To our Stakeholders,

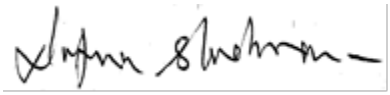
As the province of Ontario lifted restrictions in terms of travel and meetings/conferences, UHN being the lead site for the IPART Research Program, evolves with the changes imposed by the province with strict adherence to public health guidelines – physical distancing, masking, vaccination, hand hygiene, and mandatory vaccinations remain for all its staff members.

Because of the pandemic, we have not been able to accomplish as much as we would have liked to. The restrictions prohibited us from evaluating patients in our clinics and prevented us from collecting biological samples during those restricted times. As the restrictions are easing, we are seeing more patients in the clinic, and are able to obtain biological samples. We hope that the situation will continue to improve and that we are able to resume our normal activities.

Despite the limitations, our research continued with active projects ongoing either collectively and individually per collaborating site, and we have made significant progress. We are therefore providing a summary of what did happen in the past year and ongoing until date.

For our scientific and investigators' meetings this year, we have decided to proceed with a hybrid format. Those of us who can attend in person hopefully will, and those who are unable to join us in person will be able to attend virtually.

Thank you for your continued support to the IPART Research Program.



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PROGRESS REPORT

DATABASE AND BIOBANKING UPDATE

DATABASE

	TWH	WCH	St. John's	Vancouver	Ann Arbor	Rochester	London	Winnipeg	Israel	Halifax	Argentina	Ottawa
PsA	1641	279	609	99	22	276	187	75	243	4	4	19
Psoriasis	712	385	82	44	69	221	5	193	27	21	9	0
Total	2353	664	691	143	91	497	192	268	270	25	13	19
Female (%)	44.7	56.0	53.2	51.1	47.6	56.9	41.7	50.6	57.0	36.0	92.3	55.6
Caucasian (%)	84.2	73.6	99.2	64.0	98.8	89.7	94.1	82.7	76.3	92.0	75.0	94.4
Visits Ps	4.0	1.9	1.0	1.7	2.6	1.8	1.0	3.7	1.2	1.4	1.0	-
Visits PsA	14.7	5.5	1.4	2.0	2.3	3.2	5.2	4.9	3.7	1.3	1.0	1.3
Age Ps	29.0	31.9	29.7	31.2	30.2	32.3	33.1	31.0	37.0	28.4	31.1	35.9
Age PsA	38.4	42.7	39.5	37.5	41.5	41.2	42.7	41.1	46.4	46.0	40.3	45.2
DD Ps	20.0	16.8	18.1	23.2	14.2	18.9	18.1	24.0	17.8	23.5	18.4	-
DD PsA	17.3	7.3	10.7	14.4	11.8	12.6	14.8	13.2	12.5	3.0	10.9	13.9

Number of patients within database as of March 28, 2022.

Ps = Psoriasis; PsA = Psoriatic arthritis; DD = disease duration at last visit

In summary:

	PsA	PsC	**TOTAL**
Number of patients	3458	1768	**5226**

IPART TORONTO BIOBANK

Here is the latest update of biospecimen samples stored in our facility:

	TWH PsA	TWH PsC	Women's College	St. John's	London	Halifax	Winnipeg
DNA	1363	664	549	168	168	26	223
Serum	9807	1911	1004	490	363	35	264
RNA	8482	767	872	41	393	35	169
Synovial Fluid	181		24				

RESEARCH UPDATE (2QTR 2021 – 1QTR 2022)

In the past years, IPART has made significant progress in its research program, particularly in the areas of clinical, genetic, and biomarker studies. The following projects are ongoing in all sites:

A Progress Report by Dr. James T. Elder
IPART Core Site - University of Michigan, USA

GENETIC AND GENOMIC DISSECTION OF PSORIATIC ARTHRITIS

This project has been funded from September 2012 until now by the National Institutes of Health (NIH), National Institutes of Arthritis and Musculoskeletal and Skin Diseases, to the University of Michigan (Dr. James T. Elder, PI), and Sub-award to the University Health Network -IPART Research Program (Dr. Dafna Gladman, PI).

GENETIC STUDIES

Because transethnic analysis may facilitate prioritization of causal genetic variants, we performed a genomewide association study (GWAS) of psoriasis in South Asians (SAS), consisting of 2,590 cases and 1,720 controls. Comparison with our existing European-origin (EUR) GWAS showed that effect sizes of known psoriasis signals were highly correlated in SAS and EUR (Spearman ρ = 0.78; $p < 2 \times 10^{-14}$). Transethnic meta-analysis identified two non-MHC psoriasis loci (1p36.22 and 1q24.2) not previously identified in EUR, which may have regulatory roles. For these two loci, the transethnic GWAS provided higher genetic resolution and reduced the number of potential causal variants compared to using the EUR sample alone. We then explored multiple strategies to develop reference panels for accurately imputing MHC genotypes in both SAS and EUR populations and conducted a fine-mapping of MHC psoriasis associations in SAS and the largest such effort for EUR. HLA-C*06 was the top-ranking MHC locus in both populations but was even more prominent in SAS based on odds ratio, disease liability, model fit and predictive power. Transethnic modeling also substantially boosted the probability that the HLA-C*06 protein variant is causal. Secondary MHC signals included coding variants of HLA-C and HLA-B, but also potential regulatory variants of these two genes as well as HLA-A and several HLA class II genes, with effects on both chromatin accessibility and gene expression. This study highlights the shared genetic basis of psoriasis in SAS and EUR populations and the value of transethnic meta-analysis for discovery and fine-mapping of susceptibility loci. These studies have recently been published [1].

In other HLA-related genetic studies, we collaborated in the generation of a high-resolution HLA reference panel capturing global population diversity, which was published in Nature Genetics [2]. We also collaborated to carry out large-scale imputation of Killer Immunoglobulin Receptor (KIR) copy number and HLA alleles in EUR psoriasis case-control cohorts, which found an association of the inhibitory KIR2DL2 with psoriasis [3].

We also spearheaded an international effort (UK, USA, Canada, Germany, Norway, Estonia) to increase the power of psoriasis GWAS by meta-analysis of 18 case-control European-ancestry (EUR) GWAS datasets (36,466 cases, 458,078 controls; cumulative effective sample size: 103,614). After stringent quality control, each dataset underwent genome-wide imputation. GWAS analyses were performed locally at collaborating centers, with standard-error weighted meta-analysis undertaken centrally. We identified 360 variants independently associated with psoriasis susceptibility at genome-wide significance ($P<5\times10^{-8}$), 223 outside the MHC. Merging variants <1Mb apart revealed 108 associated non-MHC genomic regions. Sixty regions map to psoriasis susceptibility loci reported previously in European populations. Thirty of these (excluding MHC) include multiple independent association signals; a few, notably at *IL12B* and *TYK2*, include many such signals. We report 49 newly associated psoriasis susceptibility regions, six with multiple independent signals. The most strongly associated signals were chr11p12 within *PRR5L* and near *TRAF6* (OR=1.25, $P=5.6\times10^{-20}$), chr22q12.3 near *NCF4* (OR=1.11, $P=1.6\times10^{-15}$), and chr1p36.22 within *MFN2* (OR=1.09, $P=1.6\times10^{-15}$). Bioinformatic analysis suggests the susceptibility loci are enriched for a

range of immune functions. Enriched cell types prominently feature NK cells and pDCs in addition to CD4+ and CD8+ T-cells. We undertook LD-based fine-mapping to reveal candidate causal variants, both protein-altering and putative regulatory variants. Candidate genes in new loci include *CPVL* and *IL7R* (with immune roles) and *POU2F3* (in skin). This study demonstrates the power of expanded sample size via meta-analysis to identify new psoriasis loci and hone in on causal variants as well as disease-associated cell types and biological functions. This work, which has been presented as an abstract [4], is currently being written up for publication.

We participated in trans-disease meta-analyses involving psoriasis, revealing relationships between psoriasis and COVID-19 [5] and Type II diabetes [6]. We also participated in several Mendelian Randomization studies exploring potential genetic relationships between psoriasis/PsA and other diseases, including osteoporosis [7], body mass index [8], adiposity [9], and periodontitis [10].

EPIGENOMIC STUDIES

eQTL Studies of Disease-relevant Immunocytes

With the support of R01 AR042742, we utilized the U-M Flow Cytometry Core to generate 9 cell fractions from PBMC: myeloid dendritic cells (mDC), four fractions of unstimulated CD3+CD45RO+ memory T cells (CD4+CLA-, CD4+CLA+, CD8+CLA-, CD8+CLA+) and the same 4 fractions after 24 hours of stimulation of the CD1c- column flow-through (primarily T-cells) with anti-CD3/anti-CD28 beads.

While characterizing this culture system, we found that CD14+ monocytes remained with the T-cells in the flow-through after magnetic bead capture of CD1c+ cells. Interestingly, these CD14+ monocytes were rapidly lost from the CD3-CD28 activated cultures, as demonstrated by (a) markedly reduced expression of the monocyte signature genes CD14, CD36, S100A8, S100A9, and S100A12 at 24h vs. 0 h of CD3/CD28 activation, (b) by flow cytometric demonstration of CD14+CD3- cells prior to CD3/CD28 activation, and (c) by an independent set of single-cell RNA-seq experiments performed on CD3/CD28-activated vs. non-activated whole PBMC (unpublished data). This is important because previous work by ourselves [11] and others (Evans et al., Proc Natl Acad Sci U S A 104: 17034, 2007) demonstrated a stringent requirement for monocytes for Th17 polarization of memory T-cells in CD3/CD28-activated PBMC.

We have completed flow-sorting, RNA-seq and ATAC-seq library formation and sequencing, as well as high-density genotyping using Illumina Infinium Omni5Exome-4 arrays containing ~4.6 million whole-genome and functional exonic variants, followed by imputation using the TOPMed reference panel (Taliun, et al., Nature 590, 290-299, (2021) These experiments generated an unprecedented collection of 153 individuals (86 psoriasis cases and 67 healthy controls) for genetic analysis of gene expression. We generated 1,057 RNA-seq and 1,090 ATAC-seq libraries from these 153 subjects, derived from 8 flow-sorted T-cell subsets (defined by CD4/CD8, CLA+/ CLA-, and 0/24h CD3/CD28 stimulation). Effects of activation and skin-homing were analyzed by DESeq2, using a Wald test to assess true main effects with significance criteria of FDR < 0.05 and $|\log2\ FC| \geq 0.585$) to identify differentially expressed genes (DEGs) and differentially accessible regions (DARs).

RNA-seq

From the RNA-seq libraries, we identified 2,795, 3,629, and 10,673 genes for CD8/CD4, CLA+/CLA-, and resting vs. activated T-cells, respectively. CD4/CD8 DEGs revealed top KEGG enrichment for "Cytokine-cytokine receptor interaction (CCRI)" (FDR = 8.3e-19) and included "Th17 cell differentiation" (FDR = 7.8e-03), with up-regulation of *IL17A* (3.2-fold), *IL17F* (1.8-fold), and *IL22* (2.9-fold) in CD4. CLA+/CLA- DEGs also revealed top enrichment for "CCRI" (FDR=2.4e-18), with up-regulation of *IL17A* (3.3-fold), *IL17F* (2.2-fold), and *IL22* (1.9-fold) in CLA+. Activation-related DEGs were also enriched for "CCRI" (FDR = 2.1e-04), with dramatic up-regulation of *IL17A* (109-fold), *IL17F* (1052-fold), and *IL22* (146-fold) at 24 h. Examination of two-way interactions between skin-homing and activation using DESeq2 followed by functional enrichment analysis using KEGG revealed top enrichment for "Th17 cell differentiation".

ATAC-seq

After peak calling, 78,234 consensus peaks were present in ≥ 30 ATAC-seq libraries. A Wald test identified 9,072, 3,934, and 21,174 consensus peaks as differentially accessible regions (FDR < 0.05, |log2 FC|≥ 0.585) in CD4 vs CD8, CLA+ vs CLA-, and resting vs. activated T-cells, respectively. For functional annotation, DARs were assigned to the closest genes using ChIPseeker. CD4/CD8 DARs were most significantly enriched for the KEGG pathway "Th17 cell differentiation" (FDR=2.4e-07). CLA+/CLA- DARs were most enriched for "MAPK signaling pathway" (FDR=1.5e-06) and included "Th17 cell differentiation" (FDR=4.1e-04). Activation-responsive (0/24h) DARs were most enriched for "T cell receptor signaling pathway" (FDR = 1.0e-07) and included "Th17 cell differentiation" (FDR=2.3e-06). We next performed an analysis of differentially bound transcription factor (TF) binding motifs (DBMs) utilizing CENTIPEDE (Pique-Regi et al., Genome Res 21, 447-455, 2011), highlighting a marked and highly significant increase in accessibility corresponding to binding of AP-1 family TFs after 24 hr of CD3/CD28 stimulation.

Joint Analysis of RNA-seq and ATAC-seq

Notably, the marked increase in TF binding identified by CENTIPEDE after 24h of CD3/CD28 activation could not be explained by increased expression of the cognate AP-1 TFs themselves, suggesting that CD3/CD28 stimulated activated AP-1 TF function. *IL17*A, *IL17F*, and *IL22* were among the 479 DAR/DEG pairs identified by both the CD4/CD8 and 0/24h comparisons. Taken together, these results support a link between skin-homing and Th17 polarization.

Preliminary data freezes of these results have been presented in abstract form at recent SID meetings [12-14] and are currently being written up for publication.

BIOMARKER STUDIES

Progress of biomarker studies has been significantly hampered by COVID-related restrictions on longitudinal patient sampling. At present, we are utilizing GWAS-based analytical tools such as Regulatory Element Locus Intersection (RELI) (Nat Genet 50:699, 2018) to explore the potential role of Epstein-Barr virus (EBV) encoded TFs in shaping the landscape of psoriasis-associated regulatory signals. Of the 121 SNPs listed in GWAS catalog in 2018, we identified 61 independent loci by linkage disequilibrium pruning. We applied RELI to determine whether the binding of transcription factors (TFs) and coactivators were concentrated at the 61 psoriasis risk loci. We evaluated 1,535 human and 52 virally encoded TF ChIP-seq (chromatin immunoprecipitation with DNA sequencing) datasets. We found that Epstein-Barr nuclear antigen leader protein (EBNALP), EBNA3C and EBNA2 occupied 32 (52.5%), 22 (36.0%), 17 (27.9%) of the 61 psoriasis loci with 11.3, 6.6 and 5.2-fold enrichment and with $p=3.2*10^{-12}$, $p=1.6*10^{-09}$ and $p=2.5*10^{-6}$ after Bonferroni correction, respectively. The viral (n=3) and human TFs (n=38) cluster together in an optimal subset of ~30 of the 61 psoriasis loci at $p=1.1*10^{-178}$. More than 75% of the most highly associated viral and human TF ChIP-seq datasets were collected from EBV transformed B cell lines in the EBV Latency III expression program of viral expression. These as-yet-unpublished results nominate EBV for a role in the pathogenesis of psoriasis by a mechanism operating in transformed B cells through the EBV Latency III program of viral expression. We are currently in the process of confirming these results in a larger GWAS dataset.

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A Progress Report by Dr. Christopher Ritchlin
IPART Core Site - University of Rochester, USA

The following projects are ongoing at the University of Rochester:

Metabolomic Profiling to Examine the Transition from Ps to PsA

We enrolled 3 patient cohorts from the IPART registry for metabolomic analysis. These included cross-sectional PsA, Ps patients who did not progress to PsA and Ps patients who went on to develop PsA. We found that secondary bile acids, butyrate and were low prior to onset of PsA. We also noted that oxylipins increased following the development of PsA. The combination of the level of and were highly predictive for the development of PsA with AUC of 94%. These data were presented at the ACR Meeting in 2021 and a manuscript describing this work is under review at Arthritis and Rheumatology.

Metabolomic Profiles in PsA

We sent Ps and PsA serum samples from the IPART Registry with phenotypic data to Monica Guma at UCSD and she analyzed the oxylipin profiles and published the results in Arthritis Research and Therapy.

Novel Animal Model to Examine Pathophysiologic Mechanisms in Ps and PsA

In a Discovery Grant, sponsored by the NPF, we are injecting immunodeficient mice with PBMCs and sera from psoriasis and PsA patients enrolled in the IPART registry and analyzing the T cell repertoires in the skin and joints of these mice. The mice injected with PBMCs and sera from PsA patients develop psoriasiform skin lesions and synovial enthesial disease, findings not observed in mice injected with PBMCs and sera from healthy controls. We are analyzing the T cell repertoire with Nanostring technology. We plan to submit an abstract to the 2022 ACR Meeting in June.

DC-STAMP as a Biomarker of Treatment Response

Dendritic Cell Transmembrane Protein (DC-STAMP) is expressed on monocytes and stromal cells and is directly involved in cell-cell fusion required for the formation of multinucleated osteoclasts. Circulating osteoclast precursors are increased in the circulation of PsA patients but the assays to identify these cells are quite labor intensive and expensive. We previously demonstrated that DC-STAMP expressed on cells and measured by flow cytometry is a surrogate marker, along with CD16 for osteoclast precursors. We monitored the change in DC-STAMP in 40 PsA patients before and after therapy in an RO1 proposal sponsored by the NIH. The patients were recruited from the IPART Registry. These data are currently being analyzed and we anticipate submitting a manuscript this summer.

Mechanisms Underlying the Transition from Psoriasis to PsA

In a Team Grant sponsored by the NPF, Dr. Ritchlin directed a multidisciplinary team (Scher:NYU, Ogdie:UPenn, Eder:U Toronto, Adamopoulos:Beth Israel, Boston) to identify risk factors and biomarkers associated with the transition to PsA. The team performed epidemiologic analyses from administrative databases, performed flow cytometery, ECITEseq and spatial transcriptomics on blood samples and imaging mass cytometry on skin biopsies. The studies in this project are will be completed by May 15th and we will have several manuscripts for submission in the fall of 2022. We recruited patients from the IPART Registry from the Rochester and Toronto sites.

CURRENT PROPOSALS THAT WILL DRAW PATIENTS FROM THE IPART REGISTRY IN ROCHESTER

PAMPA Trial

Drs. Scher and Ritchlin are leading a randomized controlled trial to analyze the ability of guselkumab to delay or prevent the onset of PsA in Ps patients at increased risk for arthritis (specific risk factors and positive MSK ultrasound). The trial has 6 sites: Rochester, NYU, Penn, Brigham and Women's Hospital, Women's Hospital Toronto, University of Newfoundland. It is a 4-year study and will enroll 350 patients.

Patients in Toronto, Newfoundland and Rochester will be recruited through the IPART Registry. The study is sponsored by Janssen Pharma.

AMP-AIM ELLIPSS Psoriatic Spectrum Disease Team

Drs Ritchlin, Scher, Gudjonsson (U Mich), Liao (UCSF), Ogdie (U Penn) are mPIs on the Psoriatic Spectrum Disease Team as part of the Accelerating Medicine Partnerships Autoimmune and Immune Mediated Diseases Program. This consortium supported by 54 million dollars is now getting underway. We will be recruiting psoriasis and PsA patients over the next 5 years and those in Michigan and U Rochester will recruited through the IPART Registry. This consortium is sponsored by pharma, the NIH and the FNIH.

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The following projects are ongoing at the genetic core site in Newfoundland:

Pharmacogenetic Profiling of JAK I Inhibition in PsA (*in progress*)

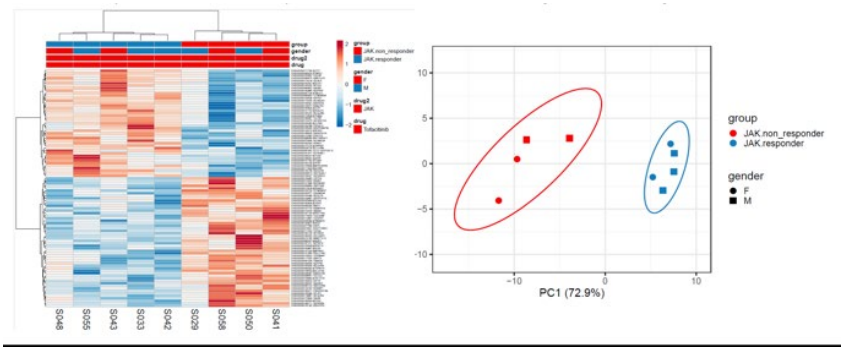
We have previously explored differential transcript profiling and microRNA sequencing for TNFi and IL-17Ai agents. We are extending this work and also have included JAK inhibitors. The number of samples in this exploratory analysis is extremely small thus needs to be interpreted with caution but the results are of potential interest and need further exploration.

Transcriptome sequencing for expression analysis was performed with libraries prepared from $CD4^+$ total RNA using NEBNext Ultra II Directional RNA Library Prep Kit for Illumina (Cat # NEB-E7760L, D-Mark Biosciences) and the NEBNext rRNA Depletion Kit (Cat # NEB_E6310X, D-Mark Biosciences). Briefly, total RNA was depleted of ribosomal RNA, enzymatically digested into fragments and reverse transcribed. Double stranded cDNA was purified with Agencourt AMPure XP beads (Cat # A63881, Beckman Coulter). This was followed by end repair and dA-tail addition and adaptor ligation. Adaptor-ligated DNA was further purified then unique dual index barcodes attached (NEBNext Dual Indexed Primer Set 1, Cat # E7760D-Mark) and fragments amplified in a PCR reaction. Final libraries were size selected with bead purification and the quality and quantity assessed with the Tape Station D1000 kit (Agilent). Library concentrations were normalized and pooled for sequencing on the Illumina NovaSeq 6000 for 2x150bp reads and ~40Million reads/sample.

MicroRNA sequencing was performed on 200ng $CD4^+$ Total RNA and Nextflex Small RNA-Seq Kit V3 with UDIs (D-Mark Biosciences, Cat. #5132-22). Briefly, adapters were ligated to the 3' end of the RNA, excess adapters removed by purification with cleanup beads, 5' adapter ligated, excess 5' adapter removed, and ligated products reverse transcribed. First strand synthesis product was amplified, and unique dual indices attached. PCR products were size selected with bead purification. Final library size was measured on Tape Station D1000 kit where the quality was assessed, and concentration quantified. Libraries were normalized prior to pooling. Sequencing was performed on the Illumina NovaSeq 6000 with a SP Reagent Kit (Illumina, Cat#20027464), for 50 single read cycles, targeting 10 million reads per sample. MicroRNA was analyzed against miRBase sequence database version 22.

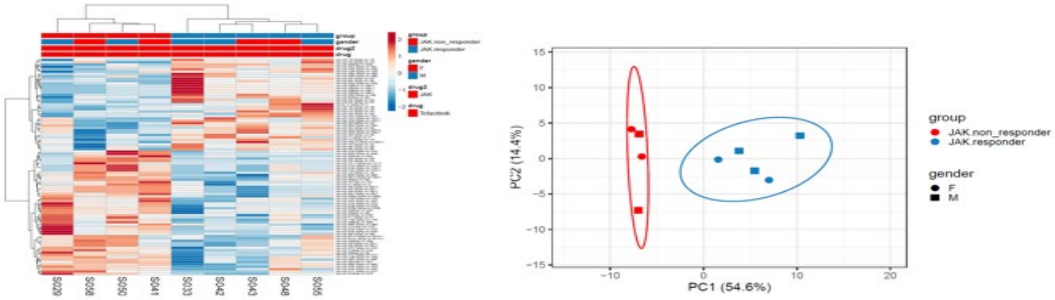
Overall to date 62 Pre-treatment samples have been completed including 32 IL-17i, 20 TNFi and 11 JAKi. Also 56 post-treatment samples including 28 IL-17i, 20 TNFi and 8 JAKi. For the pre-treatment analysis (A) we had 5 responder and 4 non-responders. 270 differential genes were identified with $P<0.05$ and Fold Change>1.5 in the pre-treatment analysis. For the post-treatment analysis (B), there were 140 differential genes with $P<0.05$ and Fold Change>1.5.

A **B**



For the miRNA Seq there 5 responder vs 4 non-responder. For the pre-treatment analysis (A), there were 92 miRNAs that were differentially noted to have P<0.05 and Fold Change>1.3, 92 miRNAs and for Post-treatment (B) 100 miRNAs had differential expressions at P<0.05 and Fold Change>1.3.

A **B**



Psoriasis Polygenic Risk Score Modeling (*in progress*)

Polygenic risk scores (PRSs) can stratify patients according to their risk for a complex human disease. Our objective was to explore the power of PRS to estimate the genetic liability to psoriasis and test the prognostic value of PRS to identify psoriasis.

Six methods were used to develop PRS psoriasis prognostic models using genome-wide association studies (GWAS) data that comprised 5,405 psoriasis cases and 418,126 control subjects of European ancestry from the UK Biobank (UKB). In addition, we validated the model in an independent Caucasian psoriasis cohort from the University of Michigan (UM) that comprised 2,927 psoriasis cases and 3,117 controls. Finally, the discriminatory accuracy as measured by the area under the curve (AUC) was calculated to score the performance of the models.

PRS using 89 GWAS significant variants identified from previously published reports had the lowest discriminatory performance (AUC = 0.59). Utilizing canonical PRS approaches, the performance was highest from PRSice (AUC=0.96 in UKB and AUC = 0.83 in UM validation cohort). The distributions of the PRS in psoriasis cases and controls were significantly different in UK Biobank. The stratified PRS, according the percentiles, showed that psoriasis cases were highly enriched in the "high-risk" group compared with "low-risk" group.

PRSice-derived PRS exhibited the best performance to differentiate psoriasis from healthy controls. After additional independent validation in diverse cohorts, this model may offer a risk-stratified approach to screen psoriasis.

Real World Studies of Psoriasis and Mental Illness in Newfoundland and Labrador

This study aims to illustrate an association between psoriasis and psychiatric disorders using real world data gathered from the Newfoundland and Labrador population. Data on 15,100 patients with psoriasis and 75,500 controls (1:5) was collected from the Newfoundland and Labrador Centre for Health Information's Electronic Health Records as part of the JANLHiP initiative. The cases and controls were matched for age, sex, and geography. Indicators for psychiatric disorders include diagnosis of mental illnesses from physician's visits and hospitalization records (all coded for mental health using ICD-9 and ICD-10 codes).

9,991 (66.2%) cases were identified to have at least one visit with a diagnostic code for mental illness compared to 42,276 (56.0%), p<0.0001 in the control group. The percentage of people coded for anxiety was 36.50% compared to 28.95%, p<0.0001; depression was 37.04% compared to 30.19%, p<0.0001; and adjustment disorder was 6.89% versus 5.48%, p<0.0001, among those with and without psoriasis, respectively. The greatest risk for anxiety [OR 1.4 (1.20-1.67)] and depression [OR 1.65 (1.36-2.00)] among

psoriasis patients was between the 0 to 20 age group. Women with psoriasis are more likely to have anxiety [OR 1.08 (1.03-1.13)], depression [OR 1.04 (1.01-1.09)] and adjustment disorder [OR 1.07(0.98-1.17)] compared to female controls. Our result shows that patients with psoriasis have an increased prevalence of mental illness. Using real world data to carry out further investigations will better elucidate this association and provide an increased understanding of the association between psoriasis and mental disorders.

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A Progress Report by Dr. Jan Dutz, PI, and Dr. Jonathan Chan, Co-I

IPART Core Site – University of British Columbia (UBC), Vancouver, Canada

The following clinical studies are ongoing in the Vancouver core site:

Roflumilast a PDE4 Inhibitor for Treatment of Mild/Moderate Psoriasis and Psoriatic Arthritis

(In progress)

Roflumilast is a PDE4 inhibitor which has been approved for treatment of COPD. Roflumilast has recently been shown to have activity against psoriatic skin lesions when applied topically (N Engl J Med. 2020 Jul 16;383(3):229-239). We hypothesize that oral administration may have a beneficial effect for patients with mild/moderate psoriasis and psoriatic arthritis in a similar fashion as apremilast. Advantages of roflumilast therapy would include once daily dosing and decreased cost. We have collected a number of patients who would be good candidates for apremilast but who do not have extended benefits for coverage of apremilast. With their consent, we have tried using roflumilast for some success for treating their disease. We are currently compiling a case series for publication.

Improving Therapy for Patients with Psoriasis and Psoriatic Arthritis (in progress)

Many patients have benefited from therapy with biologic response modifying medications. A common side effect is pain with injection and injection site reaction. We hypothesize that these reactions may be in part mediated by innate immune activation within the skin. We are collecting a series to patients who

have tried applying clobetasol to the injection site 1 day prior to each dose to see if that improves injection pain, swelling, and erythema.

Online Screening Tool for the Early Identification of Psoriatic Arthritis (in progress)

Roughly, a third of patients with psoriasis will develop psoriatic arthritis. Most of the time the psoriasis occurs initially and some studies have suggested up to 15% of patients may have undiagnosed psoriatic arthritis at dermatology offices. We created an online website utilizing a modified PEST questionnaire (included questions to screen for axial involvement). Patients from Dr. Jan Dutz's clinic were used as a pilot to see whether the website ran smoothly and collected adequate information. Each patient was mailed a letter asking them to log onto the website. Additionally, there was a link from the UBC skin care center directing them to this page. Patients were given a unique PIN to identify how many individuals had accessed the site. In this initial pilot, 16 patients have filled out the questionnaire and 9 scored positive on the PEST. Our next step is to try to scale this by increasing patient awareness of the website and including patients from other dermatologists.

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Progress Report by Drs. Dafna Gladman, Vinod Chandran and Cheryl Rosen
IPART Toronto Core Site – UHN – Toronto Western Hospital, Canada

The following projects are ongoing at the IPART core lead site at University Health Network (UHN):

CLINICAL STUDIES

Cardiovascular Disease Prediction in Psoriatic Disease

We looked for serum metabolites associated with cardiovascular events and investigated whether they could improve cardiovascular risk prediction beyond the Framingham Risk Score. 70 of 977 patients with psoriatic disease had incident cardiovascular events. We performed Cox regression models adjusted for cardiovascular risk factors and found that alanine, tyrosine, degree of unsaturation of fatty acids and high-density lipoprotein particles were associated with decreased cardiovascular risk whereas glycoprotein acetyls, apolipoprotein B and cholesterol remnants were associated with increased risk. Age and sex adjusted model including the 13 metabolites improved prediction beyond age and sex alone. However, adding the metabolites to the Framingham risk score did not improve cardiovascular risk discrimination.[1]

We performed carotid ultrasounds on 358 patients with psoriatic disease and measured carotid total plaque area (TPA), as well as cardiac troponin (cTuI) and N-terminal pro-brain natriuretic peptide (NT-proBNP). While both cTuI and NT-proBNP were associated with TPA, after adjusting for cardiovascular risk factors the association remained significant only for cTuI. We then assessed 1000 patients with psoriatic

disease for cardiovascular risk prediction. There was no improvement on the Framingham risk factor model. However, cTul may reflect the burden of atherosclerosis independent of traditional risk factors. 898.[2]

Heart Failure

We assessed the incidence and risk factors of heart failure (HF) among patients with PsA. The incidence rate was 2.85/1000 patient years. Independent risk factors for HF were ischemic heart disease, adjusted mean tender and swollen joint counts, as well as acute phase reactants and physical function. Minimal disease activity state was protective for HF.[3]

Osteoporosis

We investigated the factors associated with bone mineral density (BMD) testing among patients with PsA, and the effect of clinical activity on BMD. We found that 214 of 1479 patients followed had BMD testing. Osteopenia occurred in 45% of the patients while osteoporosis was detected in 13%. Increasing age, menopausal status, elevated acute phase reactants, and use of biologics, methotrexate and glucocorticoids were associated with a higher change of undergoing BMD testing, while increased body mass index and biologics were associated with a lower chance of having osteoporotic range of BMD. Polyarthritis may lead to lower BMD results over time.[4]

Depression and Minimal Disease Activity (MDA)

We aimed to determine whether the presence of depression or anxiety is associated with the achieving sustained minimal disease activity (MDA) in patients with psoriatic arthritis (PsA). Among 743 patients included in the study the presence of depression/anxiety was associated with reduced probability of achieving sustained MDA, regardless of which definition was used to define anxiety/depression. In addition, the Charlson comorbidity index and fibromyalgia were associated with a reduced probability of achieving MDA.[5]

Oligoarticular Disease in PsA

To determine whether oligoarticular PsA was different from polyarticular disease we studied patients who entered the clinic within 12 months of diagnosis and who had at least 2 clinic visits. 47% presented with oligoarthritis and they had less dactylitis and enthesitis than those with polyarthritis. However, similar joint distribution was observed with small joints of the hand and feet being most commonly affected. 39% of the patients with oligoarticular disease progressed to polyarthritis. The only predictor for progression was a lower SF-36 mental health component.[6]

We surveyed our patients to determine what the effect of COVID19 was on their disease, as well as their assessment of the virtual patient care. At the time of the survey the prevalence of COVID19 was low among our patients (4%). Most patients were not concerned about the impact of PsA or its medications on COVID19. Patients were satisfied with their pandemic virtual care.[7]

Effectiveness of DMARDs in PsA Enthesitis

We assessed the effectiveness of conventional and targeted disease modifying anti-rheumatic drugs (cDMARDs and tDMARDs, respectively) in treating enthesitis in PsA. Patients with active enthesitis, defined as at least 1 tender entheseal site (of 29 sites included in the spondyloarthritis research consortium of Canada enthesitis index, the Leeds enthesitis index, and the Maastricht ankylosing spondylitis enthesitis score), enrolled at the Toronto site were included. Medications at baseline were classified into 3 mutually exclusive categories: 1.'no treatment/non-steroidal anti-inflammatory drugs (NSAIDs)', 2. 'cDMARDs±NSAIDs' and 3.'tDMARDs±cDMARDs/NSAIDs'. Complete resolution of enthesitis (no tender entheseal site) at 12 months was the primary outcome. Logistic regression models were developed to determine the association between medication category and enthesitis resolution. Of the 1270 patients studied, 628 (49.44%) had enthesitis. Complete resolution of enthesitis was noted in 453 (86%) patients, within a mean period of 8.73 months from baseline. In the regression analysis, though not

significant, DMARDs (Categories 2 and 3) had higher odds ratio compared to category 1 for resolution of enthesitis. Enthesitis resolution was associated with lower joint activity and male sex.[8]

Assessment of the Toronto Psoriatic Arthritis Screen 2 as a Screening Tool for Psoriasis

A screening tool for psoriasis would be useful, particularly in underserviced or research settings with limited access to a dermatologist. The Toronto Psoriatic Arthritis Screen 2 (ToPAS 2) is a validated screening tool for psoriatic arthritis containing questions specific for psoriasis. We sought to evaluate the performance of skin-specific questions from ToPAS 2 for the diagnosis of psoriasis.

Participants over age 18 were recruited from Dermatology and Family Medicine clinics and completed the ToPAS 2 questionnaire prior to being examined by a dermatologist for evidence of psoriasis. Two scoring indexes were derived from the ToPAS 2 skin-related questions using backward selection regression models. Statistical analysis was performed using receiver operating characteristic (ROC) curves to measure their performance.

Two hundred and fifty eight participants were recruited. 32 (12%) were diagnosed with psoriasis by the dermatologist's assessment. Index 1 includes all five skin-related questions from ToPAS 2, while Index 2 includes three of the five questions. Both indexes demonstrate high specificity (82% to 92%), sensitivity (69% to 84%), and excellent negative predictive value (NPV) (>95%) for a diagnosis of psoriasis. The overall discriminatory power of these models is 0.823 (Index 1) and 0.875 (Index 2)

In conclusion, the skin-related questions from ToPAS 2 have discriminatory value in detecting psoriasis, specifically questions relating to a family history, a prior physician diagnosis of psoriasis or a rash consistent with images of plaque psoriasis. This study is a valuable step in developing a screening tool for psoriasis.

TRANSLATIONAL STUDIES

Using genome wide DNA methylation, we studied peripheral blood from 60 psoriasis without arthritis patients that developed arthritis and 60 psoriasis patients who did not develop arthritis matched on sex, age and duration of psoriasis. We identified a set of 36 highly significant methylation markers associated with the development of PsA in psoriasis patients. This work shows that DNA methylation patterns at an early stage of psoriatic disease can distinguish between psoriasis patients that will develop PsA from those that will not.[9]

Single-cell RNA seq (scRNA-seq) helps with analysis of the gene expression in individual cells. Using 10x scRNA-seq along with TCR immune profiling we profiled peripheral blood mononuclear cells (PBMCs) of 3 PsA, 3 PsC and 2 healthy controls. 18 cell clusters and over 600 differentially expressed genes were identified. TNFAIP3 and NFKBIA were the most significant differentially expressed genes in CD4+T-cells and CD8+T-cells. Immunoblotting of TNFAIP3 (A20) and NFKBIA (IKBA), revealed a striking pattern-discordance between relative transcript and protein levels, in CD8+T-cells.[10]

MicroRNAs (miRNA) modulate gene expression at a post-transcriptional level and can trigger immune and inflammatory responses that are associated with the pathogenesis of several disorders including psoriatic disease. We have demonstrated that miRNA miR-190a-5p is significantly downregulated in PsA compared to PsC and both miR-190a-5p and miR-26b-5p are down-regulated in PsA patients vs. healthy controls. Significantly enriched pathways targeted by both miRNAs include canonical and non-canonical Wnt, TGF beta, and Hedgehog signaling pathways.[11]

We assessed miRNA expression from RNA obtained from serum samples from 70 biologic naïve patients before and after 6 months of methotrexate (MTX) treatment. Articular response defined by DAPSA low disease activity was achieved by 20 patients while skin response defined by PASI50 was achieved by 24 patients. miRNA 127-3p was significantly lower in patients showing an articular response. A set of 8-miRNA were associated with cutaneous response to MTX.[12]

We have established a mass spectrometry-based metabolomics facility at the Schroeder Arthritis Institute. Sample processing is done using a novel solid phase microextraction (SPME) method. We have recently

shown that Psoriasis patients who developed PsA had similar metabolomic profiles to patients with mild PsA and were also indistinguishable from patients with psoriasis who did not develop PsA. Elevated levels of selected long-chain fatty acids (e.g., 3-hydroxytetradecanedioic acid) that are associated with dysregulation of fatty acid metabolism, were observed in patients with severe PsA. In addition, 1,11-undecanedicarboxylic acid-an unusual fatty acid associated with peroxisomal disorders-was also identified as a classifier in PsA patients vs. healthy individuals. Furthermore, a number of different eicosanoids with either pro- or anti-inflammatory properties were detected solely in serum samples of patients with moderate and severe PsA.[13] Ongoing studies include those determining metabolites associated with TNFi and IL17Ai treatment response as well as metabolites associated with PsA disease activity as determined by the PASDAS.

We have also conducted an observational cohort study on the immunogenicity of SARS-CoV-2 mRNA vaccines in adult patients with inflammatory bowel disease, rheumatoid arthritis, ankylosing spondylitis, or psoriatic disease, with or without maintenance immunosuppressive therapies. Antibody and T cell responses to SARS-COV-2, including neutralization against SARS-CoV-2 variants were determined before and after 1 and 2 vaccine doses. In 150 subjects, 26 healthy controls, 9 IMID patients on no treatment, 44 on anti-TNF, 16 on anti-TNF with methotrexate/azathioprine (MTX/AZA), 10 on anti-IL-23, 28 on anti-IL-12/23, 9 on anti-IL-17, and 8 on MTX/AZA, antibody and T cell responses to SARS-CoV-2 were detected in all participants, increasing from dose 1 to dose 2 and declining 3 months later, with greater attrition in IMID patients compared to healthy controls. Antibody levels and neutralization efficacy against variants of concern were substantially lower in anti-TNF treated patients than in healthy controls and were undetectable against Omicron by 3 months after dose 2. Our findings support the need for a third dose of mRNA vaccine and for continued monitoring of immunity in these patient groups[14].

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Progress Report by Dr. Lihi Eder

IPART Toronto Collaborating Site – Women's College Hospital, Toronto, Ontario, Canada

The following projects are ongoing at the Toronto Site 2 – Women's College Hospital:

Cardiac Biomarkers Predict Cardiovascular Events in Psoriatic Disease

Cardiovascular diseases are increased in psoriasis and PsA, however, existing cardiovascular scoring systems underestimate cardiovascular risk. In patients with psoriatic disease (PsD), we determined whether cardiac troponin I (cTnI) and N-terminal pro-brain-type natriuretic peptide (NT-proBNP) were associated with carotid plaque burden and the development of cardiovascular (CV) events independent of the Framingham Risk Score (FRS).

Methods: Among 1,000 patients with PsD, carotid total plaque area (TPA) was measured in 358 participants at baseline. cTnI and NT-proBNP were measured using automated clinical assays. The association between cardiac biomarkers and carotid atherosclerosis was assessed by multivariable regression after adjusting for CV risk factors. Improvement in the prediction of CV events beyond the FRS was tested using measures of risk discrimination and reclassification.

Results: In univariate analyses, cTnI (β coefficient 0.52 [95% CI 0.3, 0.74], p<0.001) and NT-proBNP (β coefficient 0.24 [95% CI 0.1, 0.39], p<0.001) were associated with TPA. After adjusting for CV risk factors, the association remained statistically significant for cTnI (adjusted β coefficient 0.21 [95% CI 0, 0.41], p=0.047), but not NT-proBNP (p=0.21). Among 1,000 patients with PsD assessed for CV risk prediction, 64

patients had incident CV events. When comparing a base model (with the FRS alone) to expanded models (with the FRS plus cardiac biomarkers), there was no improvement in predictive performance.

Conclusion: In patients with PsD, cTnI may reflect the burden of atherosclerosis, independent of traditional CV risk factors. cTnI and NT-proBNP are associated with incident CV events independent of the FRS, however, further study of their role in CV risk stratification is warranted.

Defining Imaging Subphenotypes in Psoriatic Arthritis

Psoriatic arthritis is a heterogneous disease which may affect disease course and response to therapy. Imaging helps to study and define this heterogeneity by accurately assessing the location and severity of musculoskeletal inflammation. We aimed to define imaging sub-phenotypes in patients with psoriatic arthritis (PsA); determine their association with whole blood gene expression, and identify biological pathways characterizing the sub-phenotypes.

Methods: 55 patients with PsA ready to initiate treatment for active disease were prospectively recruited. We performed musculoskeletal ultrasound assessment of the extent of inflammation in the following domains: synovitis, peritenonitis, tenosynovitis, and enthesitis. Peripheral whole blood was profiled with RNAseq, and gene expression data were obtained. First, unsupervised cluster analysis was performed to define imaging sub-phenotypes that reflected the predominant tissue involved. Subsequently, principal component analysis was used to determine the association between imaging-defined sub-phenotypes and peripheral blood gene expression profile. Pathway enrichment analysis was performed to identify underlying mechanisms that characterize individual sub-phenotypes.

Results: Cluster analysis revealed three imaging sub-phenotypes: 1) Synovitis predominant (N = 31 [56%]); 2) Enthesitis predominant (N = 13 [24%]); 3) Peritenonitis predominant (N = 11 [20%]). The peritenonitis-predominant sub-phenotype had the most severe clinical joint involvement whereas the enthesitis-predominant sub-phenotype had the highest tender entheseal count. Unsupervised clustering of gene expression data identified three sub-phenotypes that partially overlapped with the imaging sub-phenotypes suggesting biological and clinical relevance of these sub-phenotypes. We therefore characterized enriched differential pathways, which included: immune system (innate system, B cells and neutrophil degranulation), complement system, platelet activation and coagulation function.

Conclusions: We identified three sub-phenotypes based on the predominant tissue involved in patients with active PsA. Distinct biological pathways may underlie these imaging sub-phenotypes seen in PsA, suggesting their biological and clinical importance.

Characterizing Axial Psoriatic Arthritis

A substantial proportion of patients with PsA have axial pain however there is no accepted definition of psoriatic spondylitis. Spine MRI is an important tool in assessing axial involvement in SpA however there is limited data on MRI axial abnormalities in PsA. We aimed to describe the prevalence of inflammatory and structural lesions using whole spine MRI in patients with psoriatic disease, and to assess their correlation with clinical features and with axial spondyloarthritis (axSpA) classification criteria.

Methods: This retrospective analysis included patients with whole spine and sacroiliac joints (SIJ) MRI, selected from 2 populations: (1) active psoriatic arthritis (PsA), irrespective of axial symptoms; (2) psoriasis with confirmed or suspected PsA and axSpA symptoms. MRI spondylitis and/or sacroiliitis (MRI-SpA) was defined according to Assessment of Spondyloarthritis International Society (ASAS) consensus and by radiologist impression. Agreement between MRI-SpA and different inflammatory back pain (IBP) definitions (Berlin/ASAS/rheumatologist criteria) and the axSpA classification criteria were calculated considering MRI as gold standard. Logistic regression determined MRI-SpA-associated factors.

Results: 93 patients were analysed (69.9% PsA; 30.1% psoriasis). Back pain was present in 81.7%, defined as IBP in 36.6%-57%. MRI-SpA was found in 9.7% of patients by ASAS definition and in 12.9% by radiologist impression, of which 25% had isolated spondylitis.Low agreement was found between the three IBP definitions and MRI-SpA. Rheumatologist criteria was the most sensitive (50%-55.6%) while ASAS and

Berlin criteria were the most specific (61.9%-63%). axSpA criteria had poor sensitivity for MRI-SpA (22.2%-25%). Late onset of back pain or asymptomatic patients accounted for most cases with MRI-SpA not meeting axSpA or IBP criteria. Male sex was associated with MRI-SpA (OR 6.91; 95% CI 1.42 to 33.59) in multivariable regression analysis.

Conclusion: Prevalence of MRI-defined axSpA was low and showed poor agreement with IBP and axSpA criteria.

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Progress Report by Dr. Devy Zisman
IPART Israel Collaborating Site – Carmel Medical Center, Haifa, Israel

The following projects are ongoing at the Israel Site – Carmel Medical Center:

High Dimensional Analyses of Circulating Immune Cells in Psoriatic Arthritis Detects Elevated Phosphorylated STAT3.

Psoriatic arthritis (PsA) is a chronic inflammatory arthritis, affecting up to 40% of patients with psoriasis. Constitutive expression by CD4+ T cells of an active form of STAT3, a signal transducer and transcription factor, has been shown to induce many of the major features of PsA in an animal model. We used high dimensional mass cytometry (CyTOF) to probe *ex-vivo* levels of phosphorylated STAT3 (pSTAT3) in circulating immune cell subpopulations from PsA patients during active and inactive states. We evaluated the frequency of 16 immune cell populations and the levels of the activated forms of STAT3 (pSTAT3) and, for comparison, STAT1 (pSTAT1) and Src (pSrc) in whole blood fixed shortly after collection. In addition to PsA patients, we studied active rheumatoid arthritis (RA) patients. Increased levels of pSTAT3 were found

in all the CD4+ T cell subsets analyzed, specifically, Th1, Th2, Th17, T follicular helper (Tfh) and T regulatory (Treg) as well as in CD14+CD16- (classical) monocytes from active PsA patients compared to inactive patients. After correcting for body mass index (BMI), smoking and conventional disease modifying antirheumatic drugs (c-DMARDs), levels of pSTAT3 levels remained increased in Th1 and Tfh CD4+ T cells, and in CD14+CD16- monocytes from active patients compared to inactive patients. No differences between the patient groups were observed for pSTAT1 or pSrc. No differences were found between the active PsA and active RA groups after correction for multiple testing. During active PsA, circulating Th1 and Tfh CD4+ T cells, and CD14+CD16- monocytes expressing high levels of pSTAT3 may play a role in PsA pathophysiology, perhaps by migration to inflamed sites.

Implementation of the Treat to Target Concept in Evaluation of Psoriatic Arthritis Patients

The Treat to Target approach was recently adopted for psoriatic arthritis (PsA) management.

Objective: To assess the implementation of the "Treat-to-Target" (T2T) concept in daily management of PsA by use of composite scores of disease activity vs clinical judgement alone.

Methods: 117 PsA patients from a longitudinal PsA cohort were enrolled consecutively in the study during each patient's first clinic visits. Clinic notes from the treating rheumatologist were reviewed by an independent rheumatologist noting clinical impression of disease activity, treatment changes based on clinical judgement, and rationale. Treatment changes were then compared to use of formal disease activity parameters in Minimal Disease Activity (MDA) and Disease Activity Index for PSoriatic Arthritis (DAPSA) composite measures. All associations were assessed using Chi square test or Mann-Whitney test, as appropriate.

Results: The 117 PsA patient cohort consisted of 65.5% women, mean age 58.4 ±13.6 years. Clinical judgement of treating rheumatologist concorded with MDA and DAPSA in 76 (65.5%) and 74 (64.9%) patients, respectively. Agreement between clinical judgement and composite measure criteria did not correlate with patient age, sex, alcohol/tobacco use, or treatment regimens chosen. Disagreement between physician assessment and MDA occurred in 40 (34.5%) cases: in 30 cases, the MDA status was over-estimated due to disregard of patient reported outcomes (PRO), while underestimation of MDA status occurred in 25% of cases with treatment changes made in patients with a single active joint or enthesis. Underestimation of disease activity using DAPSA occurred in 22 cases and could be attributed to disregarding tender joint count, patient pain visual analogue scale and C-reactive protein level.

Conclusion: In our cohort, agreement between clinical impression and formal composite measure utilization for implementation of T2T strategy occurred in 65% of patients. Discordance resulted from physicians' overlooking PRO and emphasizing objective findings when using clinical judgement alone.

The Association of Psoriatic Arthritis with All-Cause Mortality and Leading Causes of Death in Psoriatic Arthritis

Epidemiological studies have shown that patients with psoriatic arthritis (PsA) are often affected by numerous comorbid conditions which carry significant associated disease burden and which can lead to increased mortality. We aimed to examine the association between PsA and all-cause mortality from a population-based large database.

Methods: PsA Patients from the Clalit Health database, the largest healthcare provider in Israel, were identified between 2003-2018 and matched to 4 controls by age, sex, ethnicity and index date. Patient's Demographics, comorbidities and treatments were extracted. Mortality data was obtained from the Notification of Death form. The proportionate mortality rate (PMR) of the leading causes of death was calculated and compared to the general population. Cox-proportional hazard regression models were used to estimate the crude and the multivariate adjusted hazard ratio (HR) for the association between PsA and all-cause mortality, and for factors associated with mortality within the PsA group.

Results: 5275 PsA patients and 21,011 controls were included and followed for 7.2±4.4 years. The mean age was 51.7±15.4 years, and 53% were females. 38.2% of PsA patients were on biologics. 471(8.9%)

patients died in the PsA group compared to 1,668(7.9%) in the control group. The crude HR for the association of PsA and all-cause mortality was 1.16(95%, CI 1.042-1.29) and 1.096(95%, CI 0.977-1.229) on multivariate analysis. Malignancy was the leading cause of death (26%), followed by ischemic heart disease (15.8%) in keeping with the order in the general population. Male sex, increased body mass index, Charlson comorbidity index scores and history of hospitalization in a year prior to death were positive predictors for mortality.

Conclusions: No clinically relevant increase in mortality rate was observed in PsA patients, specific PMRs were similar to the general population.

The Association between Psoriatic Arthritis and Venous Thromboembolism: A Population-based Cohort Study

Although the risk of cardiovascular disease has been discussed extensively in both psoriasis (PsO) and psoriatic arthritis (PsA), very few studies have addressed the occurrence of venous thromboembolic (VTE) events among PsO patients, and even fewer in PsA. Thus, our goal was to assess the association between PsA and VTE events using a large population-based database.

Methods: This retrospective cohort study includes all 5,275 patients with newly diagnosed PsA from the largest health care provider in Israel between January 2003 and December 2018. Identified PsA patients were matched by age, sex, ethnicity, and index date with 21,011 controls without PsA from the same database. Both groups were followed through June 30, 2019 for the occurrence of VTE event. Cox proportional hazard regression models were used to assess the association between PsA and VTE.

Results: PsA cohort consisted of 53.2% females with mean age of 51.7±15.4 Sixty-two patients (1.2%) were diagnosed with VTE in the PsA group and 176 patients (0.8%) in the control group (p=0.023, HR=1.40, 95% CI 1.05-1.87). However, there was no increased risk of VTE among PsA patients on multivariable analysis (p=0.16, HR=1.27, 95% CI 0.91-1.80). Within the PsA group, patients with VTE were more often of older age and with history of VTE.

Conclusions: This study suggests that the increased risk of VTE in PsA patients appears to be related to the underlying comorbidities and not independently associated with PsA. Age and previous history of VTE were the only risk factors associated with increased risk of VTE in patients with PsA. Addressing VTE risk is recommended especially in the era of Janus kinase inhibitors.

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EDUCATION, TRAINING & ADVOCACY COMPONENTS

IPART will continue to collaborate with the **Psoriatic Arthritis Research Program (PsARP),** UHN-Toronto Western Hospital, likewise spearheaded by Drs. Dafna D. Gladman (Director) and Vinod Chandran (Co-Director), with the following initiatives:

- **PsA Patient Advisory Committee** – The Psoriatic Arthritis Clinic at the UHN-Toronto Western Hospital (TWH), being the core patient resource of the IPART Research Program, is dedicated to patient care and research in psoriasis and PsA. One of the mandates of the research program is to ensure that the knowledge learned from this research be made available to the patients of the clinic, their families and other interested lay groups. In the past, dissemination pathways were limited to newsletters and annual patient symposiums. The Toronto site investigators spearheading the Psoriatic Arthritis Clinic at TWH deemed it crucial to obtain feedback and participation from its patients and therefore, the Patient Advisory Committee has been formed in 2012, which now has 8 members in the group. They have actively been involved in reviewing educational materials from a patient perspective, and provide suggestions and ideas on patient symposium formats, and how to effectively spread information on psoriatic disease updates and the latest trend on new therapies for psoriatic diseases.
- **Psoriatic Arthritis Patient Forum** – Annually, IPART collaborates with PsARP, the latter taking the lead in conducting educational symposiums for patients with psoriasis and PsA registered in the Psoriatic Arthritis Program for the last 17 years. The goal for these events is to provide patient education related to psoriatic diseases as well as share information on ongoing and planned research activities in psoriasis and PsA, providing updates on newer clinical management approaches and therapies for these conditions. These educational forums also feature other important related topics like diet, physiotherapy and exercise, skin, stress and pain management, and patient advocacy.

  Due to the restrictions during the COVID-19 pandemic, these events, for the last couple of years, were conducted in virtual platform. However, PsARP plans to conduct an in-person patient forum event in 2022, which is now tentatively scheduled for September 11, 2022 from 1-5PM at the Courtyard Marriott Downtown Toronto. Hopefully, the pandemic would already have ended by then and we can proceed as planned.
- **Fellows Training** – Training of fellows is an important activity in the program, increasing potential future recruitment of rheumatologists. These fellows contribute significantly into the program and stipends paid for each annually, solicited from various sources. These fellows take active roles in the execution of the various projects ongoing in the IPART and PsARP programs. Several of these have resulted in the publications described above.
- **Studentship** – Through the PsARP and IPART programs, medical students likewise take part in projects and core activities as outlined above. The program normally accepts 4-6 students each year. Because of the COVID-19 pandemic, we have not been able to accept summer students on site but have been able to engage some students remotely, and several have had a productive summer investigating our patients.
- **IPART Annual Scientific and Investigator Meetings** – The IPART core investigators, collaborating site investigators and its key coordinators meet annually as one of its medium of dissemination to its stakeholders, to coordinate research activities and unveil new discoveries.

  For 2022, the scientific meeting will be in hybrid format (in person and virtual) and is scheduled for May 6, 2022 from 10AM to 2PM at the Parkdale Room of the DELTA Toronto Hotel located at 75 Simcoe Road, Toronto, Ontario. The investigators/collaborators' general meeting follows thereafter.
- **Knowledge Transfer and Exchange** - Knowledge transfer occurs at several levels i.e. presentations at

professional meetings and publications as described in the previous pages. Another aspect of knowledge translation is with other stakeholders, which include patients and their involvement in disseminating information, assistance during grant submissions, etc.

INFRASTRUCTURE

The **International Psoriasis and Arthritis Research Team (IPART)** is a highly successful, international consortium of rheumatologists and dermatologists across Canada and the United States with expertise in genomics, inflammation, immunology and epidemiology. IPART was formed in 2007 and spearheaded by Dr. Dafna D. Gladman, its Principal Investigator.

IPART has five core sites namely:

Toronto, Ontario, CANADA	**Dr. Dafna D. Gladman,** Division of Rheumatology, University of Toronto, Toronto Western Hospital **Dr. Cheryl F. Rosen**, Division of Dermatology, University of Toronto, Toronto Western Hospital **Dr. Vinod Chandran**, Division of Rheumatology, University of Toronto, Toronto Western Hospital
St. John's, Newfoundland,	**Dr. Proton Rahman** - Division of Rheumatology and Genetics, Memorial University of Newfoundland
Vancouver, British Columbia, CANADA	**Dr. Jan Dutz** - Divisions of Rheumatology and Dermatology, University of British Columbia, Vancouver
Ann Arbor, Michigan, USA	**Dr. James T. Elder** - Division of Dermatology, University of Michigan, Ann Arbor, Michigan
Rochester, New York, USA	**Dr. Christopher Ritchlin** - Division of Rheumatology, University of Rochester, New York

IPART has other active collaborating sites across Canada and internationally as follows:

1) London, Ontario (University of Western Ontario – **Dr. Sherry Rohekar and Dr. Tristan Boyd**)
2) Toronto, Ontario (Women's College Hospital – **Dr. Lihi Eder**)
3) Haifa, Israel (Carmel Medical Center – **Dr. Devy Zisman**)
4) Detroit, MI (Henry Ford Health System – **Dr. Qing-Sheng Mi and Dr. So Yeon Paek**)
5) India (Sanjay Gandhi Post Graduate Institute of Medical Sciences (SGPGIMS) – **Dr. Vikas Agarwal**)
6) Ottawa, Ontario (University of Ottawa – **Dr. Sibel Aydin**)
7) Vancouver, BC (ARTUS Health Center - **Dr. Jonathan Chan** joined our core site at the University of British Columbia – Dr. Jan Dutz)
8) Vellore, India – (Christian Medical College - **Dr. Ashish Matthew and Dr. Debashish Danda**)
9) Quebec City, Quebec (CHU de Quebec, Université Laval – **Drs. Paul Fortin and Louise Bessette)**

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At present, IPART is funded by multi-industry support from **ABBVIE, PFIZER, ELI LILLY and UCB** granted through the IPART Toronto core site at the University Health Network, Toronto Western Hospital.

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