associerad vaskulit, korrelerar nivån av antikroppar mätt med traditionell PR3-ANCA ELISA och EliA-PR3 bättre till SR och CRP. Den dåliga korrelationen till inflammatorisk aktivitet med capPR3- och hsPR3-ANCA förklaras sannolikt av deras låga upplösning vid hög antikroppskonscentration. I klinisk praxis kan det därför vara missvisande att använda de högkänsliga metoderna för att följa sjukdomsaktivitet vid vaskulit.

Östrogen påverkar IL-17-producerande celler vid experimentell artrit

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Behandling med östrogen har i tidigare studier visats kunna hämma reumatoid artrit (RA). Tidigare studier har även visat

att östrogenbehandling resulterar i minskad produktion av det proinflammatoriska cytokinet IL-6, vilket är nödvändigt för differentieringen av IL-17-producerande T hjälpar-celler, s.k. Th17-celler. Th17-celler har nyligen visats spela en betydande roll vid autoimmuna sjukdomar som RA, specifikt genom att IL-17 attraherar neutrofiler och monocyter till leden samt stimulerar synoviala fibroblaster och osteoklaster, vilket i slutändan resulterar i erosioner på brosk och ben. I kliniska studier har nyligen en anti-IL-17 antikropp testats för behandling vid RA med positivt resultat. Östrogens effekt på IL-17-producerande celler i autoimmun artrit har inte tidigare studerats och syftet med vår studie är att undersöka om en möjlig mekanism för östrogens dämpande effekt på artrit kan vara att inhibera differentieringen av Th17-celler, och/eller hämma produktionen av IL-17.

Kollagen-inducerad artrit (CIA) inducerades hos ovariektomerade DBA/1 honor, som behandlades med 17 β-estradiol (E2) eller placebo. För att titta på östrogens effekt på IL-17-producerande celler vid fullt utvecklad artrit avslutades ett försök 42 dagar efter första immunisering, och för att undersöka effekten av E2 under induktionsfasen av CIA avslutades andra försök vid dag 7, 14 samt 23 efter första immunisering. IL-17-producerande celler från dränerande lymfkörtlar studerades med hjälp av IL-17 ELISPOT samt flödescytometri.

Vid fullt utvecklad artrit hade E2-behandlade möss signifikant färre funktionella IL-17-producerande celler jämfört med placebo-behandlade möss. E2-behandlade möss avslutade dag 7 uppvisade också en hämning av Th17-celler, men däremot hade E2 en stimulerande effekt på andelen Th17-celler dag 14 och 23, jämfört mot placebobehandlad grupp.

Dessa resultat tyder på att östrogen har förmågan att påverka IL-17-producerande celler vid experimentell artrit, en effekt som kan vara stimulerande eller inhiberande beroende tidpunkt i den inflammatoriska processen, men vilken eller vilka mekanismer som ligger bakom denna effekt är fortfarande oklart. Kompletterande experiment är planerade.

Tyrosin kinases are essential mediators in the development of antigen induced arthritis regulating formation of dendritic cells and antigen presentation

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Tyrosine kinases (TKs) are a family of intracellular signaling molecules participating in cell proliferation, development and apoptosis. Inhibition of TKs is effective in the treatment of various malignancies as well as diabetes mellitus. Several families of TKs are implicated in the pathogenesis of rheumatoid arthritis regulating processes in disease onset as well as progression. In previous work we demonstrated that a ligand to TK Flt3 is accumulated in the joints of RA patients and has proarthritic and erosive properties. Here we evaluate the role of TKs and Flt3-signaling in the antigen-induced model of arthritis.

Mice (n=75) were immunized with mBSA followed by an i.a. injection of mBSA on day 21. Treatment with TK inhibitor sunitinib (10 an 40 mg/kg/day) was started on day 7 (n=30) and on day 21 (n=30) and continued until day 28. Controls (n=15) received citrate buffer. The mBSA-injected joints were evaluated morphologically and compared to circulating levels of bone (CTX-I) and cartilage (CTX-II) degradation marker and to anti-mBSA antibodies measured by ELISA. The effect of sunitinib on the levels of TK ligands Flt3-L, RANKL and VEGF were measured by ELISA. Expression of Flt3 and development of dendritic cells (DC) was evaluated in the bone marrow and spleen by flow cytometry.

Sunitinib treatment alleviated mBSA-induced arthritis, reducing intensity of synovitis and frequency of bone erosions. This was accompanied by a reduction of mBSA antibodies and marker for bone degradation, CTX-I.

Sunitinib induced a pronounced increase in Flt3-ligand levels, while levels of VEGF and RANKL were changed only slightly, indicating relative specificity on Flt3-signaling. Following sunitinib treatment, the expression of Flt3 was selectively decreased on CD3+ population in bone marrow.

In spleen, sunitinib induced a significant decrease of pDCs as well as cDCs affecting all cDC subsets. However, sunitinib increased CD8+ population in spleen while the populations of B-cells and CD4+ T-cells were unchanged.

Sunitinib blocks TKs through Flt3 pathway alleviating synovial inflammation and bone resorption in antigen induced arthritis. This effect is potentially mediated through downregulation of DCs and decreased antigen presentation.

C4 gene copy number associates with autoantibody profile in systemic lupus erythematosus

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Systemic lupus erythematosus (SLE) is a heterogeneous and complex systemic autoimmune disease characterized by autoantibody profile. Copy number variation (CNV) has been shown to be one of many possible sources of phenotypic heterogeneity. The region with strongest linkage to SLE (6p21.3) harbors the genes C4A and C4B which are known to exhibit CNV. In this study, we aimed to analyze the associations between C4 CNV and SLE. In addition, we analyzed the association of C4 CNV with plasma levels of complement and autoantibodies among SLE patients.

283 SLE patients and 180 controls matched for age, sex and region of living participated. C4 CNV was determined with RT-PCR. Plasma levels of C4, C3, and C3d were measured in patients by rate nephelometry and autoantibodies with enzyme linked immuosorbent assay. The Lupus anticoagulant (LAC) test was performed with a Dilute Russel Viper Venom method. Associations were determined with Chi-square and Mann-Whitney tests.

SLE patients displayed more often low gene copy number of C4A (<2) (OR: 2.3, 95% CI: 1.4-3.7) or < 4 copies of 'C4 total' (C4A+C4B) (OR: 2.3, 95% CI: 1.4-3.6) compared to controls. No association between C4B CNV and SLE was observed. Presence of SSA/SSB was significantly associated with SLE patients carrying < 2 copies of C4A or < 4 copies of C4tot (C4A+C4B) (OR C4A: 1.8, 95% CI: 1.1-3.1) (OR C4tot: 4.1, 95% CI: 2.4-7.00). SLE patients carrying < 2 copies of C4A or < 4 copies of C4tot, were less likely to have β2GP1 IgG (OR C4tot: 0.4 95% CI: 0.2-0.7), anticardiolipin (aCL) IgM (OR C4A: 0.5, 95% CI 0.2-0.9) or a positive LAC test (OR C4tot: 0.3, 95% CI: 0.1-0.5). In addition,

our data reveal association between low copy numbers (<4 copies) and low serum levels of C4 (p = 0.02) among SLE patients. No association between C4 CNV and plasma levels of C3 and C3d was observed.

Our study demonstrates a significant association between C4 CNV and autoantibody profile in SLE. Low gene copy numbers of C4 were strongly associated with the presence of SSA and SSB antibodies while SLE patients with high numbers of C4 gene copies were more likely to have aPL antibodies. Our data support previous findings that low gene copy number of C4 is associated with SLE and with low levels of C4 protein in plasma. Further studies related to the complement system are warranted to understand how genetics is related to subgroups of SLE patients with different autoantibody profile.

Interaction analysis for the HLA-DRB1 shared epitope alleles and the MHC class II transactivator CIITA gene variant in the risk of rheumatoid arthritis

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Several risk factors for rheumatoid arthritis (RA) have been found to interact with HLA-DRB1 shared epitope (SE) alleles. Recently we found a variant of the MHC class II transactivator (CIITA) gene, which associates with inflammatory diseases. This association was not consistently replicated in different populations. CIITA is known to be the key regulator of MHC2 expression and may be involved in development of RA in relation with SE alleles. We hypothesize that the risk variant rs3087456 in the CIITA gene may interact with the HLA-DRB1 SE in development of rheumatoid arthritis.

Interaction between HLA-DRB1 SE alleles and rs3087456 in CIITA was first investigated in a cohort of 2519 RA cases and 1347 matched controls from Swedish EIRA study and later repeated in two cohorts from UK (1916 cases and 1270 controls) and The Netherlands (486 cases and 283 controls). Genotyping was performed by Taqman genotyping assay (CIITA) and by SSP-PCR (HLA). The ACPA (anti-citrullinated protein antibody) status was identified for all RA patients by anti-CCP ELISA. We have used departure from additivity of effects as a measure of interaction between rs3087456 (homozygous for G allele) and HLA-DRB1 shared epitope alleles defined as any of DRB1*01, DRB1*04 or DRB1*10. This measurement gives the proportion of risk among those carrying both genetic risk factors that is attributed only to the interaction (attributable proportion due to interaction, AP).

In the analysis of the 3866 individuals from Swedish population for interaction between rs3087456 and SE we found no significant interaction (AP=0.15, 95%CI: -0.24-0.53). Since SE is primarily a risk factor for ACPA positive disease we stratified data according to positive (AP=0.27, 95%CI: -0.05-0.59) and negative (AP=-0.19, 95%CI: -1.0- 0.62) autoantibody status. We further found no significant interaction between the subgroups of SE (DRB1*01, DRB1*04 or DRB1*10) and CIITA. Similar analysis of two independent RA cohorts from two European populations confirmed an absence of interaction between genetic marker in CIITA and SE alleles in development of RA.

We did not observe a significant interaction between rs3087456 and SE alleles with regard to risk of RA. Since a biological link between products of these genes is evident, this finding may point towards a more complex relation between CIITA and class 2 antigens in the autoimmune process.

Development of disease activity and disability in women and men with early rheumatoid arthritis: 8 years of follow-up from the Swedish TIRA-project

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Previous studies have reported that disability is strongly associated with disease activity in rheumatoid arthritis (RA) and disability at time of diagnosis has also proved to be a consistent predictor of disability over time. The present study was done to investigate the course of disease activity and disability over 8 years in early RA and to analyse differences between women and men.

149 patients with disease duration<1 year were included in the Swedish early RA-cohort cohort "TIRA". Patients were followed prospectively for 8 years from the time of diagnosis. Disease activity was assessed by DAS28. Disability was measured by pain (VAS), grip force (Grippit), 'grip ability test' (GAT), range of motion in hand, upper and lower extremity (SOFI), walking speed and Health Assessment Questionnaire (HAQ). Changes over time and differences between women and men were evaluated.

Disease activity decreased over time from inclusion to the 8-year follow-up for both women and men. Disability as measured by SOFI (hand, upper and lower extremity) and walking time was improved during the first year after diagnosis but at the 7 and 8 year follow-up, the level of disability was comparable to the level at inclusion. Pain, grip force and GAT were also improved during the first years but thereafter remained stable. HAQ scores were similar in men and women at inclusion. After initial improvement, HAQ remained at a stable level in men, while scores for women deteriorated from year 2 onwards and had reached back to baseline levels at 8 year follow-up. More disability in women than men was also seen in grip force whereas men had more disability than women in SOFI upper extremity. There were no significant differences between women and men in disease activity or disability as measured by VAS pain, GAT, SOFI hand or SOFI lower extremity during the 8-year follow-up.

Although disease activity was well managed, disability deteriorated over 8 years with a less favourable course in women than men. Besides controlling disease activity, there is accordingly a need for regular assessments to detect and prevent progressing disability in RA-patients, not only in the early phase of disease, but also over the following years.

DAS28 at 3 months after diagnosis of early rheumatoid arthritis is strongly associated with direct and indirect costs over the following 4 years. The Swedish TIRA project

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From the Swedish TIRA cohort we previously reported that average disease activity in patients with early RA was significantly improved 3 months after diagnosis and thereafter remained rather unchanged over the following years. There was a significant association between DAS28 at the 3 month follow-up and

DAS28 values over the following 3 years for men and for women and for all age groups. DAS28 was also associated with functional capacity over the following years. The present study was done to explore a possible association between disease activity as measured by DAS28 at the 3-month follow-up after diagnosis and costs over the following 4 years.

320 patients with early ≥ 1 year) RA were assessed at regular intervals. Clinical and laboratory data were collected and patients reported health care utilization and number of days lost from work. At 3-month follow-up, patients were divided into 2 groups according to disease activity, using DAS28 with a cut-off level at 3.2. Direct and indirect costs and EQ-5D over following 4 years were compared between the groups. Multivariate regression models were used to control for possible covariates.

A DAS28 level of ≥ 3.2, 3 months after diagnosis was associated with high direct and indirect costs over following 4 years. Patients with DAS28 ≥ 3.2 at 3-month follow-up had more visits to physician, physiotherapist, occupational therapist and nurse, higher drug costs, more days in hospital and more extensive surgery compared to patients with 3-month DAS28<3.2. Number of days lost from work due to sick-leave and permanent work disability was also higher in this group. The effect of disease activity on health-related quality-of-life was highly significant. In regression models, DAS28 at 3-month follow-up was significantly associated with costs over the following years.

DAS28 3 months after diagnosis is an important prognostic marker regarding healthcare utilization and costs. Achieving remission or low disease activity 3 months after diagnosis is likely to decrease morbidity, increase quality of life and save costs for the patient and for the society over the following years.

Fatigue in patients with ankylosing spondylitis

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Ankylosing spondylitis (AS) is a common rheumatic disease that characteristically affects the sacroiliac joints and the spine. The disease may cause reduced physical activity and spinal mobility, stiffness, fatigue and depression. Pain and stiffness is known as the primary symptoms of AS. Fatigue which is a mulitfactorial phenomenon has also shown to be a symptom significantly impacting patient quality of life.

The aim was to study if fatigue varies between genders and if fatigue is associated with leisure time physical activity, self reported pain, depression and global health.

212 patients, 90 women and 121 men, with AS (New York criteria) were recruited from the Rheumatology unit's SU/Sahlgrenska, and SU/Mölndal, the medicine clinic in Alingsås and in Borås. The participants responded to the Multidimensional Fatigue Inventory (MFI20) questionnaire which consists of questions about five subscales of fatigue: general fatigue, physical fatigue, reduced motivation, reduced activity and mental fatigue. They also answered leisure time physical activity (LTPAI), EQ5D and global fatigue (VAS 0-100mm).

Statistics. The means and standard deviations (SD) are presented. Possible differences between the groups were analyzed by Mann-Whitney test and associations between the variables were calculated by Spearman´s correlation coefficient (rho).

The mean age ±SD of the study population was 50 (±12,8) years, the mean age of women was 50,5 (±12,2) years and for men 49,9 (±13,4) years. 70% of the women and 53% of the men rated their global fatigue as 50mm or higher (p=0.002). The mean rating in global fatigue for women was 58,4±23,6 mm and for men 46.9 ±26.9mm. There was a similar gender difference for ratings of MFI general fatigue (p=0.033). The mean rating in general fatigue in women was 14,1±3.7 and for men 12.7±4.5. No gender differences were found for MFI physical fatigue, reduced motivation, reduced activity and mental fatigue.

High degree of moderate to vigorous leisure time physical activity showed low-to-fair correlations with low general fatigue, physical fatigue and reduced activity in both genders(rho 0,26 p=0,01, rho 0,41 p=0,001). EQ5D Depression and EQ5D Self-rated health were associated with all the MFI subscales and the VAS Global fatigue (rho -0,39 -0,75).

The level of fatigue differs between genders. Physical activity, depression and self-related health are associated with fatigue in AS.

Lower Body Mass Index is Associated with an Increased Risk of Giant Cell Arteritis

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There is limited data on predictors of giant cell arteritis (GCA). In a previous case-control study of women with GCA, a history of smoking, low body mass index (BMI) and several hormonal factors were associated with GCA. Smoking and a low level of formal education have been found to predict other chronic inflammatory disorders, including rheumatoid arthritis.

We used two population based health surveys performed in the same catchment area, the Malmö Preventive Medicine Program (MPMP) and the Malmö Diet Cancer Study (MDCS). Information on medical history and life style factors was obtained using standard physical examinations and self-administered questionnaires. From this population, individuals who developed GCA after inclusion were identified by linking the MPMP and MDCS databases to the local patient administrative register and the national hospital discharge register. A structured review of the medical records of all identified cases was performed. Four controls for every confirmed case, matched for sex, year of birth and year of screening, were selected from the MPMP and the MDCS databases. Potential predictors of GCA were examined in conditional logistic regression models.

Eighty-three patients (70 % women, 64 % biopsy positive, mean age at diagnosis 71 years) had a confirmed diagnosis of GCA after inclusion in the MPMP or the MDCS. In logistic regression analysis, a higher BMI was associated with a significantly reduced risk of subsequent development of GCA (Odds ratio (OR) 0.91 per kg/m2; 95 % confidence interval (CI) 0.84-0.98). Smoking was not a risk factor for GCA overall (OR 1.36; 95 % CI 0.77-2.57), although there was a trend towards an increased risk in female smokers (OR 2.14, 95 % CI 0.97-4.68). Level of formal education and breast-feeding history did not predict GCA. In multivariate analysis, adjusted for smoking and level of formal education, the inverse association between BMI and GCA remained significant (OR 0.91 per kg/m2; 95 % CI 0.85-0.99)

In this study, GCA was predicted by a lower BMI at baseline. Potential explanations include an effect of reduced adipose tissue on hormonal pathways regulating inflammation in the context of GCA.

Osteoporosis or osteopenia in half of the patients with ankylosing spondylitis in Western Sweden

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Osteoporosis and vertebral fractures are well recognized complications of ankylosing spondylitis (AS). The aims of this study were to investigate prevalence and risk factors for osteoporosis and vertebral fractures in a Swedish AS population.

All patients meeting the Modified New York criteria of AS at the department of Rheumatology at Sahlgrenska University Hospital, in Borås and Alingsås were invited to participate. The patients answered questionnaires about medical history, risk factors for osteoporosis, BASDAI and BASFI. Physical examination including BASMI was performed. Bone mineral density (BMD) was measured by DXA in lumbar spine, in anteroposterior and lateral projection, in hip and in forearm. Lateral x-rays of spine were taken to assess vertebral fractures using Genant score and syndesmophyte formation using mSASSS.

204 patients were included; 87(43%) women. Age (median and range) 49(17-78) years, symptom duration 24(2-55) years, BASDAI 3.5 (0-9.6), ASDAS 2.3(0.8-5.9) and BASMI 3.0(0.6-7.4). Osteoporosis as defined by the WHO was found in 26 patients (12.7%), osteopenia in 78 patients (38.2%). 52 vertebral fractures were diagnosed among 29 patients (14.2%), lumbar spine being the most usual location. In only 3 patients the vertebral fractures were known since before. Osteopenia, osteoporosis, Genant score and BASMI did not differ between sexes. Men had higher mSASSS compared with women ($p<0.001$). Low BMD was significantly associated with disease duration, BASMI, mSASSS and low BMI in both sexes. In women low BMD was also significantly associated with age and being in menopause and in men also with lifetime prednisone burden. Vertebral factures in women were significantly connected with increasing age, BASMI, mSASSS and being in menopause and in men with BASMI and swollen joints count. Lumbar spine BMD was significantly lower measured with DXA in lateral projection compared with anteroposterior projection ($p<0.001$). 35% of the women and 8% of the men had undergone DXA examination before the study. 8 patients were on bisphosphonates at inclusion. Bisphosphonate treatment was initiated in additionally 30 patients after the study.

50 % of AS patients have osteoporosis or osteopenia. Osteoporosis is still often undiagnosed and untreated in AS, particularly in male patients. Vertebral fractures are frequent, but often missed. Impaired back mobility and high disease burden indicates risk for osteoporosis and vertebral fractures.

Serumnivåer av S100A4 ökar proportionellt med leddestruktioner i patienter med reumatoid artrit

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Bakgrund: S100A4 är ett Ca-bindande protein som är känt för att öka metastaseringsförmåga hos tumörvävnader. Höga nivåer av S100A4 har nyligen påvisats i synovia och ledvätska hos patienter med reumatoid artrit (RA). Preliminära resultat tyder på att S100A4 har en betydande roll för benomsättning.

Syfte: Att studera vikten av S100A4 bland andra kända benomsättningsmarkörer för leddestruktion och sjukdomsaktivitet hos patienter med RA.

Metoder: Serumprover togs för analys av S100A4 från 87 oselekterade patienter med etablerad RA (ålder 24-89 år, 69 kvinnor, 18 män, sjukdomsduration i medeltal 17 år; range 1,5 till 44 år). Alla patienterna behandlades med methotrexat och infliximab. Röntgen av händer och fötter gjordes i samband med provtagning och granskades med Sharp van der Heijde scoring (SHS) metod. Serumnivån av S100A4 analyserades med ELISA och jämfördes med inflammatoriska markörer (IL6, CRP, SR), ben- och brosk- omsättningsmarkörer (MMP3, COMP, CTX-I) och klinisk bedömning av sjukdomsaktivitet (DAS28).

Resultat: Nivån av S100A4 var signifikant högre hos patienter med uttalade leddestruktioner (total SHS medel 108; range 50-299) jämfört med de som hade måttliga leddestruktioner (SHS <50, medel 26; range 1-49) (ng/ml: 1103±1379 vs 1962±1841, $p=0.05$). Nivån av S100A4 var också signifikant högre i gruppen av patienter med hög sjukdomsaktivitet (DAS28>3,02, medel 3,54; range 3,02-4,17) jmf med hos lågaktiva patienter (DAS28<3,02, medel 2,28; range 0,99-2,97) (ng/ml: 1122±1532 vs 1797±1699, $p=0.05$). Denna skillnad var mer uttalad hos kvinnor (ng/ml: 1266±1788 vs 3486±1716, $p=0.027$). Hos manliga patienter påvisades en korrelation mellan S100A4 och DAS28 ($r=0.74$, $p=0.002$). Vi fann ingen korrelation mellan nivån på S100A4 och CRP, IL-6, CTX-I, COMP eller MMP-3.

Nivån av S100A4 var även signifikant lägre hos patienter med hög kumulativ dos av infliximab och var lägst hos patienter som fått över 21 infusioner (ng/ml: 1796±1766 vs 754±965, $p=0.03$).

Slutsats: I denna studie var S100A4 en benomsättningsmarkör hos patienter med långvarig RA och ökade proportionellt med utvecklingen av leddestruktionerna.

Circulating CTLA-4+CD25+CD4+ T cells counteract maturation and tissue homing receptor switch of CD4+ T cells in infancy

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CTLA-4 is an important cellular molecule in maintaining tolerance in animal models. CTLA-4 is expressed by both FOXP3+ regulatory T cells and by activated conventional T cells. It was thought that the tolerogenic effects of CTLA-4 were mediated mainly by the regulatory T cells. However, new data indicate that CTLA-4 on conventional activated T cells also play a crucial role in inhibiting tissue destruction and autoimmune disease in animal models.

We have analysed blood samples from a prospective birth cohort up to 3 years of age. Blood samples were drawn from cord blood and at the age 0, 3-5 days, 1, 4, 18 and 36 months of age and flow cytometric analyses have been performed staining for FOXP3 and CD25 to identify the regulatory T cells, and CTLA-4 and CD25 to indentify all cells with regulatory action whether regulatory or conventional. We also stain for the receptors CD45RA and CD45RO to determine the conversion to memory T cells, and the receptors CD62L, alfa4beta7 and CCR4 to

identify homing receptor switch. The data was analysed by multivariate factor analysis using the program SIMCA P+ followed by univariate analyses using Spearmans rank correlation test.

CTLA-4 expressing T cells proved to be the cells that were associated with tolerance induction, ie projected together with the CD45RA and alfa4beta7-expressing cells, with the CD45RO and CCR4-expressing cells projecting on the opposite side. The FOXP3 T cells projected in the centre of the of the PCA plot, indicating no or little association with the expression of the memory marker, homing receptors or CTLA-4-positive T cells. Univariate correlation tests confimed these results showing significant negative correlations between CTLA-4 positive T cells and CD45RO- and CCR4-positive T cells. We also showed that percentage of CTLA-4+CD25+CD4+ T cells and FOXP3+CD25+CD4+ T cells only correlated significantly at 1 and 4 months of age but not at earlier or later ages up to 3 years of age, in contrast to adults.

We suggest that CTLA-4 expression on T cells is the most important factor for downregulation of the immune system in children, irrespective of type of T cells that express it. CTLA-4 expression is also associated with reduced levels of tissue homing receptors, thus diminishing the possibility of extravasation of inflammatory cells into the tissue. Moreover, strong correlation between CTLA-4+ T cells and FOXP3-positive T cells that is seen in adults is not found in children.

Sustained remission over eight years retards joint damage in rheumatoid arthritis: experiences from the barfot study

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Remission is generally accepted as the goal of treatment of rheumatoid arthritis (RA).Remission sustained over 2 years has recently been shown to retard joint damage. The present study over 8 years intends to show whether this may be the case also after a prolonged period of time.

629 patients from the BARFOT early ≤ 1 year) RA cohort have been followed for 8 years. The EULAR criterion for remission was used, i.e. a DAS28 below 2.6. Sustained remission was present when a patient was in remission at all four predetermined follow-up visits at 1, 2, 5 and 8 years after inclusion, sporadic remission when the patient was in remission at one, two or three visits, otherwise never remission was present. Radiographs of hands and feet were scored by the van der Heijde modification of the Sharp score (SHS). The smallest detectable change (SDC) in SHS was 5.8.

34% of all patients were in remission at 1 year, 37% at 2, 38% at 5 and 39% at 8 years. Only 14% enjoyed sustained remission, while 51% had sporadic remissions and 35% of the patients were never in remission. Patients with sustained remission had considerably less change in SHS score from baseline to 1, 2, 5 and 8 years compared with patients with sporadic or never remission –the median changes were, respectively, 0, 0, 1 and 0 versus 1, 2.5, 8.25 and 6.5 (sporadic remission) and 1.5, 4, 10.5 and 11 (never remission), p=0.001 for both comparisons. There was no significant difference in change in SHS from baseline to 1, 2, 5 and 8 years between sporadic and never remitters, p =0.39, 0.1, 0.09 and 0.06, respectively. The proportion of patients with radiological progression was significantly smaller in patients with sustained remission compared with patients with sporadic or never remission, p=0.001, 0.001 and 0.008 after 2,5 and 8 years. DMARD and prednisolone, which were similarly used in the three groups during the first years, were subsequently less frequently prescribed to the patients with sustained remission.

Radiological joint damage was minor in the group of patients with sustained remission. In contrast, the group with occasional events of remission was associated with pronounced radiological progression almost to the same extent as that in the group who were never in remission. Sustained low disease activity over longer periods of time is needed to preserve joint structure and should be achieved in clinical practice by establishing a tight follow-up scheme with data driven adjustment of therapy.

Differences in activity limitation, pain intensity and global health in patients with RA in Sweden and the US – a five year follow-up

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OBJECTIVE: This study compares activity limitations, pain intensity and global health in patients with RA in Sweden and the US and determines if nationality is associated with these outcomes.

METHODS:Longitudinal data from the 'Swedish TIRA Project' (n=149) and the University of California, San Francisco (UCSF) RA panel study (n=85) were used. Data were collected annually concerning use of medications (DMARDS, biologics, and corticosteroids), morning stiffness, number of swollen joints and number of painful joints. Three self-reported outcome measures were examined: pain intensity (0-100 scale), activity limitation according to the Health Assessment Questionnaire Score (HAQ) and global health. To analyse the data Student's t-test, Chi-square and generalised estimating equations (GEE) were used.

RESULTS: Nationality was significantly related to HAQ and pain intensity, even after adjustment for covariates. The patients in the TIRA cohort reported a lower HAQ score and a higher pain intensity than the patients in the UCSF cohort. Nationality was not related to global health.

CONCLUSION: Patients with RA should be assessed with awareness of the psychosocial and cultural context since disability seems to be affected by nationality. These results underscore the importance of highlighting the individual levels of self-reported variables such as pain and HAQ, both for the individual but also in international comparisons. Further knowledge to clarify how a multinational setting affects disability could improve translation of interventions for patients with RA across nationalities.

A genome wide linkage scan of multi-case families with rheumatoid arthritis from northern Sweden

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Background and Statement of Purpose: Rheumatoid arthritis (RA) is an autoimmune disease affecting 0.5-1.0 % of the population with a multifactorial aetiology due to both genetic and environmental factors. The population of northern Sweden is relatively homogenous and has previously been used for the ge-

netic mapping of monogenic as well as complex genetic diseases based on large multi-case pedigrees.

The purpose was to identify novel genetic risk factors for the development of rheumatoid arthritis (RA) by performing a genome-wide linkage (GWL) scan in multi-case families from northern Sweden.

Methods: Forty-seven families, consisting of 133 individuals with RA and 215 unaffected relatives, were genotyped using microsatellite markers covering the genome at an average of every 10cM (AB Linkage Mapping Set 10cM version 2.5 [Applied Biosystems, Foster City, CA]). Non-parametric multipoint linkage analysis, using Merlin computer program, was performed to identify regions of increased sharing.

Results: Eight loci linked to RA were identified ($p>0.05$), with the HLA locus being the most highly significant ($p = 0.0004$). Further significant linkage signals were identified on chromosomes 5, 6, 9 and 14 ($p<0.005$) and on chromosomes 6, 8 and 10 ($p <0.05$).

Conclusions: This GWL study confirms a previously reported linkage of RA with the HLA-locus and further identifies a number of other, novel, loci potentially affecting the risk of RA in the population of northern Sweden.

S100A4 is a novel regulator of bone formation and potential target in patients with osteoporosis

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Background. S100A4, metastasin, is a Ca-binding protein participating in regulation of cell growth, survival, and motility. Its accumulation has been recently shown in relation to tumour metastasis and inflammation.

Objectives. Role of S100A4 protein in bone formation was studied using S100A4KO mice and their wild-type (WT) counterparts.

Material and methods. Bone mineral density (BMD) in trabecular and cortical compartments was evaluated in age and sex matched S100A4KO (Mts1, n=20) and their WT countepartes (A/Sn, n=20) using a peripheral quantitative computed tomography. The effect of sex hormones on BMD in S100A4KO was measured 5 weeks after gonadectomi (ovariectomy, n=10; orchidectomy, n=8). Changes in BMD were analysed in relation to markers for bone metabolism (CTX-I, osteocalcin, OPG, OPN, RANKL) and agiogenesis (MMPs, MetAP-2, HIF-1alpha).

Results. S100A4KO exhibited 28% higher BMD as compared to age and sex matched WT mice ($p=0.01$). Differences were more pronounced in trabecular bone in males and in cortical bone in females. Surprisingly, MMP-3 and HIF-1 levels were significantly reduced in S100A4KO mice, while RANKL/OPG ratio were similar to WT. Gonadectomi resulted in the loss of total BMD similar in S100A4KO and WT. S100A4KO males showed no significant reduction in trabecular or in cortical bone following gonadectomi, while trabecular bone in WT males was reduced by 34%. Bone loss in S100A4KO females was similar to WT mice.

Conclusions. S100A4 protein is a novel regulator of bone mineral density. Deficiency of S100A4 in mice is associated with osteopetrosis. Thus, neutralization of S100A4 protein may be a potential target preventing excessive bone loss.

Circulating COMP in young persons with or without juvenile idiopathic arthritis

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Cartilage oligomeric matrix protein (COMP) is a structural protein in hyaline cartilage. Elevated serum levels can be the result of joint cartilage degradation, de-novo synthesis, and/or deficient clearance. Thus, raised serum COMP may hypothetically reflect ongoing tissue damage as well as tissue repair or normal anabolism. The present study was done to investigate serum COMP in young persons in relation to markers of inflammation (CRP) and growth (IGF-1).

Serum COMP and IGF-1 were analysed by immunoassays (AnaMar AB; Siemens Healthcare Diagnostics Ltd) in sera from 96 persons <19 years of age who had undergone allergy tests (IgE antibodies) with negative results and CRP <10mg/L (=referents). 43 sera from patients with juvenile idiopathic arthritis (JIA) were also analysed regarding serum COMP. All results were sub-grouped according to age and sex. JIA patients were also sub-grouped regarding type of disease.

Average COMP levels were significantly lower in persons aged 16-18 years (comparable to adult levels) than in children <16 years. COMP was significantly lower in the JIA group compared to referents. IGF-1 levels correlated with age, but not with COMP (apart from patients with IGF-1 >400g/L).

In contrast to adult rheumatoid arthritis patients, where circulating COMP is often raised, we report that COMP is on average lower in children with JIA compared to referents. Others have shown that IGF-1 is lowered in JIA (Allen et al, Ann Rheum Dis 1991;50;602), which is intriguing considering that COMP gene expression is upregulated by IGF-1 (Hua & Stogiannidis, Acta Biochim Biophys Sin 2006;38:677). Further, it is known that serum COMP rises in children treated with growth hormone (Bjarnason et al, J Clin Endocrinol Metab 2004;89:5156). We hypothesize that a rise in serum COMP due to articular cartilage erosion can be masked by reduced IGF1-mediated COMP production in active inflammatory disease. The clinical utility of serum COMP measurements may possibly be enhanced by relating the results to IGF-1 levels and CRP.

Antibodies of IgG, IgA and IgM isotypes against cyclic citrullinated peptide precede the development of rheumatoid arthritis

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We have shown that the presence of anti-CCP antibodies precedes the development of RA by years. Recently we also showed that individuals who later developed RA had significantly increased levels of several cytokines and chemokines. Here we aimed to investigate the presence and predictive value of IgG, IgA and IgM anti-CCP antibodies in individuals before onset

of symptoms and to assess their relation to RFs, cytokines and chemokines, smoking, and also to evaluate the predictive effect of these predating antibodies for radiological score after RA onset.

A case-control study was nested within the Medical Biobank of Northern Sweden. Patients with RA were identified amongst blood donors antedating onset of their disease by years by co-analyzing the registers. Population based matched controls were selected randomly from the same cohorts. Anti-CCP antibody isotypes were determined using EliA anti-CCP assay on ImmunoCAP 250 (Phadia AB, Uppsala, Sweden)

Eighty-six individuals with RA were identified as being blood donors prior to onset of symptoms of joint disease, median (IQR), 2.5 (1.1-5.9) years before onset. The prevalence of anti-CCP antibodies in the pre-patients was 35.2% of IgG, 23.9% of IgA, and 11.8% of IgM with a specificity of 98.9%, 97.1% and 93.9%, respectively. IgG- and IgA anti-CCP antibodies were highly significant compared with controls. Anti-CCP antibody of the IgG and IgA isotype predicted RA significantly in conditional logistic regression models (OR=98.1, 95% CI (13.3-723.8) and OR=13.3, 95% CI (4.9-36.0), respectively), whereas the IgM isotype showed borderline significance (OR=2.5 95% CI (0.9-6.3)). The mean antedating time was longest for IgA isotype, 2.2 years, followed by IgG, 2.1 years and for IgM, 1.4 years. The concentrations of the antibodies increased significantly and the frequencies where at diagnosis of RA 70%, 40% and 30%, respectively. IgA antibodies but not IgG were significantly associated with up-regulated chemokines. In smokers IgA anti-CCP antibodies appeared much earlier before onset of symptoms of RA vs. in non-smokers. Patients positive for all anti-CCP antibody isotypes already before onset had a higher radiographic score both at baseline and after 24 months of disease compared with pre-RA individuals with fewer or no anti-CCP isotypes.

Anti-CCP antibodies of both the IgG and IgA isotypes predated the onset of RA, also, both isotypes predicted the development of RA, with the highest predictive value for IgG antibodies.