POD01: Susan Bartlett

Specific Symptom Clusters at Diagnosis Signal a Poorer Early Ra Prognosis on Mtx Treatment: Results from The Canadian Early Arthritis Cohort (Catch)

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Objectives: Symptom clusters are stable groups of symptoms that frequently co-occur. Identifying symptom clusters in early RA may point to underlying mechanisms, RA subtypes, disease trajectories, and help personalize management. We identified symptom clusters at diagnosis in MTX-naïve patients starting MTX therapy and evaluated cluster stability and likelihood of transitioning over the first 6 months.

Methods: Data were from new RA patients in the CATCH starting MTX who had clinical and PROM measures available. We used latent class analyses to identify clusters from PROMIS-29 physical (pain, fatigue, sleep) and emotional (depression, anxiety) scales (levels: minimal, mild, moderate, severe). We compared models using AIC, BIC, G-square and log-likelihoods and estimated likelihood of transitioning between clusters at 3- and 6-months using latent transition analyses.

Results: Of 310 adults, 67% were women and 78% were White with a mean age of 56 yrs, CDAI 29.3, and symptom duration of 5 months. Optimal clusters included pain, fatigue, anxiety and depression at three intensity levels. We identified 4 clusters at diagnosis: MINIMAL (12%); Moderate-Severe Physical (M-S P: 40%); Mild Physical+Emotional (MILD P+E: 11%); Moderate-Severe Physical+Emotional (M-S P+E 37%). Clusters had similar sociodemographics except the MINIMAL class were slightly older and fewer were women; M-S P+E had a greater likelihood of depression history. SJC and TJC were similar among classes; worse symptoms were associated with a higher CDAI. Classes with emotional symptoms had significantly worse mood and sleep, and the M-S P class were more likely to report a history of depression. More patients with moderate-severe symptoms were on parenteral steroids. Most transitions occurred by 3 months. The best prognosis was for the MINIMAL class; 95% were MINIMAL at 3 and 6 months. Among those with MILD P+E, most were the same at 3 (82%) and 6 (96%) months. Participants with M-S P at diagnosis were also likely to transition to MINIMAL (64%) or MILD P+E (7%). The worst prognosis was for M-S P+E; at 3 months, 13% were MINIMAL or MILD P+E (33%). Overall, patients with emotional symptoms were least likely to transition to milder symptoms.

Conclusion: Using novel strategies, we identified 4 early RA symptom classes with varying intensities of physical and emotional symptoms and evaluated transitions over 6-months of MTX treatment. At diagnosis, most had moderate-severe Physical+/-Emotional symptoms. Patients

with emotional symptoms at diagnosis were less likely to transition to better controlled symptom classes. Emotional symptoms at diagnosis may reflect important subsets and signal a poorer prognosis.

POD02: Derin Karacabeyli
Incidence of Autoimmune Rheumatic Diseases Following Exposure to Dipeptidyl Peptidase-4 Inhibitors, Glucagon-Like Peptide-1 Receptor Agonists, or Sodium-Glucose Cotransporter-2 Inhibitors: a Population-Based Study

Derin Karacabeyli (University of British Columbia, Vancouver); Diane Lacaille (Arthritis Research Canada, University of British Columbia, Vancouver); Na Lu (Arthritis Research Canada, Vancouver); Antonio Avina-Zubieta (University of British Columbia Faculty of Medicine; Arthritis Research Canada, Vancouver)

Objectives: Population-based studies suggest no increased incidence of autoimmune rheumatic diseases (ARDs) following dipeptidyl peptidase-4 inhibitor (DPP4i) exposure[1]. Glucagon-like peptide-1 receptor agonists (GLP-1-RAs) and sodium-glucose cotransporter-2 inhibitors (SGLT2is) are alternate second-line anti-diabetic drugs with differing immunomodulatory properties, but their effect on ARD incidence has been understudied. Case reports of incident rheumatoid arthritis following GLP-1-RA use and one population-based study on psoriasis incidence following SGLT2i exposure suggested increased risk[2,3]. We therefore compared the incidence of ARDs following exposure to DPP4is, GLP-1-RAs, or SGLT2is in patients with type 2 diabetes.

Methods: We performed a population-based cohort study using administrative health data from British Columbia. Data included diagnostic codes from physician visits and hospitalizations in a universal healthcare system, all pharmacy-dispensed medications, and vital statistics from January 1, 2014 to December 31, 2021. All patients with type 2 diabetes (based on ICD-9/10 codes) who newly initiated a DPP4i, GLP-1-RA, or SGLT2i (index date) were identified, forming three new user cohorts. New users were defined as not having received any of these agents for >180 days prior to the index date. Patients were followed for the duration that they had a filled prescription for one of these medications. The primary outcome was incidence of new ARDs (a composite of rheumatoid arthritis, psoriatic disease, ankylosing spondylitis, and systemic autoimmune rheumatic diseases i.e., connective tissue diseases and systemic vasculitides), defined by ICD-9/10 codes. Matching weights were applied to the three cohorts to achieve balance between covariates. For each comparison, weighted Cox proportional hazards models were used to estimate hazard ratios (HRs) and 95% confidence intervals (CIs).

Results: We enrolled 186,391 patients (68,399, 34,409, and 83,583 who initiated a DPP4i, GLP-1-RA, or SGLT2i, respectively), with mean follow up of 0.88-1.53 years. Before matching weights, incidence rates (IRs) per 1000 person-years (95% CI) did not differ significantly between groups [2.77 (2.46-3.11) with DPP4i exposure, 2.72 (2.16-3.37) with GLP-1-RA exposure, and 2.46 (2.17-2.77) with SGLT2i exposure]. There were also no significant differences after matching weights [IRs of 2.96, 2.72, and 2.86 for DPP4i-, GLP-1-RA-, and SGLT2i-exposed groups, respectively]. Compared to the DPP4i-exposed cohort, HRs for developing an ARD were 0.93 (0.66-1.30) and 0.97 (0.76-1.24) with GLP-1-RA and SGLT2i exposure, respectively.

Conclusion: Among patients with type 2 diabetes, there was no difference in the risk of developing an ARD if prescribed a DPP4i, GLP-1-RA, or SGLT2i. Extended longitudinal data are needed to assess risk and benefit with longer term exposure.

POD03: Liam O'Neil
Health Care Access in an Indigenous North American Population of Rheumatoid Arthritis Patients and Their At-Risk First-Degree Relatives

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Objectives: Rheumatoid Arthritis (RA) is a chronic autoimmune disease that requires access to subspecialty care. Although Canada has a universal healthcare system, there are complex and interrelated factors that lead to inequitable healthcare access and delivery. These factors are particularly relevant to Canada's geographically dispersed First Nations People (FN), who bear a disproportionate burden of RA and its complications. In the context of a longitudinal study of RA onset in a FN population, we sought to identify factors that influence access to healthcare in a cohort of FN RA patients and their First-Degree Relatives (FDR).

Methods: A longitudinal cohort of FN RA patients (n=214) and their FDR (n=617) was recruited between 2005 and 2017 to participate in a prospective study of RA risk in the FDR (total n=831). Study participants were recruited in both urban and rural locations in Manitoba, Canada. The study enrollment visit included a healthcare access survey which measured access on a Likert scale, which was converted to a binary variable to determine overall access difficulty.

Results: Overall, RA and FDR participants living in rural communities reported more difficulties with healthcare access compared to urban dwellers (p<0.0001), and rural RA patients reported more access difficulty than unaffected rural FDR (p=0.002). In contrast, there were no differences reported between RA patients and FDR living in urban locations. In the entire RA cohort, no differences in access were reported based on disease duration, age, or sex, although those with higher mHAQ scores tended to report worse access. A logistic regression model suggested that variables which independently associated with healthcare access difficulty were female sex (Figure1A, OR:1.47, 1.07-2.01), older age (OR:1.51, 1.12-2.04) and living in a rural community (OR 1.99, 1.45-2.71). The model suggested that females living in rural locations, irrespective of an RA diagnosis, were particularly disadvantaged for healthcare access, but also that males with an RA diagnosis experienced substantially more access difficulty compared to FDR males (Figure1B).

Conclusion: Perceived difficulties in accessing healthcare were more frequent in FN RA patients as well as their unaffected at-risk FDR who were living in rural locations compared to those living in urban locations. Importantly, we identified sex-based differences in perceived healthcare access that were compelling and were further compounded by the geographic factors. In order to achieve equitable healthcare delivery, interventions to address geographic factors, such as transportation and availability of healthcare providers, need to also incorporate complex factors related to sex and gender.

POD04: Caseng Zhang
Genetics of Sex Dimorphism in Clinical Manifestations of Systemic Lupus Erythematosus

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Objectives: Systemic lupus erythematosus (SLE) is a complex chronic autoimmune disease with multi-organ involvement and a strong female predominance. Prior studies demonstrated sex dimorphism, with female SLE patients more commonly having malar rash and arthritis, and male SLE patients typically with renal disease. Genetics play a role in SLE risk, but few have identified sex chromosome loci for differences in disease manifestations. This study aimed to examine X chromosome loci for SLE sub-phenotypes in a multi-ethnic cohort of children and adults with SLE.

Methods: Our study cohort included patients with childhood-onset (cSLE) and adult-onset (aSLE) from 9 tertiary care centers in North America and Europe who met American College of Rheumatology (ACR) or Systemic Lupus International Collaborating Clinics (SLICC) SLE classification criteria, and were genotyped on a multi-ethnic array. Ungenotyped SNPs were imputed using TopMed as a referent. SNPs were linkage disequilibrium (LD) pruned using LDLink, with $R2 > 0.1$ and minor allele frequency $> 1\%$ to identify 19,607 unique loci. Principal Components (PCs) were generated to account for ancestral variation. Phenotypic variables derived from SLE classification criteria were tested for sex dimorphism in the entire cohort and age stratified groups, with significance set at $P < 0.05$. An X chromosome analysis was performed of SLE phenotypes, controlling for sex and 5 PCs (X-wide significance $P < 2.6 \times 10^{-6}$).

Results: Our study included 1553 participants and 88% were female. A total of 819 (53%) were cSLE patients with a median age at diagnosis of 14.1 years (IQR: 11.8 – 15.9), while the median age at diagnosis for aSLE patients was 31.2 years (IQR: 24.8 – 42.4). Among females there was a higher prevalence of arthritis, mucocutaneous, and hematologic features, while renal features and anti-Smith, Ro, and RNP antibodies were more prevalent among males. Chromosome X analysis revealed two SNPs significantly associated with hematologic features (P = 1.22×10^{-6}) and Ro antibody (P = 1.37×10^{-6}) [Figure 1.].

Conclusion: Our multi-ancestral study of children and adults with SLE identified X chromosome SNPs associated with sex dimorphic SLE features: hematologic abnormalities and anti-Ro antibody positivity. To investigate genetics of sexual dimorphism in SLE manifestations further, we will complete stratified analyses by aSLE and cSLE, as well as examination of potential mechanisms by which loci are influencing sex differences in disease manifestations. Validation studies are warranted to replicate our findings.

POD05: Arielle Mendel
Association of Trimethoprim Sulfamethoxazole Prophylaxis with Infections During Treatment of Granulomatosis with Polyangiitis with Rituximab: a Population-Based Study
Arielle Mendel (McGill University Health Centre, Department of Medicine, Division of Rheumatology, Montreal); Hassan Behlouli (McGill University, Montreal); Évelyne Vinet (McGill University Health Centre, Department of Medicine, Division of Rheumatology, Division of Clinical Epidemiology, Montreal); Jeffrey Curtis (University of Alabama at Birmingham, Birmingham); Sasha Bernatsky (McGill University Health Centre, Department of Medicine, Division of Rheumatology, Division of Clinical Epidemiology, Montreal)
Objectives: Infections are an important unintended consequence of ANCA-associated vasculitis (AAV) treatment. Trimethoprim sulfamethoxazole (TMP-SMX), recommended for pneumocystis jirovecii pneumonia (PJP) prophylaxis, has broad antimicrobial activity. We assessed associations between TMP-SMX prophylaxis and subsequent infections within a United States population sample of granulomatosis with polyangiitis (GPA) treated with rituximab (RTX).

Methods: We included adults with GPA (2011-2020) within the Merative™ Marketscan® Research Databases with a minimum 6 months of insurance enrollment prior to first (index) RTX. 'Baseline' TMP-SMX prophylaxis was defined as a >=28-day prescription dispensed within 30 days (before/after) RTX. We defined serious infections as an inpatient ICD-9/10 primary diagnostic code for infection (excluding viral and mycobacterial codes). Secondary outcomes were outpatient infections and PJP. Multivariable Cox proportional hazards regression assessed the association of baseline and time-dependent TMP-SMX with the outcomes of interest. Models were adjusted for age, sex, prednisone (>=20 mg/day dispensed < 30 days prior to index RTX), hospitalization and/or serious infection in the 6 months prior to index RTX, and having >=1 co-morbidity: interstitial or obstructive lung disease, diabetes, chronic kidney disease, or dialysis. Finally, we evaluated if TMP-SMX prophylaxis was associated with adverse events potentially attributable to TMP-SMX. Follow-up ended at the end of insurance enrolment or Dec 31, 2020.

Results: In the cohort of 919 patients, 53% were female, mean age was 52.1 years (SD 16), and 281 (31%) were dispensed TMP-SMX at baseline. Over a median (IQR) follow-up of 496 (138, 979) days, the rate of serious infection was 6.1 (95% confidence interval, CI 5.0-7.4) per 100 person-years. TMP-SMX use was negatively associated with serious infections, considering

baseline (adjusted HR 0.5; 95% CI 0.3-0.8) and time-varying TMP-SMX exposure (aHR 0.5; 95% CI 0.3-0.9). TMP-SMX was also negatively associated with outpatient infections (aHR 0.7; 95% CI 0.5-0.9). Thirteen PJP infections occurred, all in TMP-SMX unexposed subjects. After adjusting for age, sex, co-morbidity and prior hospitalization, time-dependent TMP-SMX use was potentially associated with adverse events (aHR 1.4; 95% CI 1.0-2.0), the majority being acute kidney injury (58%).

Conclusion: TMP-SMX prophylaxis was associated with reduced serious and outpatient infections in RTX-treated GPA. Further study is needed to determine how to weigh potential benefits and harms from prophylaxis in individual patients, and determine optimal prophylaxis duration.

POD06: Eugene Krustev

Autoantibodies Against Myxovirus Resistance Protein 1 Are Associated with Myositis and Interstitial Lung Disease in Systemic Lupus Erythematosus

Eugene Krustev (University of Calgary, Calgary); Marvin Fritzler (University of Calgary, Calgary); Sasha Bernatsky (McGill University Health Centre, Department of Medicine, Division of Rheumatology, Division of Clinical Epidemiology, Montreal); Évelyne Vinet (McGill University Health Centre, Department of Medicine, Division of Rheumatology, Division of Clinical Epidemiology, Montreal); Christian A Pineau (McGill University Health Centre, Department of Medicine, Division of Rheumatology, Montreal); Arielle Mendel (McGill University Health Centre, Department of Medicine, Division of Rheumatology, Montreal); Fares Kalache (McGill University Health Centre, Department of Medicine, Division of Rheumatology, Montreal); Louis-Pierre Grenier (McGill University Health Centre, Department of Medicine, Division of Rheumatology, Montreal); Thaisa Cotton (McGill University, Montreal); Omid Niaki (McGill University, Montreal); May Choi (University of Calgary, Calgary)

Objectives: Although inflammatory myopathy and interstitial lung disease (ILD) are uncommon in systemic lupus erythematosus (SLE), they are associated with worse outcomes. The interferon associated protein, Human Myxovirus Resistance Protein 1 (MxA), is a novel sarcoplasm-expressed biomarker in muscle biopsies from patients with dermatomyositis [1]. Autoantibodies against MxA (anti-MxA) are expressed in idiopathic interstitial pneumonia [2]. We evaluated the frequency of anti-MxA autoantibodies in SLE patients with myositis and/or ILD compared to SLE patients without these disease features.

Methods: McGill Lupus Cohort participants (N=551, 2000-2017) without a history of ILD and/or myositis (ILD/myositis) meeting the 1997 American College of Rheumatology criteria [3] were followed at annual study visits from cohort enrolment until either the date of ILD/myositis diagnosis or December 31, 2017. A case-cohort analysis was performed, comparing all patients who developed ILD/myositis on follow-up with a randomly selected sub-cohort of SLE patients (N = 72). Anti-MxA autoantibodies were tested in baseline serum samples (first visit as of Jan 2000 or enrollment visit if later than this date) using addressable laser bead immunoassay with purified recombinant human protein with results expressed as median fluorescent units (MFU).

Results: Thirteen (13/551; 2.4%) SLE patients developed ILD/myositis (ILD alone, 8/551, 1.5%; myositis alone, 3/551, 0.5%; both ILD and myositis, 2/551, 0.4%). There was no significant difference in the proportion of females (ILD/myositis 85.7% vs control 84.7%; difference in proportion [diff] 0.01, 95% confidence interval [CI] -0.25, 0.15). Among cases, there were non-significant trends for less White race/ethnicity (ILD/myositis 35.7% vs controls 47.2%; diff 0.12, 95% CI -0.16, 0.34) and lower mean age at SLE diagnosis (ILD/myositis 29.5

± 11.0 years vs controls 33.6 ± 14.2 years, absolute difference 3.8, 95% CI -4.1, 11.6). More patients who developed ILD/myositis were anti-MxA positive at baseline versus controls (46.2% vs 9.7%; crude odds ratio [OR] 8.0, 95% CI 2.1, 30.4) (Table 1). Median baseline anti-MxA titres were significantly higher in ILD/myositis versus controls (161.0 vs 82.8, p=0.0004) (Table 1). At time of ILD/myositis diagnosis, 11 of 13 patients (84.6%) were anti-MxA positive (ILD alone, 6/8, 75.0%; myositis alone, 3/3, 100.0%; both ILD and myositis, 2/2, 100.0%) (Table 1). **Conclusion:** These results suggest anti-MxA is an important biomarker for ILD/myositis in SLE. A larger study is underway to confirm these findings and examine associations with other SLE features and other outcomes.

POD07: Sibel Aydin
Associations Between Disease Activity, Physical Function and Anti-Rheumatic Medications with All-Cause Mortality in Rheumatoid Arthritis (Ra): Data from a Canadian Ra Registry
Mohammad Movahedi (University Health Network, Toronto); Angela Cesta (University Health Network, Toronto); Xiuying Li (University Health Network, Toronto); Bindee Kuriya (Sinai Health System, University of Toronto, Toronto); Sibel Aydin (Ottawa Hospital Research Institute, University of Ottawa, Ottawa); Edward Keystone (University of Toronto, Toronto); Janet Pope (Department of Medicine, University of Western Ontario, St. Joseph's Health Centre, London); Claire Bombardier (University of Toronto, Toronto); OBRI investigators (University Health Network, Toronto)
Objectives: Objectives: Patients with rheumatoid arthritis (RA) are at increased risk of hospitalizations and mortality due to RA itself, associated comorbidities, and treatment-related complications. The purpose of this real-world study was to investigate the association between RA disease activity, physical function, comorbidity, and anti-rheumatic medications and the risk of all-cause mortality.
Methods: Methods: RA patients enrolled in the Ontario Best Practices Research Initiative (OBRI) between 1st of June 2008 and 1st of Jan 2023 were included. Patients were eligible if they had clinical disease activity index (CDAI) and health assessment questionnaire disability index (HAQ-DI) scores at cohort entry and ≥ 6 months of follow-up. Patients also had to be be on at least one anti-rheumatic medication. Multiple imputation (Imputation Chained Equation, N=20) was used to deal with missing data. We conducted multivariable Cox regression analyses to estimate the hazard of death, controlling for sociodemographic, clinical, medication and comorbidity factors. All variables included in the regression models were time-dependent except BMI, Gender, Positive RF, and Education which were only measured at cohort entry.
Results: Results: A total of 3384 patients were included. 78.4% were female and mean (SD) age and disease duration were 57.9 (12.9) years and 8.2 (9.8) years, respectively. The mean (SD) CDAI was 20.2 (13.6) and HAQ-DI was 1.1 (0.8). Over a median 77.7 months follow-up, 218 deaths (6.4%) were recorded. Table 1 shows the results for multivariable analysis. Use of csDMARD (HRs: 0.17; 95%CI: 0.12-0.24), bDMARD mono (HRs: 0.25; 95%CI: 0.15-0.44), tsDMARD mono (HRs: 0.17; 95%CI: 0.04-0.70), bDMARD/csDMARD (HRs: 0.16; 95%CI: 0.10-0.25), and tsDMARD/csDMARDs (HRs: 0.20; 95%CI: 0.06-0.64) showed a significantly negative association with all-cause mortality. With respect to clinical profile, only higher HAQ-DI (HRs: 1.75; 95%CI: 1.40-2.19) and positive RF (HRs: 1.53; 95%CI: 1.05-2.21) showed a significant association with risk of death. Lung disease (HRs: 1.58; 95%CI: 1.06-2.36), cancer (HRs: 2.94; 95%CI: 1.90-4.54), current smoking (HRs: 1.95; 95%CI: 1.24-3.05), use of csDMARDs before enrolment (HRs: 1.49; 95%CI: 1.10-2.02) were also significantly associated

with risk of death.

Conclusion: Conclusions: In this real-world study, we found that higher HAQ-DI, lung disease and cancers were associated with all-cause mortality in RA but the use of csDMARD, bDMARD and tsDMARDs were negatively associated with all-cause mortality in patients with RA.

Podium Session B: Friday, March 1, 2024 at 8:00-9:15 AM CT

POD08: Kasra Moolooghy
Survival on Treatment After Transition to a Biosimilar: Population-Based Evidence from a Natural Experiment Due to a Policy Change

Diane Lacaille (Arthritis Research Canada, University of British Columbia, Vancouver); Kasra Moolooghy (Arthritis Research Canada, University of British Columbia, Vancouver); Antonio Avina-Zubieta (University of British Columbia Faculty of Medicine; Arthritis Research Canada, Vancouver); Yufei Zheng (Arthritis Research Canada, Vancouver); Na Lu (Arthritis Research Canada, Vancouver); Hui Xie (Arthritis Research Canada/Faculty of Health Sciences at Simon Fraser University, Vancouver)

Objectives: British Columbia's (BC) health policy mandated that all new biologics initiations after June 2017 use biosimilars when available, and in May-December 2019, a further policy mandated that current users of etanercept and infliximab transition to the corresponding biosimilar, providing the context for a natural experiment. Our study objective was to compare drug survival, as surrogate marker of safety and effectiveness, between biosimilar switchers versus originator anti-TNF users for inflammatory arthritis (IA), after and before the health policy change.

Methods: Study Cohort: Using administrative data, we identified etanercept and infliximab users with rheumatoid arthritis (RA), psoriasis or psoriatic arthritis (Pso/PsA), or ankylosing spondylitis and other spondyloarthritis (SpA) in BC. Biosimilar switchers were current biologic users who transitioned to the corresponding biosimilar during the period of May to December 2019. Historical controls were randomly selected from all new users of originator etanercept and infliximab before July 2017, matched to biosimilar switchers on sex, previous number of biologics used, and IA disease. Controls were assigned an index date such that duration of originator anti-tumor necrosis factor (anti-TNF) was the same at switching/index date for switchers and controls. Outcomes: Discontinuation was defined as no prescription renewal for at least 6 months. Statistical analysis: We followed patients from switching/index date for 2 years or until discontinuation, moving out-of-province, or end of follow-up (04/30/2019 for originators and 12/31/2021 for switchers), whichever occurred first. Weighted Cox proportional hazards models with propensity score overlap weighting estimated the HR of discontinuing anti-TNF agents for controls and switchers, adjusting for duration of anti-TNF use at switch/index date, age, sex, socio-economic status, rural vs. urban residence, health authority, arthritis type, number of prior biologic agents, comorbidities, and other IA drugs used (MTX, non-MTX csDMARDs and glucocorticosteroids), measured at switching/index date.

Results: Our sample includes 1631 biosimilar switchers/controls (1402 eternercept; 229 infliximab): 556(67.2%) RA, 178(21.5%) SpA, 93(11.2%) Pso/PsA patients. Discontinuations were observed in 347 originator and 354 biosimilar etanercept users; and 44 originator and 36 biosimilar infliximab users. Discontinuation rates in biosimilar and originator users (etanercept: 15.42 vs. 15.63; infliximab: 8.76 vs. 11.29 per 100PY), and adjusted risk of discontinuation [aHR(95% CI): 1.02(0.87;1.19) p=0.718 for etanercept; and 0.85(0.54;1.36) p=0.503 for

infliximab) did not differ significantly. Figure 1 shows survival on treatment.
Conclusion: Population-based data from BC on real-world experience mandating transition from originator to biosimilar etanercept and infliximab for IA revealed the biosimilar transitions have comparable duration of treatment to the original medications. Supported by a CIORA grant.

POD09: Ines Colmegna
Mesenchymal Stromal Cells in Scleroderma Have an Incomplete Myofibroblast-Like Phenotype with Preserved in Vitro Anti-Inflammatory and Anti-Fibrotic Effects

Marianela Brizio (Mc Gill University, Montreal); Maximilien Lora (Research Institute MUHC, Montreal); Christopher Moraes (Mc Gill University, Montreal); Marie Hudson (McGill University, Jewish General Hospital, Lady Davis Institute for Medical Research, Montreal); Ines Colmegna (The Research Institute of the MUHC, Montreal)

Objectives: Objectives: Mesenchymal stromal cells (MSCs) are non-hematopoietic progenitors, located in the stroma of every tissue surrounding small vessels and capillaries, that contribute to tissue homeostasis [1]. MSCs have proangiogenic, tolerogenic, and anti-fibrotic effects that mainly results from paracrine effects mediated by the secretion of several soluble factors (MSC secretome) [2]. In in vitro cultures, the secretome is assessed through the analysis of conditioned medium (CM). Systemic sclerosis (SSc), a prototypic fibrotic condition, is characterized by vasculopathy, chronic inflammation, and skin/visceral fibrosis [3]. It is unknown if MSCs and their CM are dysfunctional contributing to the progression of fibrotic diseases like SSc. Here, we compared the in vitro phenotype and function of healthy controls (HC) and SSc-MSC, and their CM.

Methods: Methods: MSCs from 10 SSc patients and 10 age/sex matched HC-MSC were isolated from the adipose tissue obtained from two 4mm punch forearm skin biopsies. At passage 3, MSCs were characterized phenotypically (i.e., plastic adherence, surface markers, tri-lineage differentiation, α-SMA and PPAR-γ expression) and functionally [i.e., proliferation, stemness - (CFU-F assay) and immunopotency (Flow cytometry)]. The antifibrotic effects of MSC-CM were tested in the following in vitro assays: prevention of fibroblast activation and myofibroblast deactivation. The readouts of these assays were Western blot for α-SMA and procollagen I. We assessed the effect of MSC-CM on fibroblast cellular contractility following 24h treatment of a 3D collagen gel containing fibroblasts with MSC-CM.

Results: Results: SSc- and HC-MSCs fulfilled the required phenotype and had similar proliferation rates. The SSc-MSC immunopotency capacity was preserved, as they were equally effective as HC-MSCs in suppressing activated T-cell proliferation. The clonogenicity capacity was reduced in the SSc-MSC. Treatment naïve SSc-MSC exhibited myofibroblast characteristics including higher expression of α-SMA and lower PPAR-γ. Despite this, the anti-fibrotic potency of SSc-MSC-CM in vitro was preserved. To the same extent as controls, SSc-MSC-CM prevented TGF-β induced fibroblast activation and deactivated myofibroblasts. Both HC- and SSc-MSC-CM promoted collagen contraction.

Conclusion: Conclusion: SSc-MSC are less clonogenic, have decreased PPAR-γ transcripts and increased α-SMA expression. These findings suggest a more differentiated profile of SSc-MSCs. Despite this, the in vitro anti-inflammatory and anti-fibrotic effects of SSc-MSC seem unaffected. Whether the preserved in vitro function of SSc-MSC-CM is a compensatory response, requires to be tested in animal models.

POD10: Megan Thomas
Equity, Diversity, and Inclusion in Canadian Rheumatology Research: a Qualitative Study Exploring Researcher Perspectives

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Objectives: Despite known variations in treatment and outcomes according to patient characteristics, identity, and geography, including underrepresented populations in arthritis research remains a challenge. We conducted interviews to explore how researchers in rheumatology have used equity, diversity, and inclusion (EDI) to inform recruitment and information collection of participants in their research.

Methods: Guided by the Campbell and Cochrane Equity Methods Group's PROGRESS-Plus framework on risk factors that lead to inequities in health (Place of residence; Race, culture, ethnicity, language; Occupation; Gender, sex; Religion; Education; Socioeconomic status; and Social capital), semi-structured interviews were conducted with individuals who 1) Have experience conducting research studies in arthritis; 2) Reside in and/or conduct their research in Canada; and 3) Speak English or French. Participants were recruited using purposive and snowball sampling. Interviews were conducted over Zoom and audio-recordings were transcribed. Template analysis was applied to explore participant experiences and perceptions of EDI in arthritis research. Cognitive interviewing was conducted to gather participants' feedback on a demographic survey with questions on based PROGRESS-Plus factors, including those that have not been typically asked in research (e.g., religion). A narrative summary was produced from the findings.

Results: Overall, participants (n=15) identified that a lack of representation in rheumatology research translates to a lack in the ability to provide comprehensive care. Participants emphasized that EDI needs to be considered early on in all rheumatology research in order to effectively impact the study from design through to knowledge translation. Themes were constructed and categorized as barriers and facilitators. Barriers included: 1) Mistrust from historically exploited populations; 2) Unintended consequences (e.g., increasing disparities by isolating specific populations); 3) Lack of access to research opportunities; and 4) Logistical challenges (e.g., time-consuming, and more expensive). Supports and facilitators included: 1) Building partnerships with community members to establish trust; 2) Curating diverse research teams; 3) Incentivizing increased data collection and support from funding agencies; and 4) Fostering humility in research environments.

Conclusion: Improving representation in research is needed in order to improve health outcomes for diverse groups of people living with arthritis. Identified barriers to EDI in research must be addressed, while partnerships and supports must be facilitated to achieve more representation in rheumatology research within Canada.

POD11: Alison H. Clifford
Does 18F-Fluorodeoxyglucose Positron Emission Tomography (Pet) Correlate with Disease

Activity in Patients Who Are Receiving Treatment for Giant Cell Arteritis (Gca): a Systematic Review and Meta-Analysis

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Objectives: The utility of obtaining follow up 18-F fluorodeoxyglucose positron emission tomography (FDG PET) imaging in patients with giant cell arteritis (GCA) is unclear. We performed a systematic review and meta-analysis to determine how often vascular FDG PET uptake improves or normalizes in GCA patients after starting immunosuppressive treatment.

Methods: An electronic literature search of MEDLINE, EMBASE, CINAHL, Scopus, and Cochrane Library from inception through November 4 2020 was performed. Longitudinal studies assessing the correlation of follow-up 18F-FDG PET (or hybrid PET imaging) and clinical or biochemical disease activity in GCA patients starting or escalating treatment were included. For inclusion, patients must have had a positive baseline PET documenting large vessel vasculitis, and at least 1 follow-up scan over time (≥3 months after treatment start or escalation), along with a clinical assessment of disease activity. Screening, full text review and data extraction was performed by 2 independent reviewers. Study quality was assessed using QUADAS-2 instrument. Meta-analysis of the pooled sensitivity of improved PET for those with clinical or biochemical improvement, and normalized PET for those in clinical remission was performed. Subgroup analyses were performed to examine utility of PET in patients treated specifically with tocilizumab (TCZ subgroup), and those studies using international consensus criteria for PET interpretation (CC subgroup).

Results: The search yielded 1932 unique studies, of which 1914 were excluded after either title/abstract screening (1764), or full text review (150.) For baseline details of 18 included studies, see Table 1. Most described improvement of FDG uptake in GCA patients after starting immunosuppressive treatment, but normalization of PET occurred less commonly among patients in remission. The pooled sensitivity of improved PET uptake for patients with clinical improvement was 0.85 (95% CI 0.76-0.93, I2=0), the pooled sensitivity of improved PET uptake for patients with biochemical improvement was 0.84, (95% CI 0.74-0.93, I2=0), and the pooled sensitivity for normalized PET for patients in clinical remission was 0.43 (95% CI 0.34-0.53, I2=9.2). Results were similar in the CC subgroup (pooled sensitivity for PET normalization 0.41, 95% CI 0.28, 0.55), however more heterogeneity was observed (I2=50.3%.) The pooled sensitivity for PET normalization improved to 0.80 (95% CI 0.65-0.93) in the TCZ subgroup, with low heterogeneity (I2=0.)

Conclusion: Vascular FDG uptake improved in the majority (85%) of GCA patients who experienced clinical improvement on treatment, and normalized in 43% of those in clinical remission. Limited data suggested follow up PET scans normalized more often (80%) in TCZ-treated patients.

POD12: Carolina Munoz-Grajales
Elevated Serum Levels of S100A8/a9 Discriminate Systemic Lupus Erythematosus Patients with Cognitive Impairment from Patients Without Impairment

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Objectives: Cognitive impairment (CI) is one of the most common manifestations of Neuropsychiatric Systemic Lupus Erythematosus (NPSLE). Studies have reported that SLE patients with different NPSLE syndromes have alterations in the cerebrospinal fluid or their serum levels of various cytokines and proteases (analytes) that can lead to neuroinflammation. However, studies focused on analytes in CI are scarce. In this study, we investigated the ability of various serum analytes to discriminate SLE patients with CI from those without impairment.

Methods: Two hundred ninety individuals 18-65 years old who met the 2019 EULAR/ACR classification criteria for SLE were included. Cognitive ability was measured utilizing the 1-hr ACR-Neuropsychological Battery (ACR-NB). CI was defined as z-score of $\leq$-1.5 in two or more domains. The serum levels of nine analytes (IL-6, IL-10, IFN-g, MMP-9, NGAL, S100A8/A9, S100B, TNF-a, and TWEAK) were determined using ELISA. The data were randomly partitioned into a training (70%) and a test (30%) sets. A predictive regression model was performed to evaluate the measured analytes' ability to discriminate SLE patients with CI from patients without impairment. The optimal cut-off values to discern between CI and non-CI for each analyte were obtained by Youden's index. For patients that have completed cognitive assessment at 6 and 12 months (n=125, 43%), pairwise comparisons of the S100A8/A9 serum levels between time points were performed.

Results: Of 290 patients, 40% had CI (n=116). Overall, no differences in demographic or clinical characteristics were observed between patients with and without CI. S100A8/A9 had the highest AUC (0.74, 95%CI: 0.66-0.88) and displayed the greatest discriminative ability to differentiate between patients with and without CI. Cognitive status remained unchanged for most of the patients with 6- and 12-month follow-up visits (57 and 28 remained in the non-CI and the CI groups, respectively, whereas 20 with CI changed to non-CI and 20 from non-CI to CI). S100A8/A9 serum levels increased over time in group 4 (from non- CI to CI) and there was a trend to reduced levels from the baseline and 6-month visits to the 12-month visit in group 3 (from CI to non-CI) (Figure 1).

Conclusion: Amongst all measured analytes, S100A8/A9 had the greatest discriminatory ability in differentiating between SLE patients with and without CI. Replication of these findings is needed to confirm the utility of S100A8/A9 as a biomarker for CI in SLE. Research into the underlying mechanisms is also needed.

POD13: Elliot Hepworth
Treat (Depression to Reach)-To-Target in Rheumatoid Arthritis

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Objectives: Depression is a prevalent comorbidity in Rheumatoid Arthritis (RA), affecting up to 38.8% of individuals (1). Depression can profoundly affect physical well-being, including increased pain perception and fatigue. Moreover, untreated depression may hinder treatment adherence and overall disease management in RA (2). Psychological distress can influence the perception of joint tenderness and swelling, potentially leading to fluctuations in these clinical measures (3). In this study, our aim was to investigate the subjective and objective measures of disease activity according to the severity of depression, with a focus on disease activity on musculoskeletal ultrasound (US).

Methods: At the ORCHESTRA (Ottawa Rheumatology CompreHEnSive TReatment and Assessment) Clinic, RA patients starting a new bDMARD/tsDMARD therapy are assessed using a comprehensive screening process which includes a protocoled US scan at baseline and three months after new therapy initiation. In our research , we utilized Patient Health Questionnaire (PHQ) scores as a means to measure depression. The B-mode and Doppler findings were scored according to the OMERACT definitions on a scale between 0-3 per joint. Analyses was performed to compare disease features, clinical and US detected disease activity, according to the severity of depression.

Results: Within 80 RA patients, 40, 18 and 22 patients had none, mild or moderate-to-severe depression, respectively (Table-1). Demographic features were comparable across depression states. Subjective disease measures, including duration of morning stiffness, tender joint counts, VAS scores reported by both patients and physicians, HAQ scores as well and composite indices (CDAI scores, DAS28-ESR and DAS28-CRP scores) were higher in patients with moderate-severe depression, compared to mild or no depression (table-1). In contrast, the depression severity did not have any impact on objective measures, including the swollen joint counts and ultrasound scores (both GLOESS and Doppler scores).

Conclusion: Depression is a frequent comorbidity in RA, and affects how much the patient is impacted with the disease. RA patients with moderate-to-severe depression report higher subjective patient-reported outcomes, despite similar ultrasound scores for inflammation. This observation suggests that the presence of moderate-severe depression reduces the reliability of PROs in assessing disease activity in RA and objective measures are needed to choose the right therapeutic approach. When the target of RA is set as remission, a comprehensive approach is required, which includes addressing depression as an integral part of the management.

POD14: Hillary Chan
Improving Access to Temporal Artery Biopsy for Giant Cell Arteritis Patients

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Objectives: Temporal artery biopsy (TAB) is the gold standard for diagnosis of giant cell arteritis (GCA); however, average wait times can vary significantly depending on available resources and operational procedures [1]. Our aim was to assess our current TAB wait times in an outpatient rheumatology clinic and improve TAB wait times to be 4-6 days, the standard of care reported in the literature.

Methods: We conducted a gap analysis of patients who underwent TAB at a University of Toronto academic hospital between January 2022 and August 2023. Consecutive patients with TAB were identified by pathology reports which were routinely obtained as part of clinical care. Data collected included patient demographics, specialty of first consulting physician, time to first appointment with rheumatology, presence of GCA symptoms including presence of visual changes, lab values including ESR and CRP, empiric dose of steroids, side effect of steroids, time to biopsy, and biopsy result.

Results: A total of 19 patients were included in the study. Thirteen (68.4%) patients were female. The average age was 73.9 (range: 59-95). Patients presented first to emergency (n=11), ophthalmology (n=5), rheumatology (n=1) or neurology (n=1). If rheumatology was not the first consulting specialty, the average time to rheumatology consult was 9.5 days (range: 1-34). Most (68.4%) patients had GCA symptoms and 8/19 (42.1%) had vision loss on presentation. All patients had steroids empirically started before biopsy except one who refused steroids. Ten (55.5%) patients experienced steroid side effects which included facial fullness (n=2), pedal edema, gastritis, hyperglycemia (n=3) and weight gain (n=2). The average time to TAB was 14.8 days (range: 1-61). Four (21.1%) patients had biopsy-positive GCA. There was no statistically significant difference in biopsy result between patients who received TAB <7 days from their first visit compared to patients who received TAB more than 7 days (p = 0.9499).

Conclusion: Our findings suggest there is significant variability in time to biopsy and time to first rheumatology appointment. Next steps include identifying factors that may lead to delay in biopsy and rheumatology care, and creating pathways to expedite care.