1

Inflammation and Socioeconomic Status in SLE

Mai Nguyen (University of Manitoba, Winnipeg); John McVagh (University of Manitoba, Winnipeg); Carol Hitchon (University of Manitoba, Winnipeg); David Robinson (University of Manitoba, Winnipeg); Navjot Dhindsa (University of Manitoba, Winnipeg); Hani El-Gabalawy (University of Manitoba, Winnipeg); Christine Peschken (University of Manitoba, Winnipeg)

Objective:
Worse outcomes in systemic lupus erythematosus (SLE) patients from lower socioeconomic strata (SES) have been well documented. Low SES is associated with higher chronic stress, which in turn may result in increased inflammation and immune dysfunction. We examined the relationship between SES, autoantibody frequency, and inflammation in SLE patients.

Methods:
Adult incident and prevalent SLE patients were enrolled in a prospective cohort at a single centre. Sociodemographic variables, data on health-related habits, diagnostic criteria, disease activity, autoantibodies, treatment, and damage were collected annually using standardized tools. SES was measured as educational level achieved and annual household income. Disease activity was evaluated using the Systemic Lupus Activity Measure (SLAM). Organ damage was measured using the SLICC/ACR Damage Index (SDI). Autoantibodies measured included antinuclear antibody, dsDNA antibody, extractable nuclear antigens and anti-phospholipid antibodies. Inflammation was measured using the erythrocyte sedimentation rate (ESR) score from the SLAM. Baseline data was analyzed, testing for differences in ESR score and total number of autoantibodies positive between income and education groups. Significant variables from univariate analyses were then included in multivariate regression models examining for predictors of total autoantibody frequency, ESR score, and organ damage.

Results:
Two hundred seventy-three patients were enrolled in the cohort, mean disease duration was 13.7 years, and mean age was 48.5 years. Ninety percent were female, 14% had incomes below the poverty line, while 51% had annual incomes >$50,000. Seventy-seven percent had completed high school. No associations were found between SES and autoantibody frequency. Less education and low income were associated with increased ESR scores ($p< 0.001$, $p=0.035$ respectively) in univariate analysis. Both income and education were predictors of higher ESR scores in linear regression ($p=0.025$ and $p=0.047$ respectively). Higher ESR score and lack of high school completion ($p=0.032$ and $p=0.04$ respectively) were predictors of SDI scores when total ACR score, age, and income were included in the regression model.

Conclusion:
In our cohort, low SES was a predictor of increased inflammation. Both increased inflammation and lower educational attainment were independent predictors of organ damage. Thus inflammation may be a mediating factor between low SES and poor disease outcomes in SLE.

2

An Evaluation of the Validity of Cardiovascular Diagnoses in Administrative Data: A Systematic Review

Natalie McCormick (University of British Columbia, Vancouver); Jamie Thomas (Arthritis Research Centre, Centre for Health Evaluation and Outcome Sciences, Vancouver); Diane Lacaille (Arthritis Research Centre, University of British Columbia, Vancouver); Juan Antonio Avina-Zubieta (Arthritis Research Centre, University of British Columbia, Vancouver)

Objective:
To conduct a systematic review of studies reporting on the validation of diagnostic codes for identifying cardiovascular conditions in administrative health data and to compare the validity of the codes.

Methods:
A comprehensive literature search was conducted using Medline and EMBASE, from inception to November 2010, using two strategies: (1) all studies where administrative data was used to identify cardiovascular conditions, and (2) all studies reporting on the validation of administrative data to identify these conditions. From a title and abstract screen relevant articles were selected for thorough review for inclusion by two investigators working independently; discrepancies were resolved by consensus. Additional studies were located through hand-searching. A predesigned data abstraction form was used to extract pertinent data, including sensitivity, specificity, positive (PPV) and negative (NPV) predictive values, and kappa, and the study quality was evaluated using the QUADAS tool.

Results:
A total of 76 articles were included in the final review. Two cardiovascular events, acute myocardial infarct (AMI) and cerebrovascular accidents (CVA), were selected because of their frequent selection as outcomes of interest in cardiovascular studies; the diagnosis of congestive heart failure (CHF) was also evaluated. PPV was the most commonly reported statistic, followed by sensitivity, whereas NPV and kappa were rarely reported; most data pertained to hospitalizations. While some variability in results was observed, mainly relating to the selection of gold standard with studies using stricter criteria, such as the MONICA criteria for AMI, finding lower sensitivity and PPV values, overall the sensitivity and specificity of hospitalization data was high (>80%) in most studies for identifying AMI (sensitivity ranging from 16-100%, specificity from 80-100%) and CVA (sensitivity >80% in most, range 25-100%; specificity 92-97%). In contrast, validation studies of CHF found less accurate results, with low sensitivity (< 70% in most studies, range 0-87%), highly variable but often low PPV, but acceptable specificity (>70% in most, range 69-100%). The results support the use of hospitalization data for identifying AMI and CVA, but not CHF. It was noted that the accuracy of AMI as a cause of

death on death certificates was limited.

Conclusion:
Hospitalization data can be used to identify AMI and CVA as a covariate or outcome. Authors should take into consideration that hospitalization data to identify CHF has significant limitations due its relatively low sensitivity and specificity. When using vital statistics data, authors need to acknowledge that the accuracy of AMI as a cause of death is limited.

3

Shared Risk For Chronic Inflammatory Diseases In The Family Members of First Nations Rheumatoid Arthritis Patients

Konstantin Jilkine (University of Manitoba, Winnipeg); Keng Wong (University of Manitoba, Winnipeg); Hani El-Gabalawy (University of Manitoba, Winnipeg)

Objective:
< span class="Apple-style-span">RA is prevalent and severe in First Nations (FN). As our previous studies have shown that RA is familial in FN, we have studied the disease< /span>-free first-degree relatives (FDR) of FN RA patients to better understand risk in FN. Our studies have shown that compared to FN controls, FDR have a high prevalence of RA autoantibodies and their cytokine profile resembles that of the RA patients. Because of a high prevalence of other chronic diseases such as obesity, diabetes, and cardiovascular disease in FN and the role that adipokines play in chronic inflammation, we studied the serum< span class="Apple-style-span"> concentrations of four adipokines (adiponectin, leptin, resistin, and retinol binding protein 4 [RBP4]) in RA patients, their FDR, and FN controls with no family history of autoimmunity. < /span>

Methods:
Using commerically available ELISA for adiponectin, leptin, RBP4, and resistin, MCP-1, and hsCRP, we tested banked sera from four cohorts: RA (n=104), FDR (n=273), FN controls (FNC, n=200), and Caucasian controls (CC, n=150). Body mass index data were available for most of the FDR. SPSS 19 was used for analysis.

Results:
Serum adiponectin levels were highest in FDR (FDR=9.1 vs RA=8.0 p=0.108, FNC=7.6 p=0.002, CC=6.1ug/ml p< 0.000). In contrast, leptin levels were highest in RA (RA=9.8 vs FDR=6.8, NAN=6.7, CC=6.1pg/mL, p< 0.000), as were resistin (RA=66.5 vs FDR=58.5, FNC=56.0, CC=55.6ng/mL, p< 0.000) and RBP4 (RA=10.9 vs. FDR=10.0, FNC=10.0ng/mL, p=0.443). MCP-1 levels were comparable in RA vs. FDR (594 vs. 536pg/mL, p=0.256), and both were dramatically higher than levels in controls (FNC=219, CC=190, p< 0.000). Similarly, hsCRP levels were highest in RA (9.1mcg/mL) but levels in FDR were higher than control groups (FDR=4.9 vs. FNC=1.6, CC=2.2 p< 0.000). Adiponectin levels correlated positively with MCP-1 (r=0.113 p=0.003) and inversely with leptin (r=-0.112 p=0.005). There was a strong correlation between the proinflammatory adipokines leptin, resistin and hsCRP, MCP-1 (leptin vs. resistin r=0.316, hsCRP r=0.266, hsCRP r=0.227; resistin vs. hsCRP r=0.227, MCP r=0.137; hsCRP vs MCP1 r=0.340; p< 0.000). In FDR, BMI correlated with adiponectin, leptin and hsCRP (r=-0.209,0.566,0.293, p< 0.001).

Conclusion:
We demonstrate that FDR of RA patients exhibit a proinflammatory cytokine and adipokine

profile, although the high levels of the anti-inflammatory adipokine, adiponectin, are unexplained. The levels of the proinflammatory adipokines leptin, resistin, the cytokine MCP-1, and hsCRP were all associated with high BMI in the FDR. We hypothesize that this proinflammatory phenotype predisposes these individuals not only to RA, but to a spectrum of other chronic inflammatory diseases, particularly accelerated atherosclerosis and cardiovascular disease.

4

An Evaluation of Comorbidity Indices Derived from Administrative Health Data: a Systematic Review

Marko Yurkovich (Arthritis Research Centre, University of British Columbia, Vancouver); Juan Antonio Avina-Zubieta (Arthritis Research Centre, University of British Columbia, Vancouver); Jamie Thomas (Arthritis Research Centre, Centre for Health Evaluation and Outcome Sciences, Vancouver); Diane Lacaille (Arthritis Research Centre, University of British Columbia, Vancouver)

Objective:
To conduct a systematic review of studies reporting on the development or validation of comorbidity indices using administrative health data, and to compare the validity of the indices.

Methods:
A comprehensive literature search of Medline and EMBASE, until June 2011, was conducted in a two-step process. We identified: (1) all comorbidity indices used in administrative data studies, and (2) all validation studies of these indices. From a title and abstract screen, relevant articles were selected for review by two independent investigators; discrepancies were resolved by consensus. Inclusion criteria included: English, full-length articles, of studies which developed, adapted, validated or compared the validity of comorbidity indices derived from administrative health data. A standardized data abstraction form was used. Predictive validity and model fit were measured by the c-statistic for dichotomous outcomes, and R2 for continuous outcomes.

Results:
A total of 81 articles were included in the final review. Two categories of comorbidity indices were identified: 1) those identifying co-morbidities based on diagnoses, using ICD codes from hospitalization or out-patient data and 2) those based on medications, using pharmacy claims data. Articles included 40 diagnosis-based studies, 36 related to the Charlson Comorbidity Index (CCI) and its adaptations, 2 to the Elixhauser Index (EI), and 2 to study-specific indices. An additional 14 studies investigated medication-based indices, such as the Chronic Disease Score (CDS) and the RxRisk-V. The remaining 27 articles compared predictive ability or validity across the above-mentioned indices. The predictive ability of the indices studied ranged from poor (c-stat< 0.7) to excellent (c-stat>0.8) depending on the specific index, outcome measured, and study population. Diagnosis-based measures typically resulted in higher predictive ability for short- and long-term mortality outcomes, whereas medication-based indices demonstrated better performance for predicting healthcare utilization or cost. The Deyo and Romano adaptations of the CCI were the most commonly used diagnosis-based indices. In 3 studies directly comparing the Deyo and Romano adaptations, the Romano-CCI consistently demonstrated superior ability to predict mortality outcomes. A total of 11 studies demonstrated superior performance of the EI compared to CCI adaptations in predicting mortality outcomes. Of the Medication-based indices, the RxRisk-V demonstrated superior performance over the CDS.

Conclusion:
A number of comorbidity indices derived from administrative data are available. Some demonstrate excellent predictive ability. Selection of an appropriate comorbidity index should consider predictive ability, as well as the type of data available and the outcome of comorbidity one wishes to capture.

5

Frequency and Characteristics of Prolonged Remission in Systemic Lupus Erythematosus (SLE)

Anjali Papneja (University of Toronto, Toronto); Amanda Steiman (University of Toronto, Toronto); Murray Urowitz (University of Toronto, Toronto); Dominique Ibanez (University of Toronto, Toronto); Dafna Gladman (University of Toronto, Toronto)

Objective:
SLE is a chronic autoimmune disorder, characterized by a relapsing/remitting course. A small subset of patients experiences prolonged clinical remission, and represents an important group that may provide further insight into SLE pathophysiology. The aim of the study was to characterize the clinical course of SLE patients who achieve prolonged remission.

Methods:
Patients followed regularly in the Lupus Clinic between July 1970 and May 2011 were studied. Prolonged remission was defined as SLEDAI-2K =0 (serologically quiescent clinically quiescent (SQCQ)), or =2 or 4 on the basis of active serology only (serologically active clinically quiescent (SACQ)) for at least five consecutive years, with visits ≤ 18 months apart; patients could be taking antimalarials, but not corticosteroids or immunosuppressives. Each patient's pre-remission clinical course was classified as monophasic (single flare followed by remission), relapsing/remitting (≥2 fluctuations in SLEDAI-2K of ≥4 on the basis of clinical activity, with an intervening period of clinical remission (SLEDAI-2K clinical activity=0), or chronic active (persistent clinical activity with SLEDAI fluctuating by ≤3 at each visit). Patients were then matched 1:3 to SLE controls on the basis of sex, age, decade of entry to study, and disease duration at 1st clinic visit, and compared clinically. Descriptive statistics were used. Comparisons were made using t- and McNemar's tests.

Results:
38 of 1613 (2.4%) patients achieved prolonged remission, with one experiencing two discrete remissions. Thus, 39 periods were studied. 32 (84.2%) patients were female. Mean clinic follow up was 21.8±10.3 years, and the average time to remission from clinic entry was 9.2±8.8 years. Mean remission duration was 11.6±6.4 years. 17 remission periods were SQCQ, 11 were SACQ and 11 were mixed SQCQ/SACQ. When subdivided by type, mean remission duration was 9.8±5.7, 9.7±3.5 and 16.5±6.4 years for SQCQ, SACQ and mixed remissions, respectively. Prior to remission, 27 (71.0%) patients had relapsing/remitting disease, 11 (28.9%) had monophasic illness; none was chronically active. Remission patients differed significantly from SLE controls in terms of ethnicity, disease severity and organ manifestations prior to remission onset and used significantly less corticosteroid and immunosuppressive drugs.

Conclusion:
Prolonged remission is an infrequent outcome among SLE patients, lasts approximately a

decade, and is preceded by an atypically monophasic course in a significant minority. Remission patients had milder disease and used less corticosteroid and immunosuppressive medication prior to remission compared to controls. These disease patterns may reflect unique pathophysiologic mechanisms, and warrant further investigation.

6

Homology-mediated CNVs Arising from Segmental Duplications in Autoimmune Rheumatic Diseases

Mohammed Uddin (Memorial Univesity of Newfoundland, St. John's); Darren O'Rielly (Memorial Univesity of Newfoundland, St. John's); Mitch Sturge (Memorial University of Newfoundland, St. John's); Proton Rahman (Memorial University of Newfoundland, St. Johns)

Objective:
Recent studies have demonstrated that copy number variations (CNVs) are an important source of genetic variability among patients with rheumatic disease. Our objective was to elucidate the mechanism that mediates the formation of CNVs derived from segmental duplications (SDs) in rheumatoid arthritis (RA) and psoriasis/psoriatic arthritis (PsV/PsA).

Methods:
A hierarchical method was employed to fragment SDs into multiple smaller SD units. Combining an end space free pairwise alignment algorithm with a 'seed and extend' approach, an exhaustive search of 409 million alignments was performed to detect complex structural rearrangements within the reference-guided assembly of the NA18507 human genome (18x coverage). We have interrogated every SD unit >100 bp to infer the complexity of duplication blocks within in human genome. Fluorescence in situ hybridization (FISH) was performed to validate the in silico predictions of genomic rearrangements with highly homologous derivatives.

Results:
We have identified 1,963 rearrangement hotspots within the duplicated regions which overlap 166 genes. Among these hotspots, we have identified non-allelic homologous recombination (NAHR) regions that are associated with autoimmune/rheumatic disease. Further analysis of these regions have revealed: 1) five breakpoints within the human chemokine ligand (CCL) gene cluster; a gene which is associated with RA; 2) extreme rearrangement within SD blocks in close proximity to the VPEB1 gene; a gene which is associated with RA; 3) four SD breakpoints with complex intra- and inter-chromosomal rearrangements in the beta-defensin gene cluster; a gene which is associated with PsV/PsA. We have also demonstrated that different breakpoints within the same gene are responsible for mediating CNV formation for different autoimmune diseases.

Conclusion:
Our study suggests that critical regions which are prone to rearrangement are important targets for the identification of CNVs associated with autoimmune/rheumatic disease. These CNV's likely account for a significant proportion of the missing heritability in autoimmune/rheumatic disease.

7

Is Enthesitis in Psoriasis a Predictor for the Development of Psoriatic Arthritis in Psoriasis?

Jai Jayakar (Toronto Western Hospital, Toronto); Lihi Eder (Toronto Western Hospital, Toronto); Arane Thavaneswaran (Toronto Western Hospital, Toronto); Sutha Shanmugarajah (Toronto Western Hospital, Toronto); Gideon Kalman-Lamb (Toronto Western Hospital, Toronto); Daniel Pereira (Toronto Western Hospital, Toronto); Dafna Gladman (Toronto Western Hospital, Toronto)

Objective:
Psoriasis (PsC) is an immune mediated skin disease affecting 2-3% of the population, and Psoriatic arthritis (PsA) is an inflammatory arthritis that affects 30% of people with PsC. One of the hallmark features of PsA is enthesitis, inflammation at the sites where tendons attach to bone. It has been suggested that subclinical enthesitis, as identified by ultrasound, commonly occurs in PsC patients and may precede the development of PsA. However, ultrasonographic entheseal abnormalities also occur in the general population, being associated with age, injuries and obesity. Our objectives in this study were twofold: 1. To assess the prevalence of ultrasonographic entheseal abnormalities in patients with PsA, PsC, and healthy controls. 2. To correlate the presence and site of ultrasonographic entheseal abnormalities with age, gender, obesity and occupation in the three groups.

Methods:
In this cross-sectional study, PsA patients were studied during their visits to the Toronto PsA clinic, PsC patients were recruited from the University of Toronto Psoriasis cohort, and controls were healthy volunteers. All participants were clinically evaluated for enthesitis bilaterally at calcaneus, knee, and olecranon sites, and underwent ultrasonographic evaluation of these sites. Ultrasound recorded the presence of enthesophytes, bony erosions, tendon thickness, bursitis, calcifications, and doppler signal within the tendon. These abnormalities were then scored using two validated ultrasonographic enthesitis indices, the GUESS and MASEI. Univariate analyses included ANOVA for continuous variables and chi-squared tests for dichotomous variables. Multivariate analyses were performed using stepwise logistic regression models.

Results:
We assessed 60 controls, 79 PsC, and 59 PsA patients in total. Demographically, the PsA and PsC groups were older, obese, and had more males than the control group. Univariate analyses revealed that the number of sites with ultrasonographic entheseal abnormalities, GUESS scores, and MASEI scores were significantly higher in the PsA group than the PsC group, with controls having the lowest scores ($p < 0.001$). Multivariate analyses revealed the same relationship (PsA>PsC>controls) for these three variables in study groups under age 50 ($p < 0.05$).

Conclusion:
Our results show that the prevalence of ultrasonographic entheseal abnormalities and indices of

ultrasonographic enthesitis burden are significantly higher in PsA patients compared to PsC patients, with both these groups being higher than controls. Furthermore, our results suggest that age may modulate the effect of disease status on enthesitis. These findings strengthen the plausibility of enthesitis being a predictor for the development of PsA in PsC, warranting future cohort studies to investigate this in depth.

8

CCN2 is Required for the Fibrosis Observed in Two Models of Systemic Sclerosis

Andrew Leask (University of Western Ontario, London); Shangxi Liu (University of Western Ontario, London)

Objective:
CCN2 (CTGF) is overexpressed in scleroderma (systemic sclerosis, SSc) fibroblasts and may represent a good target for anti-fibrotic drug intervention in this disease. However, this hypothesis has yet to be thoroughly investigated. Our aim was to assess whether CCN2 was essential for fibrogenesis.

Methods:
We used two models of skin fibrosis. In one, we used the bleomycin-induced model of skin scleroderma. In the other, we used the PTEN-deficient model of skin and lung scleroderma, which we recently developed. We used mice deleted specifically for CCN2 in fibroblasts to assess if loss of CCN2 resulted in resistance to fibrosis that developed in response to bleomycin or in response to loss of PTEN expression. Fibrosis was ascertained by histological measurement of skin thickness, collagen protein expression, myofibroblast formation (using an anti-a-SMA antibody), pericyte recruitment (using an anti-NG2 antibody) and proliferation (using an anti-PCNA antibody).

Results:
Loss of CCN2 expression resulted in resistance to both models of fibrosis, as visualized by skin thickness, collagen production, myofibroblast and pericyte recruitment ($N=6$, $p< 0.05$). All myofibroblasts that appeared in response to the fibrotic stimulus were NG2-positive, indicating a pericyte origin($N=6$, $p< 0.05$). However, proliferation was not affected by loss of CCN2 ($N=6$, $p< 0.05$).

Conclusion:
CCN2 is required for fibrosis in two models of scleroderma, but not for cell proliferation. CCN2 may represent a good target for ant-fibrotic drug intervention in SSc.

9

Serum 25 OH Vitamin D Levels are Low in Early Inflammatory Arthritis but do not Correlate with Immune Responses to Pathogens nor Clinical Activity or Outcome

Carol Hitchon (University of Manitoba, Winnipeg); Neeloffer Mookerjee (University of Manitoba, Winnipeg); Marianna Newkirk (McGill University, Montreal); Christine Peschken (University of Manitoba, Winnipeg); Hani El-Gabalawy (University of Manitoba, Winnipeg)

Objective:
Gene-environment interactions, (shared epitope, smoking, infection), have been implicated in Rheumatoid Arthritis pathogenesis. Vitamin D has immunoregulatory function of relevance to autoimmunity and host response to infection. Low 25 OH vitamin D (VitD) levels are associated with inflammatory arthritis and altered responses to pathogens. We determined the prevalence of VitD deficiency in a cohort of early inflammatory arthritis (EIA), its contribution to disease severity and outcome, and the association of vitamin D deficiency with altered immune responses to common pathogens and shared epitope alleles in EIA.

Methods:
Early inflammatory arthritis (< 12 months symptoms, 1+ active joint) subjects were followed for one year and clinical outcomes (remission, EULAR treatment response) determined. Treatment was at the discretion of the attending rheumatologist. Shared epitope was determined by DNA sequencing. 25 OH vitamin D (VitD) levels were measured in baseline serum by ELISA and categorized as deficient (< 25 nmol/L), insufficient (25- < 75 nmol/L), optimal (75-250 nmol/L) or toxic (>250 nmol/L). Antibody titers (IgG, IgA and IgM) to Proteus mirabilis and E coli were measured by ELISA. Smoking was by self report and confirmed with serum cotinine levels. Statistical significance was considered as $p< 0.05$ using non-parametric Mann Whitney U and Chi2 tests and multivariate regression models.

Results:
At baseline, 77% of EIA had insufficient (61%) or deficient (16%) levels of vitD. Baseline VitD levels were lower in North American Natives compared to Caucasian even after correcting for season of first visit (49 (32) vs 59 (30) nmol/L p=0.008). No associations with gender, serology (RF and/or ACPA), shared epitope, baseline disease activity (DAS28(3variable)CRP, individual components, or ESR) or smoking status were seen. Baseline vitD levels were not associated with clinical outcomes of remission or treatment response in univariate or multivariate models. Repeated VitD levels were available at 6 months (n= 50)and 12 months (n=164) on selected subjects without adjustment of vitD supplementation. At one year, the majority had vitD levels similar to their baseline vitD category, 33 (20%) improved and 28 (12%) worsened. No significant seasonal variability was seen. Change in VitD correlated with DAS28(3variable CRP) at one year (r= -0.215 p=0.01) but not with change in DAS28(3variable CRP) p=NS). Serum VitD correlated with cotinine levels ($p< 0.05$) but not with antibody titers to pathogens.

Conclusion:
The prevalence of VitD deficiency is high in this Canadian cohort of EIA. However, serum levels do not correlate with disease activity or outcome or antibody titers to pathogens. VitD may be more important in predisposing individuals to future inflammatory arthritis.

10

Rheumatoid Arthritis Patients Have Anti-Homocitrullinated Fibrinogen Antibodies

Lillian Barra (St. Joseph's Health Care, London, London); Mathias Scinocca (The University of Western Ontario, London); David Bell (University of Western Ontario, London); Janet Pope (University of Western Ontario, London); Ewa Cairns (The University of Western Ontario, London)

Objective:
Homocitrulline is generated by the chemical modification of lysine and is structurally similar to citrulline; the latter has been detected in the joints of RA patients using antibodies to modified citrulline (AMC). A recent study indicates that AMC cannot distinguish citrulline from homocitrulline. Antibodies to citrullinated peptides (ACPA), including citrullinated fibrinogen, are thought to be specific to RA and strongly linked to the Shared Epitope (SE), the major genetic risk factor for this disease. However, it is unclear whether RA patients also have antibodies to homocitrullinated peptides. Our specific objective was to determine the presence of anti-homocitrullinated fibrinogen antibodies (AHFA) in the sera of patients with RA and other rheumatic conditions and whether homocitrullinated peptides of fibrinogen are predicted to bind to the SE.

Methods:
A commercial preparation of human fibrinogen (CalBiochemTM) was homocitrullinated via a reaction with potassium isocyanate and confirmed by mass spectrometry. It was used in ELISA to detect AHFA and anti-citrullinated fibrinogen antibodies (ACFA) from patient serum (RA, Systemic Lupus Erythematosus (SLE) and Psoriatic Arthritis (PsA) meeting ACR criteria). The cutoff value for positive samples was determined using the average reactivity of normal patients + 2 SD (n=27). All RA patients were anti-CCP2 positive.

Results:
85/103 lysines showed evidence of homocitrullination present in all three chains of fibrinogen, comprising 34 peptides predicted to bind to the SE using a modified algorithm by Hammer et al. Of these 34 peptides, 5 homocitrullinated peptides were previously shown to be capable of being citrullinated. Using this in vitro homocitrullinated fibrinogen as antigen, 41/84 RA patients tested positive for AHFA and the average reactivity among these positive individuals was 18.7 +/- 40.3 RU/mL. No normal subjects tested positive for AHFA and only 1/37 psoriatic arthritis patients and 2/37 systemic lupus erythomatosus patients tested positive for AHFA (mean reactivities among positive patients were 7.2 and 3.7 +/- 0.2 RU/mL, respectively); $p < 0.0001$ for RA compared to others. 53/74 RA patients were positive for anti-citrullinated fibrinogen antibodies (ACFA) and of these 35/53 were also AHFA positive. Four ACFA negative patients tested positive for AHFA.

Conclusion:

Fibrinogen can be extensively homocitrullinated and citrullinated. Both citrullinated and homocitrullinated fibrinogen appear to be autoantigens specific to RA.

11

Reduced Resource Use and Increased Engagement in Activities of Daily Living and Employment in Patients Attaining Remission in the First Year of Biologic Therapy

Cheryl Barnabe (University of Calgary, Calgary); Anthony Russell (University of Alberta Hospital, Edmonton); Susan Barr (University of Calgary, Calgary); Joanne Homik (University of Alberta, Edmonton); Liam Martin (University of Calgary, Calgary); Walter Maksymowych (University of Alberta, Edmonton)

Objective:
To compare resource use, engagement in activities of daily living, and employment status by treatment response to biologic therapy in rheumatoid arthritis.

Methods:
In addition to the prospective collection of clinical efficacy and safety data in an inception cohort of biologic treated patients with rheumatoid arthritis, we collect data on self-reported resource use (hospital services, community services, out-of-pocket costs), activities of daily living, and changes in employment status. We compared differences in resource use reported in the first year of treatment between patients achieving any definition of remission (2011 ACR/EULAR Boolean definition, SDAI $\leq$3.3, CDAI $\leq$ 2.8, 1981 ACR Remission Definition or DAS28 $\leq$2.6), minimal disease activity (0 tender or swollen joints and ESR < 10 mm/hr, DAS28 < 2.85, ACR core set definition, SDAI < 11 or CDAI < 10) and those not achieving remission.

Results:
A total of 1,777 patients (70% female, disease duration 12 years, median DMARD exposure 3) initiated a new biologic therapy between July 2000 and March 2010. Baseline disease activity scores were: HAQ 1.15 (SD 0.76), DAS28 4.36 (SD 1.90), tender joint count 7.1 (SD 8.2), swollen joint count 4.7 (SD 5.5), patient global 4.6 (SD 2.8), and mean morning stiffness duration 70 minutes (SD 143.3). Over the first year of biologic therapy, 556 individuals met remission criteria (31.3%), and an additional 393 met minimal disease activity criteria (22.1%), with the remainder (n=828) remaining in moderate or high disease activity. Patients attaining remission (relative to those in moderate or high disease activity) had decreased hospitalizations (5.2% vs 7.1%, p=0.0329), fewer over-the-counter drug purchases for arthritis symptoms (32.5% vs 40.0%, p< 0.001), fewer days lost due to arthritis symptoms (2.5 (SD 6.5) vs 3.1 (SD 7.1), p=0.007), fewer required help from others for activities of daily living (26.8% vs 36.7%, p< 0.001), and fewer reduced their working hours (11.6% vs 16.6%, p=0.011). Patients only achieving minimal disease activity had similar resource use, impairments in activities of daily living and employment status compared to patients in moderate or high disease activity.

Conclusion:
Achieving remission, relative to minimal, moderate or high disease activity, results in significantly less resource use, increased independence to complete activities of daily living, and

remain in usual work activities in the first year of biologic treatment.

12

Barriers to Paediatric Rheumatology Subspecialty Care in British Columbia

Natalie Shiff (University of Saskatchewan, Saskatoon); Jaime Guzman (BC's Children Hospital, Vancouver); Victor Espinosa (Child and Family Research Institute, Vancouver); America Uribe (University of British Columbia, Vancouver); Janusz Kaczorowski (University of Montreal, Montreal); Lori Tucker (BC's Children Hospital, Vancouver)

Objective:
We conducted a survey of family physicians to assess perceived barriers to paediatric rheumatology subspecialty services.

Methods:
We surveyed a stratified random sample of family physicians from all 5 geographic Health Regions in British Columbia. We followed Dillman's modified tailored design method using paper (mail and fax) and web-based questionnaires that included personalized letters, incentives, and reminders to maximize response rates.

Results:
428 out of 2286 eligible participants responded (19%); 31% practiced within 50 km of BC Children's Hospital where most paediatric rheumatologist services are provided, while 39% practiced ≥300 km from this centre. 59% of respondents had had a paediatric patient with a rheumatic disease in their practice, yet only 40% of all respondents had ever referred to a paediatric rheumatologist. Practitioners consulted instead of referring to a paediatric rheumatologist included adult rheumatology (11% of respondents), adult orthopaedic surgeon (9%), paediatric orthopaedic surgeon (7%), paediatrician (49%), other specialist (2%), chiropractor (1%), physiotherapist (5%). Approximately 60% of respondents indicated that wait time, distance, ease of transportation, and cost of travel would affect their likelihood to refer to paediatric rheumatology. The local availability of related services was also a factor; for example 38% of respondents reported that the availability of a local adult rheumatologist would affect their likelihood of referring to paediatric rheumatology. Other local resources reported to have this effect included: local paediatric orthopaedic surgeon (31% of respondents), local paediatrician (75%), local chiropractor (11%), and local physiotherapist (18%). Although 66% of respondents reported routinely performing a screening paediatric musculoskeletal exam and 74% stated they were at least somewhat comfortable doing this, 90% could not name a screening tool for this exam and only 1% identified the Paediatric Gait Arms Legs Spine (pGALS) as an appropriate tool for this purpose.

Conclusion:
Despite the high percentage of respondents who have followed a paediatric patient with a rheumatic disease in their practice, less than half had ever referred to a paediatric rheumatologist in BC. While initial referral to a paediatrician may be appropriate in many cases, referral to other

practitioners instead of a paediatric rheumatologist was common practice. Limited access to paediatric rheumatology services and local availability of alternative practitioners were cited as the main factors. Most respondents were unaware of the availability of simple validated paediatric screening musculoskeletal examination tools.

13

Patient Reported Co-Morbidities Predict Risk of Infection in an Inception Cohort of Rheumatoid Arthritis Patients Receiving Anti-Tumor Necrosis Factor Therapy

Joanne Homik (University of Alberta, EDMONTON); Nguyen Thanh (Institute for Health Economics, Edmonton); Arto Ohinmaa (Institute of Health Economics, Edmonton); Cheryl Barnabe (University of Calgary, Calgary); Liam Martin (University of Calgary, Calgary); Susan Barr (University of Calgary, Calgary); Walter Maksymowych (University of Alberta, Edmonton)

Objective:
Objectives: To evaluate the frequency of serious infections in Rheumatoid Arthritis (RA) patients treated with anti-Tumor Necrosis Factor (anti-TNF) therapy.

Methods:
Methods: RA patients treated with anti-TNF therapy between January 2004 and March 2009 were followed prospectively in our biologics program to assess treatment efficacy and adverse events. Clinical and self-reported data were linked with provincial health care administrative databases. Infections were identified by using ICD 9 and 10 diagnosis codes and categorized as serious if there was an associated hospitalization. We used multivariate Cox-regression to assess independent predictors of the risk of infection.

Results:
Results: The cohort consists of 1,086 patients (70% female, mean age of 54 years) with a mean follow-up time of 2.3 years. Seventy percent of patients (n=764) reported an infection during follow-up, while 4% (n=42) suffered a serious infection, for an incidence density rate of 1.67 per 100 patient years of follow up. The most common infections were bronchitis, cellulitis, sinusitis, cystitis and upper respiratory infections. Compared to patients who remained on their first anti-TNF agent (n=731), patients who switched to another anti-TNF (n=212), patients on DMARD alone (n=75), and patients switched from DMARD to anti-TNF therapy (n=68) had similar Hazard Ratios (HR) ($p>0.05$) for both any and serious infections. In the cohort of patients on their first anti-TNF agent, the specific drug did not predict risk of infection. Pre-existing lung disease (HR=1.99, p=0.001), underlying anemia (HR=3.31, p=0.030) and diabetes (HR=1.57, p=0.034) were associated with increased infection risk, while male sex was protective (HR 0.81, p=0.039). There was a trend for greater risk of infection in those patients with a higher baseline DAS score (HR=3.89, p=0.072.

Conclusion:
Conclusion: Certain self reported co-morbidities, such as lung disease, diabetes, and underlying anemia significantly increased the risk of infection. The incidence density rate of serious infections was low (1.67 serious infections per 100 patient years), especially in patients who

remained on their first anti-TNF agent (1.35 per 100 patient years) and is lower than reported in other cohorts. The risk of any or serious infection did not differ significantly between specific anti-TNF agents.