SYMPOSIUM REPORT

Cardiovascular disease in psoriasis: A changing paradigm

A SCIENTIFIC SYMPOSIUM PRESENTED BY IPC'S RESEARCH COMMITTEE AT THE 2019 SOCIETY FOR INVESTIGATIVE DERMATOLOGY (SID) ANNUAL MEETING

By Thomas Scharnitz, *MD*

Dr. Scharnitz received his medical degree from Pennsylvania State University and completed his intern year in internal medicine at the University of Virginia. He is currently in his third year of training as a resident physician at the University of Michigan Department of Dermatology.

Recent research has made significant advances in understanding the link between cardiovascular disease and psoriasis. That association was the focus of a symposium presented by IPC's Research Committee at the Society for Investigative Dermatology (SID) meeting in Chicago, Illinois, in early May. Discussions explored mechanistic models, epidemiological data, imaging studies, and immuno-intervention strategies for this complex scenario.

Co-chairs for the program – entitled, "Cardiovascular disease in psoriasis: A changing paradigm" – were IPC Councilors April Armstrong, University of Southern California, Los Angeles, California, United States; Johann Gudjonsson, University of Michigan, Ann Arbor, Michigan, United States; and Nehal Mehta, National Heart, Lung and Blood Institute, Bethesda, Maryland, United States.

Part 1 of the symposium featured 5 faculty presentations, with expert-led panel discussions. Part 2 included a 1-hour session featuring a series of selected poster presentations that provided additional insights into disease mechanisms that contribute to psoriasis and its comorbidities.

PART ONE: LECTURES

Immunopathogenesis of atherosclerotic disease: Where are we now?

Dr. Hafid Ait-Oufella, a cardiologist and PhD in immunology at Université Paris Descartes, began the symposium with a discussion on the immunopathogenesis of atherosclerotic disease. He described the role of both innate and adaptive immunity as a "delicate balance" between atherogenesis and atheroprotection.

Faculty for IPC's symposium at the SID annual meeting were, from left, IPC Research Committee Chair & Board Member, Hervé Bachelez, France; Nehal Mehta, United States; Hafid Ait-Oufella, France; Johann Gudjonsson and April Armstrong, United States; Marlies Wakee, the Netherlands; and Joel Gelfand, United States.

Innate immunity in atherosclerosis is well established. Smith et al demonstrated that macrophage-deficient mice form no atherosclerosis.[1] Furthermore, Varghese et al demonstrated 30% plaque reduction in IL-1β knockout mice.[2] Ridker et al showed significant protection (lower rate of recurrent cardiovascular events) with canakinumab in patients who previously experienced myocardial infarction and had persistent chronic low-grade inflammation (CRPus>2mg/l).[3] With TNF-α inhibitors, patients with psoriatic arthritis showed 50% reduction in atherosclerotic plaque development as measured by ultrasonography in the carotid artery and reduced cardiovascular events in patients with severe psoriasis.[4,5]

The role of adaptive immunity in atherosclerotic disease is more recently described. Zhou et al demonstrated that CD4(+) T cells promote atherosclerosis in mice, and Whitman et al demonstrated the vigorous pro-atherogenic role of TH1-derived IFN-γ.[6,7] Conversely, Dr. Ait-Oufella had identified the protective role of

a subset of CD4+ T cells called natural regulatory T cells through several mechanisms, including IL-10 and TGF-beta production.[8]

Importantly, relating to psoriasis, the role of Th17 remains controversial. Some experimental studies suggest atheroprotection during IL-17 blockade, whereas others suggest atherogenesis.[9,10] In acute coronary syndrome patients, high plasma IL-17 level is associated with better cardiovascular outcome.[11] Dr. Ait-Oufella believes that the vascular impact of IL-17 may depend on global cytokine environment, being protective in IL-10-rich conditions but pro-atherogenic in the case of high concomitant production of IFN-γ, evidenced in studies by Taleb.[12]

Epidemiology of cardiovascular disease in psoriasis

In an informative and practical lecture, IPC Councilor April Armstrong, professor and associate dean at the University of Southern California, explored the epidemiologic relationship between psoriasis and cardiovascular disease.

She discussed study characteristics, data collection, and aspects of epidemiologic research, including the strengths and weaknesses of the various study types, biases, and criteria for real association. She also focused on confounding, which is especially important between psoriasis and common cardiovascular risk factors and comorbidities. Dr. Armstrong subsequently summarized several meta-analyses, evaluating associations between psoriasis and multiple comorbidities, namely obesity, diabetes, hypertension, and the metabolic syndrome.

Regarding diabetes, Dr. Armstrong's group demonstrated increased overall odds ratio (OR, 1.59) and "severity stratified" pooled ORs (mild, 1.53 and severe, 1.97) in patients with psoriasis compared to controls.[13] Regarding obesity, they found increased overall OR (1.66), and pooled ORs (mild, 1.46 and severe, 2.23).[14] This association appears even stronger in the psoriatic pediatric population, as shown in a study by IPC Councilor Amy Paller, which displayed increased overall OR (4.29) and pooled OR (mild, 3.6 and severe, 4.9).[15] Regarding hypertension, they found increased overall OR 1.58.[16] Finally, regarding the metabolic syndrome, Dr. Armstrong's group found increased overall OR (2.26) and pooled ORs (mild, 1.56, severe, 1.98), though she noted funnel plots demonstrated substantial publication bias.[17] Dyslipidemia data are lacking due to varied nomenclature and coding.

Importantly, Dr. Armstrong discussed findings from several well-conducted epidemiologic studies where no association was revealed between psoriasis and cardiovascular risk factors and events. Notably, Parisi et al, examining the CPRD database, showed no association between severe psoriasis and major adverse cardiovascular events (MACE) after adjusting for confounders.[18] She noted that the Parisi study had several strengths in rigorous identification of cohorts, modeling of risk factors that accounted for development of new risk factors over time, and using severity of psoriasis as a time-varying covariate. Given the conflicting study findings from prior literature, it remains an evolving story regarding the association between psoriasis and cardiovascular risk factors and outcomes.

In closing, Dr. Armstrong emphasized the importance of accurate identification of cohorts, careful adjustment for confounders, the need to model for development of new comorbidities over time, and accounting for inflammatory arthritis in epidemiological studies in order to maximize validity of the findings.

Is psoriasis an independent risk factor for cardiovascular ischemic disease?

Marlies Wakkee, dermatologist at the Erasmus University Medical Center Rotterdam, the Netherlands, presented an informative discussion examining studies that reported the association of psoriasis as an independent risk factor of ischemic heart disease (IHD).

The first studies describing an association between psoriasis and cardiovascular (CV) events date back more than 40 years. In 2006, IPC Councilor Joel Gelfand of the University of Pennsylvania published a landmark paper in the *Journal of the American Medical Association* positioning psoriasis as an independent risk factor for myocardial infarction.[19] Since then, many studies have examined this association. Notably, a meta-analysis further demonstrated increased risk of IHD in psoriasis, but population-based data did not show significant associations.[20] This is likely because, to date, most studies are observational, based on secondary databases, and, therefore, are not designed to investigate the causal relationship between psoriasis and IHD and confer significant risk of detection bias.

Dr. Wakkee's group highlighted detection bias in an observational study in which regular office visits for psoriasis subsequently led to increases in both comorbidity diagnoses and medications administration.[21] Furthermore, the large population-based cohort Rotterdam Study, which minimized detection bias, failed to demonstrate increased risk of IHD in both mild and severe psoriasis.[22] Residual confounding also complicates observational studies, as Egeberg et al demonstrated a role for family history in this association. This study showed that only those patients with psoriasis with family history of cardiovascular disease exhibited a personal increased risk of CV events.[23]

Dr. Wakkee concluded that, based on observational studies, there is at least a complex association between psoriasis and IHD, but at this time it remains unclear if psoriasis is an independent risk factor. Future studies investigating the effect of systemic therapies on the risk of IHD in patients with psoriasis will be highly interesting to further elucidate this association.

In vivo studies of cardiovascular disease in psoriasis: An update

IPC Councilor Nehal Mehta, who heads the Laboratory of Inflammation and Cardiometabolic Diseases at the National Heart, Lung and Blood Institute in Bethesda, Maryland, presented vast in vivo data on the pathogenesis and therapeutic interventions on atherosclerotic plaques and cardiovascular disease (CVD) in psoriasis.

Dr. Mehta first discussed atherogenesis in which high-risk lesions ultimately rupture and cause acute coronary syndrome (ACS). In unpublished data, his group discovered that psoriasis yields 9-fold elevation in TNF-α and 5-fold elevation in IL-1β during troponin-positive ACS. Additionally, psoriasis is associated with atherogenic lipid composition with an increase in apoB lipoproteins and also reduced function of HDL as measured by HDL cholesterol efflux capacity.

Using FDG-PET (fluorodeoxyglucose positron emission tomography), Dr. Mehta's group found that psoriasis severity correlates with aortic inflammation. This inflammatory level mirrors nonpsoriasis patients with known CVD.[24] Furthermore, there are more coronary plaques that occur nearly 10-15 years sooner in psoriasis. Last year, using quantitative coronary angiography, Dr. Mehta also highlighted increases in total plaque burden in psoriasis, 95% of which is noncalcified (high risk) and rupture prone.

Most recently, his group completed an observational study in which 121 biologic-naïve psoriasis patients (moderate-severe) who received biologics (n=89) were compared to those who did not (n=32).[25] At 1 year, patients on biologics had reduction in necrotic core (-57%, p=0.09), and both total (-5%, p=0.009) and non-calcified (-6%, p=0.005) plaques. In subgroup analysis, significant reductions in noncalcified plaques occurred with both anti-TNF (-6%, p =0.06, n=48) and anti-IL17 (-15%, p=0.005, n=22) treatment groups.

Dr. Mehta concluded that biologics may curtail these psoriasis-driven inflammatory CVD phenotypes, but randomized controlled trials are necessary to validate the evidence.

Effect of psoriasis treatment on cardiovascular risk: Reconciling clinical trials and observational studies

In an interactive question-and-answer lecture, IPC Councilor Joel Gelfand, dermatology professor/researcher at the University of Pennsylvania, discussed the importance of critical evaluation of the literature. Substantial evidence exists to show that patients with psoriasis have an increased risk for major cardiovascular events and mortality, with the risk being most significant in patients who require systemic or phototherapy or have >10% body surface area affected. Recent guidelines from the American Academy of Dermatology (AAD) and National Psoriasis Foundation (NPF), the American Heart Association (AHA) and the American College of Cardiology (ACC) recognize the importance of CV risk in patients with psoriasis, and advocate for more aggressive management of cholesterol levels as one approach to mitigating this risk.[26,27]

A logical hypothesis is that treatment of psoriasis is associated with a lowering of CV disease and mortality. A variety of studies have demonstrated that both methotrexate and TNF inhibitors are associated with a decreased risk of CV events in patients with rheumatoid arthritis or psoriasis. Recent work by Margolis and Gelfand (*J Am Acad Dermatol* 2019), however, has demonstrated a strong healthy-user effect for psoriasis patients treated with biologics.[28] Thus it remains uncertain whether the reduction of CV events seen in observational studies is a drug effect or the healthy-user effect. Similarly, Gelfand showed data from the VIP (Vascular Inflammation in Psoriasis) trials and compared them to observation data and demonstrated the importance of placebo control in interpreting biomarker studies.

Recently and for the first time, clinical trials evaluated the impact of immune-targeted treatments on CV events as a measure of secondary prevention (ie, all patients in these trials have established coronary artery disease). CANTOS, a study of canakinumab, a biologic that blocks IL-1β, demonstrated clear proof of principle that a targeted biologic can lower the risk of CV events. However, the Cardiovascular Inflammation Reduction Trial (CIRT), a randomized placebo-controlled study of methotrexate, failed to demonstrate any benefit of the drug on CV events in patients with established coronary artery disease. In contrast to CANTOS, patients in CIRT were not required to have elevated C-reactive protein (CRP) and, thus, had no evidence of residual CV risk related to inflammation. Therefore, it seems likely that if methotrexate were studied in an inflamed population (ie, patients with rheumatoid arthritis, psoriasis, or coronary artery disease with elevated CRP), CIRT would have yielded results similar to CANTOS and observational studies of methotrexate.

In summary, Dr. Gelfand emphasized that practitioners must act on the data they currently have and do a better job of educating, screening, and treating modifiable cardiovascular risk factors. Fortunately, psoriasis's role in cardiovascular disease is becoming more widely accepted, and joint guidelines issued by the AAD-NPF and by the ACA-AHA now recognize its importance in CVD intervention.[26,27]

PART TWO: POSTER PRESENTATIONS

Trans-disease meta-analysis between psoriasis and type 2 diabetes reveals shared genetic signals.

Matthew Patrick, PhD, University of Michigan, Ann Arbor, Michigan, United States

- Published studies suggest that psoriasis and type 2 diabetes (T2D) are significantly associated. This study performed large-scale trans-disease meta-analysis using previous association studies for psoriasis (11,024 cases, 16,336 controls) and T2D adjusted for BMI (74,124 cases, 824,006 controls), utilizing 8,016,731 well-imputed markers from both diseases.
- The study identified 11 loci with shared direction of effect, including 4 that exhibited suggestively significant p-values ($p<1x10-4$) in both diseases.
- Among these loci, the chromosome 2 signal rs840967 ($p=9.6 \times 10-9$, psoriasis OR=1.08, T2D OR=1.04) is in proximity to a shared locus (2p14) for multiple chronic inflammatory conditions, and rs840967 is an expression quantitative trait loci (eQTL) in whole blood for SPRED2 ($p=8.3x10-27$), an inhibitor of MAP kinases.
- Together with the 3 other trans-disease loci (10q24.31, 11q13.1 and 17q21.2) encompassing CHUK, PRDX5 and STAT3, respectively, results indicate the shared disease loci include common transcripts that participate in NFkB and other immune cascade signaling.
- Interestingly, only one of the shared loci (11q13.1) is in linkage disequilibrium (D'=0.81) with previously identified signals for BMI.
- Conclusion: The results highlight potentially BMI-independent genetic links shared between psoriasis and T2D, and can ultimately help guide future research aimed at treating both conditions.

The adaptor protein Act1 plays a key role in psoriatic inflammation mediated by IL-23.

Alex Lipovsky, PhD, AbbVie, Worcester, Massachusetts, United States

- Act1 is an intracellular adaptor protein and a putative ubiquitin E3 ligase. Silencing of Act1 expression in human keratinocytes and fibroblasts blocks pro-inflammatory cytokine secretion induced by IL-17.
- In this study, Act1 knockout mice were resistant to increases in CXCL1 plasma levels induced by subcutaneous injection of recombinant IL-17A. These Act1 knockout mice were also protected against psoriasiform changes, gene expression for antimicrobial peptides and chemokines, and infiltration of immune cells after injection of IL-23.
- The L286G mutation was previously suggested to compromise Act1 ligase function and inhibit IL-17 signaling. Act1 "L286G knock-in" mice were susceptible to both IL-23 and IL-17 inflammatory effects.
- Primary Act1 "L286G knock-in" mouse fibroblasts, as well as human Act1 knockout fibroblasts reconstituted with a homologous point mutant, responded normally to IL-17 stimulation (unchanged from wild type).
- Conclusion: This study highlights the critical contribution of Act1 to proinflammatory skin changes mediated by the IL-23/IL-17 signaling axis.

XCL10 expression is regulated by keratinocyte STAT3 signaling and inhibits skin inflammation.

Nate Archer, PhD, Johns Hopkins School of Medicine, Baltimore, Maryland, United States

- The role of STAT3 signaling in psoriasis is not entirely clear. This study evaluated the relative contribution of STAT3 in keratinocytes (KCs) versus T cells in the imiquimod mouse model, using cre/lox mice with either KC inducible deletion of STAT3 (K5-STAT3), or specific deletion of STAT3 in T cells (Lck-STAT3).
- Unexpectedly, psoriasiform skin inflammation was diminished in K5-STAT3 mice, whereas Lck-STAT3 mice developed wild-type-like (wt) psoriasiform inflammation.
- K5-STAT3 mice also had increased IFN-γ+ T cells but less IL-17+ T cells compared to wt-mice. This suggested loss of STAT3 signaling in KCs dampened inflammation by inhibiting IL-17 responses while promoting IFN-γ responses.

- mRNA and histologic expression of CXCL10 inversely correlated with the skin inflammation in deletion (K5-STAT3 mice) or overexpression (STAT3 overexpressed mice, KC14-stat3) of STAT3.
- Neutralizing CXCL10 signaling enhanced imiquimod-induced skin inflammation, suggesting that CXCL10 acts to inhibit skin inflammation in this model.
- Conclusion: The findings define a novel mechanism by which KC, but not T cell-intrinsic, STAT3 signaling induces psoriasiform inflammation via regulation of CXCL10 expression, proinflammatory IL-17, and anti-inflammatory IFN-γ T cell responses.

Targeting chemokine receptors CCR6 and CXCR2 in a murine model of IL-36α-induced pustular psoriasis.

Karen Ebsworth, BSc, ChemoCentryx, Mountain View, California, United States

- Generalized pustular psoriasis (GPP) is linked to loss-of-function mutations in the gene encoding IL-36RA, an important negative regulator of IL-36 signaling.
- In this murine model, intradermal injections of pre-activated IL-36α caused markedly increased total skin and epidermal thickness, and increased concentrations of CCR6 and CXCR2 and accumulations of various inflammatory cells.
- The accumulated inflammatory subsets in IL-36α-treated skin all expressed either CCR6 or CXCR2 to some extent.
- "CCX624", an orally bioavailable small molecule CCR6/CXCR2 antagonist, reversed inflammatory cell accumulation and decreased both skin and epidermal thickness. CCX624 was effective in both prophylactic and therapeutic dosing regimens, and was more effective than saturating doses of both anti-TNFα and anti-IL17RA.
- Conclusion: This study suggests CCR6 and CXCR2 are novel targets for inflammatory skin diseases involving dysregulated IL-36 signaling, such as GPP.

Comparing RNAseq analysis of the mouse IL-23 minicircle model to human psoriasis and other preclinical models of skin inflammation.

Laura Leys, BS, AbbVie, North Chicago, Illinois, United States

- Hydrodynamic delivery of a single IV injection of IL-23 minicircles (MC) in mice induces psoriasiform dermatitis and elevates key IL-23/IL-17 pathway cytokines/chemokines.
- In the study, RNAseq analyses from MC mice revealed that 15 of the top 20 affected pathways were also amongst the top 20 pathways identified in human psoriasis (Li et al, 2014) including those related to the IL-17A/F pathways.
- Though both IL-23 models (MC and imiquimod) show the strongest alignment to human psoriasis, the MC model tended to have a more amplified RNAseq signal. Most upstream regulators were shared between human psoriasis and the MC model.
- Treatment with apremilast, as well as anti-IL-23p40, anti-IL-23p19, or anti-TNF mAbs suppressed most of the gene changes in the MC model.
- Conclusion: The study demonstrates that both IL-23 models align closely with human psoriasis, but the IL-23 MC tends to have a more amplified signal of these key pathways.

Depletion of the microbiome using broad-spectrum antibiotic cocktail improves the psoriasiform phenotype via attenuation of TNFα and IL-23-IL-17A in three psoriasis mouse models.

Jessica Ludwig, MSc, Case Western Reserve University, Cleveland, Ohio, United States

- The potential contribution of the microbiome in psoriasis remains unclear. In this study, KC-Tie2, IL-17C+, and KLK6+ psoriasiform mouse models were treated with a broad-spectrum antibiotic cocktail.
- Compared to controls, antibiotic-treated IL-17C+ and KLK6+ mice each demonstrated a 41% decrease in acanthosis ($P<0.001$). KC-Tie2 mice showed no improvement in acanthosis, but treatment did lengthen the time to thrombus formation by 75% in an experimental assay in the KC-Tie2 mice.
- Using quantitative RT-PCR of signature psoriasis transcripts, antibiotic-treatment decreased the following cytokines:
  - KLK6+ mice decreased TNFα (75%, $P=0.02$) and IL-23 (59%, $P=0.004$)
  - IL-17C+ mice decreased IL-17A to undetectable levels ($P<0.001$)
  - KC-Tie2 mice decreased TNFα (33%, $P=0.05$), IL-23 (41%, $P=0.05$) and IL-17A (51%, $P=0.07$).
  - The decreases across all three models aligned with decreases in skin CD4 and CD8+ T cells, and CD11c+ and F4/80+ myeloid cells.

- Conclusion: The findings point to a key role for the microbiome in modulating the TNFα / IL-23 / IL-17A pathway in psoriasis. Further studies are ongoing.

Concerns about psoriasis differ by race: implications for patient-centered goal-setting and counseling.

Junko Takeshita, MD, PhD, MSCE, University of Pennsylvania, Philadelphia, Pennsylvania, United States

- Some data suggest that psoriasis may be more severe and have a greater negative quality-of-life impact on minorities, but little is known regarding the experience of, and concerns about, psoriasis among different racial/ethnic groups.
- This study performed semi-structured interviews of 68 individuals (white N=36, black N=32) with moderate to severe plaque psoriasis, assessing knowledge, experience, beliefs, and attitudes regarding psoriasis. Study characteristics were similar between white and black subjects.
- The team identified "concerns about psoriasis" as an important theme. Across all subjects, major themes included physical symptoms and aesthetic distress, ranging from visual unsightliness to social and emotional isolation.
- In particular, concerns about scarring and disease recurrence were prominent among blacks, whereas concerns about comorbid disease and heritability were prominent among whites.
- Conclusion: The study found that white and black patients with psoriasis had both shared and unique concerns about psoriasis, which is important in considering patient-specific goals and therapies.

Do mental health comorbidities influence patient satisfaction? A population study among U.S. adults with psoriasis.

Charlotte Read, MBBS, BSc, University of Southern California, Los Angeles, California, United States

- This study sought to determine the impact of mental health comorbidities on patients' perception of patient-provider communication quality among U.S. adult patients with psoriasis, using validated instruments and adjusting for socio-demographics and comorbidities.
- The cross-sectional study used the Medical Expenditure Panel Survey (MEPS) data from 2003-2015. Among 7.35 million U.S. adult patients with psoriasis, 73% had no or mild psychological distress, 21% had moderate distress, and 6.0% had severe distress. Additionally, 91% had no or mild-to-moderate depression and 9.0% had severe depression.
- Compared to patients in a good mental health state:
  - Patients with moderate or severe psychological distress were 4.2 times more likely to perceive low-quality patient-provider communication [OR: 4.23 (1.61-11.14); p= 0.004]
  - Patients with moderate and severe depression were 4.6 times more likely to perceive low-quality patient-provider communication [OR: 4.59 (1.89-11.15); p= 0.001].
- Conclusion: Patients' mental health state is associated with their perception of patient-provider communication, a key component of patient satisfaction.

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