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IPC INTERNATIONAL PSORIASIS COUNCIL

PSORIASIS REVIEW

UNDERSTANDING THE IMPACTS OF THE LATEST PSORIASIS RESEARCH

TOP 5 RESEARCH MANUSCRIPTS

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Generalized pustular psoriasis shows dramatic improvement after single dose of monoclonal antibody BI 655130 in phase 1 study

Inhibition of the interleukin-36 pathway for the treatment of generalized pustular psoriasis. Bachelez H, Choon SE, Marrakchi S, et al. *N Engl J Med*. 2019 Mar 7;380(10):981-983. doi: 10.1056/NEJMc1811317.

Biologic therapy for psoriasis may help reduce coronary artery plaque

Coronary artery plaque characteristics and treatment with biologic therapy in severe psoriasis: results from a prospective observational study. Elnabawi YA, Dey AK, Goyal A, et al. *Cardiovasc Res*. 2019 Mar 15;115(4):721-728. doi: 10.1093/cvr/cvz009.

Connecting genetic predisposition to psoriasis with immunological causes may lead to personalized therapies

Combining understanding of immunological mechanisms and genetic variants toward development of personalized medicine for psoriasis patients. Gunter NV, Yap BJM, Chua CLL, Yap WH. *Front Genet*. 2019 May 3;10:395. doi: 10.3389/fgene.2019.00395. eCollection 2019. Review.

Study suggests potential role of IL-17 in inducing hyperglycemia in patients with psoriasis

Hyperglycemia is associated with psoriatic inflammation in both humans and mice. Ikumi K, Odanaka M, Shime H, et al. *J Invest Dermatol*. 2019 Jun;139(6):1329-1338.e7. doi: 10.1016/j.jid.2019.01.029. Epub 2019 Feb 15.

Study investigates optimal therapeutic window of secukinumab to achieve best clinical outcome for patients with psoriasis

Defining a minimal effective serum trough concentration of secukinumab in psoriasis: a step towards personalized therapy. Soenen R, Meulewaeter E, Grine L, et al. *J Invest Dermatol*. 2019 May 5. pii: S0022-202X(19)31504-0. doi: 10.1016/j.jid.2019.04.012. [Epub ahead of print]

PLUS, IN THIS ISSUE:

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SYMPOSIUM REPORT

Dissecting psoriasis: Mechanistic studies in pustular and plaque psoriasis

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IPC is a global network of psoriasis experts, thought leaders, and professionals committed to improving psoriasis care through education, research, and advocacy.

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Welcome

Letter from the President

Happy New Year and welcome to the January 2020 edition of the *IPC Psoriasis Review*.

Here at IPC, we start out 2020 with a new 3-year strategic plan focused on addressing what the World Health Organization describes as the needless suffering of millions of people worldwide who live with uncontrolled psoriasis due to inadequate medical care and treatment.

The IPC 2020-2022 Strategic Plan aims to improve how we care for patients with psoriasis in all parts of the world through key initiatives that:

- address issues that hinder access to effective treatments, timely diagnosis, and optimal care;
- lay the groundwork to individualise medical treatment of psoriasis to each patient;
- expand the knowledge of health care providers to better diagnose, treat, and manage patients.

One of these key initiatives is the IPC psoriasis severity project. On page 26 of this edition of the *Psoriasis Review*, is a synopsis of our recent publication in the *Journal of the American Academy of Dermatology (JAAD)* on psoriasis severity. In this paper, we propose assessing patients as candidates either for topical or systemic therapy based on body surface area (BSA), location of lesions, or failure of topical therapy to control skin symptoms. By foregoing the mild/moderate/severe designations, this new approach simplifies the process of getting patients on the right treatment for their level of disease involvement. We aim to have this new definition of psoriasis severity incorporated in clinical trials as well as in the clinic.

You can learn more about our strategic plan at *psoriasiscouncil.org*. In upcoming editions of the *Psoriasis Review*, I will update you on the status of the plan and how you can participate in this critical work, including the psoriasis severity project.

In the meantime, I invite you explore this issue. The "Top 5" summaries and commentaries, which begin on page 4, bring you recently published studies that detail noteworthy outcomes in specific populations treated with biologics, including how biologic therapy may reduce coronary artery plaque in patients with severe psoriasis.

For those of you who missed the 2019 annual meetings of the European Society for Dermatological Research (ESDR), the European Academy of Dermatology and Venereology (EADV), or the Japanese Society of Investigative Dermatology (JSID), our conference reports that begin on page 10 will get you up to date — no plane ticket necessary.

It's another full year for IPC education programs. Masterclasses, symposia, and more — all designed to help clinicians provide the best care for their patients with psoriasis no matter their location in the world. We hope to see you at one or more of these events, a list of which can be found on page 30.

As always, thank you for being a part of International Psoriasis Council. Here's to a happy and healthy 2020!

Cheers,

Jonathan Barker, MD, FRCP, FRCPath

President, International Psoriasis Council

The Top 5

Our semi-annual review of psoriasis papers with the most impact

EVERY 6 MONTHS, IPC'S BOARD AND COUNCILORS SUGGEST AND VOTE ON ARTICLES THAT MAKE THE GREATEST IMPACT ON PSORIASIS RESEARCH. THE 5 PAPERS THAT RECEIVED THE MOST VOTES FOR ARTICLES PUBLISHED JULY THROUGH DECEMBER 2018 ARE REVIEWED HERE.

*Summaries and commentaries were written by this issue's co-editors, IPC Councilors **Dr. Robert Kalb**, State University of New York at Buffalo School of Medicine, United States, and **Dr. Wayne Gulliver**, Memorial University of Newfoundland, St. John's, Canada.*

1. Generalized pustular psoriasis shows dramatic improvement after single dose of BI 655130 in phase 1 study

Inhibition of the interleukin-36 pathway for the treatment of generalized pustular psoriasis. Bachelez H, Choon SE, Marrakchi S, et al. *N Engl J Med*. 2019 Mar 7;380(10):981-983. doi: 10.1056/NEJMc1811317.

SUMMARY

This was a phase 1, proof-of-concept study of 7 patients with generalized pustular psoriasis (GPP). GPP has been associated with loss-of-function mutations in the interleukin-36 receptor antagonist (IL36RN). The study involved open label treatment with a single intravenous dose of BI 655130, a monoclonal antibody against the interleukin-36 receptor at 10 mg/kg of body weight (Clinical Trials.gov number NCTT02978690). Patients were evaluated using the Generalized Pustular Psoriasis Physician Global Assessment (GPPGA). This was a physician-based assessment of the severity of the pustules, erythema, and scaling of the generalized pustular psoriasis lesions. Each component is scored in a 5-point scale ranging from 0 (least severe) to 4 (most severe) and the average is calculated. Three of the 7 patients had a homozygous IL36RN mutation, one of whom had a heterozygous mutation in caspase recruitment domain family member 14 (CARD 14). Four of the 7 did not have any of the target mutations (IL36RN, CARD 14, and adapter protein family 1 [AP1 S3]). These target mutations have all been associated with GPP and pustular skin diseases. A GPPGA score of 0 or 1 (clear or almost clear skin) was achieved in 5 of the seven patients by week 1 and in all patients by week 4. Pustules were completely cleared in 3 patients within 48 hours after treatment, 5 patients by week 1, and 6 patients by week 2. The efficacy of the single dose of BI 655130 occurred regardless of the presence of the IL36RN mutation.

COMMENTARY

Identifying targeted key signaling pathways in the psoriasis pathogenesis has been amazingly successful in bringing new therapies to market. Since 2015, 6 of the 11 biologic medications now used for treating psoriasis have been approved in the United States. This phase 1 proof-of-concept study shows dramatic improvement in generalized pustular psoriasis (GPP) with a single intravenous infusion of BI 655130, a monoclonal antibody directed against the interleukin-36 (IL-36) receptor. Historically, acute GPP has been treated by other systemic agents with a rapid onset of action such as cyclosporine, infliximab, or, more recently, one of the anti-IL-17 medications such as secukinumab or ixekizumab (secukinumab is approved in Japan for treating GPP). Likely patients without the IL36RN mutation will be shown to have other mutations, which affect the IL-36 pathway. This study demonstrates irrefutable evidence that GPP is associated with the IL-36 pathway and drugs directed against this pathway may become the treatment of choice for this condition. With 11 current biologics available, health care providers want to be able to choose the single agent that will likely be the most effective and safe. The IL-23/IL-17 pathway is currently believed to be the key pathogenic mechanism in psoriasis vulgaris. This pathway plays a role in GPP that accounts for the therapeutic benefit of the anti-IL-17 drugs in this disease. As this is a phase 1 proof of concept, it remains to be determined whether the IL-36 pathway is the key therapeutic pathway for GPP and whether drugs such as BI 655130 will become the treatment of choice. – *Robert Kalb*

2. Biologic therapy for psoriasis may help reduce coronary artery plaque

Coronary artery plaque characteristics and treatment with biologic therapy in severe psoriasis: Results from a prospective observational study. Elnabawi YA, Dey AK, Goyal A, et l. *Cardiovasc Res*. 2019 Mar 15;115(4):721-728. doi: 10.1093/cvr/cvz009. PubMed PMID: 30721933; PubMed Central PMCID: PMC6432047.

SUMMARY

This was a prospective observational study of 290 participants attempting to quantify a reduction in coronary plaque indices by measuring coronary computed tomography angiography (CCTA). The goal was to compare patients treated with biologic therapy versus nonbiologic therapy. A total of 215 patients completed the 1-year follow-up study. A blinded reader quantified total coronary artery plaque burden and plaque subcomponents in the 3 main coronary vessels. Biologic therapy was associated with a 6% reduction in noncalcified plaque burden, a reduction in necrotic core with no effect on fibrous burden. The decrease in noncalcified plaque burden in the biologic treated group was significant compared with the slow plaque progression in the nonbiologic treated group. Limitations of the study included the observational nature, open-label use of therapy, the baseline variation in coronary parameters in the patients, and the lack of knowledge of the progression rate of subclinical atherosclerosis on CCTA in patients with psoriasis. This study demonstrated that biologic therapy in severe psoriasis was associated with favorable modulation of coronary plaque indices by CCTA. These findings highlight the importance of systemic inflammation in coronary artery disease and support further investigation.

COMMENTARY

One of the key unanswered questions in psoriasis is whether our treatments are truly disease-modifying. Will early institution of biologic therapy for psoriasis prevent the development of psoriatic arthritis? Will systemic or biologic therapy for patients with extensive disease decrease the risk for myocardial infarction or other cardiovascular events? Studies to definitively answer these questions based on a decreased risk of death or myocardial infarction are difficult to complete based on the prolonged duration of follow-up required and the expense involved. Studies have investigated whether improvement in surrogate markers of coronary artery disease as evidence that psoriasis treatment may be disease-modifying. Recent papers have examined the benefits of systemic psoriasis therapy in patients utilizing before-and-after fluorodeoxyglucose PET scans. This prospective study measured total coronary artery plaque burden using another surrogate marker, coronary computed tomography angiography (CCTA). Objective data showed an improvement in the biologic versus nonbiologic group. The key issue is whether this improvement in coronary plaque burden measured in this fashion will correlate with an actual decrease in the risk of death/myocardial infarction. Which surrogate marker will become the definitive choice to measure in studies such as these remains to be determined. Does treatment with biologic therapy improve cardiovascular risk in psoriasis? At this point, the current evidence is suggestive and best for the anti-TNF agents. Either way, patients with severe psoriasis need intensive management of their cardiovascular risk factors. Hopefully, the appropriate psoriasis therapy will also aid in decreasing this risk. – *Robert Kalb*

Do you have a study to nominate to IPC's Top 5?
Please email it to editor@psoriasiscouncil.org

3. Connecting genetic psoriasis predisposition to immunological causes may lead to personalized therapies

Combining understanding of immunological mechanisms and genetic variants toward development of personalized medicine for psoriasis patients. Gunter NV, Yap BJM, Chua CLL, Yap WH. *Front Genet*. 2019 May 3;10:395. doi: 10.3389/fgene.2019.00395. eCollection 2019. Review.

SUMMARY

Psoriasis is a multifactorial disease with a complex genetic predisposition. Recent advances in genetics and genomics analyses have provided insights into the relationship between specific genetic predisposition and immunopathological mechanisms. Novel approaches utilizing technologies such as genome-wide association studies (GWAS) have identified single nucleotide polymorphisms, genes, and pathways that are associated with psoriasis. The discovery of these psoriasis-associated signaling pathways has provided opportunities to bridge the gap of knowledge for new psoriatic therapies. This paper highlights how immune functions associated with psoriasis susceptibility loci may contribute to disease pathogenesis in different populations. Understanding the genetic variations and psoriasis and how these may influence the immunologic pathways to cause disease will contribute to the efforts in developing novel and targeted personalized therapies for psoriasis patients.

COMMENTARY

We have been fortunate to treat psoriasis patients in the biologic era. There are now 11 biologic medications approved for treating psoriasis in the United States. The immune pathways associated with psoriasis have been delineated, and treatments directed against tumor necrosis factor alpha, interleukin-17, and interleukin-23 have been dramatically effective with minimal side effects. In an ideal world, health care providers will choose the one biologic agent that will help each individual patient. This paper is an excellent review of genome-wide association studies and the potential application of pharmacogenomics for patients with psoriasis. Current treatments are limited by inter-individual variation in efficacy. Advances in genome-wide association studies can allow researchers to make further specific associations. We are hopeful that psoriasis treatment will be individualized such that the patient will receive the specific treatment that will produce the best long-term control of their disease with a very low risk of adverse events. – *Robert Kalb*

4. Study suggests potential role of IL-17 in inducing hyperglycemia in patients with psoriasis

Hyperglycemia is associated with psoriatic inflammation in both humans and mice. Ikumi K, Odanaka M, Shime H, et al. *J Invest Dermatol*. 2019 Jun;139(6):1329-1338.e7. doi: 10.1016/j.jid.2019.01.029. Epub 2019 Feb 15.

SUMMARY

This study by Ikumi et al from Japan outlines in detail the potential role of IL-17 in inducing hyperglycemia in patients with psoriasis. The researchers used an imiquimod-induced systemic and cutaneous inflammatory mouse model to understand the role of IL-17 in the induction of hyperglycemia. Over a 1-year period, 39 of a 153-patient cohort with A1c levels and Psoriasis Area and Severity Index (PASI) scores were studied. The investigators noted significant correlation between PASI scores and HbA1c. The HbA1c scores were significantly correlated with the erythema component of the PASI score. The authors noted that in 2 cases treated with bath PUVA (ultraviolet light A with psoralen), the patients had clearing of their psoriasis and improvement in HbA1c. These improvements also were associated with a decrease in proinflammatory cytokines including IL-6 and IL-17A. They then went on to investigate patients treated with an anti-IL-17A monoclonal antibody and found HbA1c levels were significantly reduced. The authors did not find a correlation between delta PASI and delta HbA1c, attributing this to optimization of diabetes treatment prior to biologic therapy. To understand the immunopathogenesis of hyperglycemia, psoriasis, and the role of IL-17, investigators were able to show that imiquimod-induced inflammation not only created psoriasis-like lesions but also induced hyperglycemia, confirming this with glucose-tolerance tests. After day 7 of imiquimod exposure, PASI and glucose levels were also significantly higher in the imiquimod-treated mice as compared to the controls. The imiquimod mice had lower insulin levels as compared to control mice. Inflammation induced by DNFB did not induce similar changes in glucose metabolism. Imiquimod-treated mice were not found to be insulin-resistant. No changes were noted in the histology of the pancreas or liver in the imiquimod-treated mice as compared to the control mice. Islet cell function in both the control and imiquimod-treated mice was similar. Mice treated with anti-IL-17A monoclonal antibodies had decreased fasting glucose. The researchers also noted that pancreatic islet cells expressed multiple inflammatory cytokine receptors, including those of the IL-17 receptor family. This suggests that anti-IL-17s may act directly on the pancreatic islet cells and thus improve the hyperglycemia by decreasing inflammation in the islet cells and restoring their function.

COMMENTARY

To paraphrase the Scottish poet Robert Burns, the best-laid plans of mice and men often go awry. This is true in many studies done in animal models that we then try to translate to human disease and therapeutics. In the case of IL-17 and hyperglycemia, the data may indicate otherwise, supporting the theory that IL-17 not only plays an important role in the inflammatory pathway of psoriasis, but may also be important in inducing hyperglycemia that is associated with inflammation or at least psoriatic inflammation. With this information in hand the question is, how do we use it in our day-to-day clinical practice? As we know, many of our patients with psoriasis have diabetes for which we now have some evidence to suggest may be related to psoriasis. We also have a number of patients with severe psoriasis who are prediabetic or are at risk of developing diabetes. Presently, when selecting therapy, we have very few tools to direct us. We rely totally on clinical information — such as, does the patient have psoriatic arthritis, multiple sclerosis, inflammatory bowel disease or hidradenitis suppurativa? — to help guide our biologic selection. It remains to be seen whether this data will be confirmed by a larger study, the Metabolix trial, which is presently ongoing and expected to be completed in 2021. This is a randomized control trial studying secukinumab alone vs secukinumab plus lifestyle intervention in 760 patients with a primary outcome of PASI 90 at 28 weeks. Secondary outcomes include waist circumference, change in HbA1c, and fasting glucose levels at weeks 8, 16, and 28. If the results of the Metabolix study are positive, we may have further guidance to help us select therapies for patients with moderate to severe psoriasis, especially in patients who have the accompanying comorbidity of diabetes or who are at risk of developing it. – *Wayne Gulliver*

5. Study investigates optimal therapeutic window of secukinumab to achieve best clinical outcome for patients with psoriasis

Defining a minimal effective serum trough concentration of secukinumab in psoriasis: A step towards personalized therapy. Soenen R, Meulewaeter E, Grine L, et al. *J Invest Dermatol*. 2019 May 5. pii: S0022-202X(19)31504-0. doi: 10.1016/j.jid.2019.04.012. [Epub ahead of print]

SUMMARY

In this paper authors, Soenen et al from Ghent and Leuven, Belgium, report the results of their pilot study investigating whether C_{trough} levels of the fully humanized anti-IL17A monoclonal antibody secukinumab may help find the optimal therapeutic window in patients with psoriasis who are treated with this biologic. The study used Psoriasis Area and Severity Index (PASI) response with optimal responders having a PASI of < 2 and suboptimal responders having a PASI of > 2. They also studied absolute PASI and C_{trough}. In this patient cohort, the investigators observed significant difference in C_{trough} between optimal and suboptimal responders, as well as significant correlation between secukinumab trough and absolute PASI. Based on these observations, the authors suggest that there is indeed a therapeutic window of secukinumab-treated patients who have moderate to severe psoriasis. The aim of the second part of the study was to find the minimal effective threshold of the therapeutic window, which turned out to be 33.2 µg/ml with the area under the curve of 0.76 having a sensitivity of 78.3 and specificity of 75.6. This gave a positive and negative predictive value of 0.82. Based upon these findings, the authors conclude that using this in-house, sandwich-type, enzyme-linked immunosorbent assay with a secukinumab C_{trough} of 33.2 µg/ml can distinguish optimal responders (i.e. PASI ≤ 2) from suboptimal responders (i.e. PASI ≥ 2). The authors also studied potential confounding factors and found obesity, active smoking, long treatment duration, and previous treatment to be associated with lower secukinumab C_{trough} levels and suboptimal clinical responses.

COMMENTARY

The availability of C_{trough} concentrations in biologic-treated patients who have moderate to severe psoriasis would significantly enhance our ability to optimally manage these patients. We know from real-world and registry data that up to 60% of our patients will require at least one switch of their biologic, and that obesity, previous biologic treatment, and female gender are associated with biologic failure. Presently, therapeutic approach of a biologic failure includes switching, optimization, or re-induction. Many dermatologists opt for switching. In some cases, optimization or re-induction can result in patients regaining clinical response. Without C_{trough} concentration, we are approaching biologic failure blindly and as a result may be prematurely switching patients who might otherwise respond to optimization or re-induction. Our colleagues in gastroenterology have the luxury of obtaining therapeutic drug levels on their patients and, with this information, can make informed decisions on patients' ongoing future therapy. For example, if a patient has optimal therapeutic levels but is not responding, then a switch is the obvious approach. For the patients who have subtherapeutic dose, a re-induction or optimization, i.e., increased drug dose, may allow the patient to regain therapeutic response without switching medication. In the case of patients with psoriasis, remaining on suboptimal therapy for longer than they need to while an optimization or re-induction is ongoing is unacceptable. Thus, we hope that assays can be developed for all biologics so that we can have clear and unambiguous guidelines on how to manage our patients. I do agree with and support the authors' recommendations that optimal responders do not need measurement of C_{trough} and should continue with their therapy. Suboptimal responders should have C_{trough} levels measured, and if they have subtherapeutic C_{trough}, then optimization via dose escalation or shortening of interval, or re-induction should be undertaken. In the suboptimal responders with therapeutic C_{trough} levels, the patient should indeed be switched to another biologic.

– Wayne Gulliver

SYMPOSIUM REPORT

The mechanistic model(s) of psoriasis: Autoimmune and/or autoinflammatory?

IPC SCIENTIFIC SYMPOSIUM OPENS THE 49TH ANNUAL EUROPEAN SOCIETY FOR DERMATOLOGICAL RESEARCH (ESDR) ANNUAL MEETING

By Thomas Scharnitz, *MD*

Dr. Scharnitz is a third-year dermatology resident physician at the University of Michigan Department of Dermatology, United States. He received his medical degree from Pennsylvania State University and completed his intern year in internal medicine at the University of Virginia.

The 49th annual European Society for Dermatological Research (ESDR) meeting held in September in Bordeaux, France, opened with a symposium presented by IPC that featured selected lectures and poster exhibits. Serving as co-chairs for the symposium, "The Mechanistic Model(s) of Psoriasis: Autoimmune and/or Autoinflammatory?" were IPC councilors Michael Gilliet, MD, University of Lausanne, Switzerland; Johann Gudjonsson, MD, PhD, University of Michigan, United States; and Jörg Prinz, MD, Ludwig-Maximillians University, Munich, Germany. Following are summaries of the most significant lectures presented at the symposium.

IPC SYMPOSIUM LECTURES

Autoreactive T cells in psoriasis

Symposium co-chair Jörg Prinz discussed the dynamic field of immunology in psoriasis, including his work on identifying the disease's autoantigen and target.

Biologics have energized the discussion of psoriasis immunology, and we can now define its role in risk-conveying genetic variants. More than 80 contributing variants are identified, including the Th17 pathways involving IL-17/23, pro-inflammatory CARD14 gain-of-function variants, and protective IL-23 receptor loss-of-function variants.[1]

Notably, epistasis between the virtually psoriasis-specific HLA-C*06:02 gene and nonspecific ERAP genes are vital to understanding psoriasis pathogenesis.[2] Proteins encoded by both HLA and ERAP genes are involved in antigen processing and presentation.[3] Numerous publications support the principal role of CD8+ T cells in psoriasis, including CD8 epidermal migration studies,[4,5] CD8-inhibition preventing lesions,[6] CD8 production of IL-21/22,[7] and robust lesional CD8 clonal expansion.[8]

Because T cell receptors (TCRs) recognize innumerable antigens, finding a potential target autoantigen has been challenging. Dr. Prinz's group, first searched for target cells, not antigens, by analyzing TCRs of clonally expanded CD8+ T cells. They found CD8+ T cells reacted against HLA-C*06:02 positive, but not HLA-C*06:02 negative melanocytes. This implicates melanocytes as targets of lesional psoriatic CD8+ T cells and that HLA-C*06:02 mediates this autoimmune response. Peptide analysis also showed that most psoriasis-associated HLA molecules can likely present the same autoantigen, via conserved amino acid motifs.9

To elucidate the epistasis between HLA-C*06:02 and ERAP-1, Dr. Prinz's group created ERAP-1 deficient melanoma cells lines (ERAP-1 -/-). They previously identified that the HLA-C*06:02-presented melanocytic autoantigen, ADAMTS-like protein 5 (ADAMTSL5), stimulates the psoriatic Vα3S1/Vβ13S1 TCR.[9] Now, in ERAP-1 -/-, they discovered that the autoantigenic ADAMTSL5 epitope is ERAP-1 dependent for presentation to HLA-C*06:02, and they identified both ERAP-1 risk (rs30187) and protective (rs26653, rs27044) variants.[10]

REFERENCES

1. Di Meglio P, Villanova F, Napolitano L, et al. The IL23R A/Gln381 allele promotes IL-23 unresponsiveness in human memory T-helper 17 cells and impairs Th17 responses in psoriasis patients. *J Invest Dermatol*. 2013;133(10):2381-2389.

2. Strange A, Capon F, Spencer CC, et al. A genome-wide association study identifies new psoriasis susceptibility loci and an interaction between HLA-C and ERAP1. *Nat Genet*. 2010;42(11):985-90.

3. Neefjes J, Jongsma ML, Paul P, Bakke O. Towards a systems understanding of MHC class I and MHC class II antigen presentation. *Nat Rev Immunol*. 2011;11(12):823-36.

4. Paukkonen et al. *Arch Derm Res*. 1992:284:375-379

5. Conrad C, Boyman O, Tonel G, et al. Alpha1beta1 integrin is crucial for accumulation of epidermal T cells and the development of psoriasis. *Nat Med*. 2007;13(7):836-42.

6. Di Meglio P, Villanova F, Navarini AA, et al. Targeting CD8(+) T cells prevents psoriasis development. *J Allergy Clin Immunol*. 2016;138(1):274-276.e6.

7. Ortega C, Fernández-a S, Carrillo JM, et al. IL-17-producing CD8+ T lymphocytes from psoriasis skin plaques are cytotoxic effector cells that secrete Th17-related cytokines. *J Leukoc Biol*. 2009;86(2):435-43.

8. Chang JC, Smith LR, Froning KJ, et al. CD8+ T cells in psoriatic lesions preferentially use T cell receptor V beta 3 and/or V beta 13.1 genes. *Proc Natl Acad Sci USA*. 1994;91(20):9282-6.

9. Arakawa A, Siewert K, Stöhr J, et al. Melanocyte antigen triggers autoimmunity in human psoriasis. *J Exp Med*. 2015;212(13):2203-12.

10. Ombrello MJ, Kastner DL, Remmers EF. Endoplasmic reticulum-associated amino-peptidase 1 and rheumatic disease: genetics. *Curr Opin Rheumatol*. 2015;27(4):349-56.

Lipid-driven T cell responses in psoriasis

Chyung-Ru Wang, PhD, Northwestern University Feinberg School of Medicine, Chicago, Illinois, United States, focused on the effect of hyperlipidemia (HLD) on a unique T cell population that recognizes self-lipid antigens presented by the CD1 molecule.

Lipid antigens are preferentially bound to CD1 molecules, which are virtually non-polymorphic cell-surface glycoproteins.[1,2] Human CD1 locus encodes 5 CD1 proteins, divided into 3 groups. A large portion of the group-1 CD1 (CD1-a/b/c) T cells appear to be autoreactive (from 0.3-10%) and new experiments show CD1a/b autoreactive T cell frequency is increased in patients with psoriasis.

Dr. Wang studied human-CD1-transgenic mice (hCD1Tg) and found that dendritic cells express high levels of all group-1 CD1 isoforms. Their double-transgenic mouse model, called HJ1Tg (hCD1Tg x CD1b autoreactive TCR), showed no overt autoimmunity, recognized self-lipid antigen, and secreted pro-inflammatory cytokines.[3,4]

Further crossing the HJ1Tg with HLD-prone ApoE-deficient mice (hDC1Tg/HJ1Tg/ApoE-/-) induced severe clinical dermatitis and increased both neutrophilic and T cell infiltrates (via flow cytometry) and lesional IL-17/22/23 (via mRNA profiles). Polyclonal stimulation caused IL-17A but not IFN-gamma production and anti-IL-17A treatment led to significant improvement.[5]

Many lipids were increased in the ApoE-/- transgenic mice. Polar lipids (most potent) and phospholipids (most abundant) enhanced HJ1Tg T cell cytokine production, suggesting that both activate the HJ1Tg T cells. A final cross with LDL receptor deficient (LDLr-/-) mice demonstrated HLD alone can drive skin inflammation; skin findings were similar to the ApoE-/- mutants. Additionally, autoreactive T cell receptors appear specific, as DN1Tg microbial-antigen specific LDLr-/- mutants did not develop dermatitis. (Lin et al, unpublished)

Dr. Wang's HLD model showed that preferential accumulation of the lipid in the skin drives maturation and differentiation of dendritic cells, ultimately causing IL-17A secretion, which leads to inflammation, neutrophil infiltration, and keratinocyte proliferation.[6]

REFERENCES

1. Porcelli SA. Bird genes give new insights into the origins of lipid antigen presentation. *Proc Natl Acad Sci USA*. 2005;102(24):8399-400.

2. Adams EJ. Lipid presentation by human CD1 molecules and the diverse T cell populations that respond to them. Curr Opin Immunol. 2014;26:1-6.

3. Felio K, Nguyen H, Dascher CC, et al. CD1-restricted adaptive immune responses to Mycobacteria in human group 1 CD1 transgenic mice. *J Exp Med*. 2009;206(11):2497-509.

4. Li S, Choi HJ, Felio K, Wang CR. Autoreactive CD1b-restricted T cells: a new innate-like T cell population that contributes to immunity against infection. *Blood*. 2011;118(14):3870-8.

5. Bagchi S, He Y, Zhang H, et al. CD1b-autoreactive T cells contribute to hyperlipidemia-induced skin inflammation in mice. *J Clin Invest*. 2017;127(6):2339-2352.

6. Bagchi, S, Genardi, S. & Wang, C.-R. Linking CD1-restricted T cells with autoimmunity and dyslipidemia: Lipid levels matter. *Front Immunol*. 2018; 9:1616.

The role of self in the innate immune system

Symposium co-chair Michel Gilliet presented his research on the innate immune system's role in psoriasis, focusing on the antimicrobial peptide autoantigen LL37.

Infiltration of type I interferon (IFN)-producing plasmacytoid dendritic cells (pDCs) precedes psoriasis plaque formation and is the crucial early event. Type I IFNs drive T cell expansion and IL-17 production and blocking the pDCs prevents psoriasiform lesions in a murine xenotransplant model.[1]

Dr. Gilliet's group found that endogenous antimicrobial peptides, such as the keratinocyte-produced and neutrophil-released LL37, activates pDCs and is greatly overexpressed in psoriatic plaques.[2] LL37/extracellular DNA complexes enter pDC endosomes to activate type I IFN production and co-localize with TLR-9. Human DNA alone cannot achieve this. LL37 complexes have optimal, intricate DNA spacing (3-4 nm), allowing interdigitation of the TLR-9 molecule which induces high levels of type I IFNs.[3]

Dr. Gilliet's group also found presence of LL37-specific CD4 and CD8 T cells in 40% of patients correlating with higher Psoriasis Area and Severity Index (PASI). Treatment with TNF blockers

in 2 patients with severe disease demonstrated a decrease in LL37-specific T cells (quantitative) and their skin homing receptors (qualitative, in CCR6, CLA, CCR10*) along with the clinical improvement.[4] Altogether, these data suggest that LL37 it is both a stimulator of innate immunity and a T cell autoantigen, suggesting a pathogenic role in psoriasis.

Unstable, acute psoriasis lesions are type I IFN-skewed, whereas stable, chronic lesions are characterized by Th17 inflammation. Through phenotype profiling, the two pathways can be distinctly separated. Similarly, paradoxic psoriasis (triggered by anti-TNF therapy) is driven by type I IFN, but in contrast to psoriasis, the dendritic cells cannot mature to provide T cell stimulation. In fact, the paradoxic psoriasis lesions displayed massive amounts of pDCs, excessive levels of type I IFNs, and a paucity of epidermal CD8+ T cells.[5] Paradoxic psoriasis is therefore an innate type I IFN-driven side effect that is T cell-independent and does therefore not recur in the absence of anti-TNF.

REFERENCES

1. Nestle FO, Conrad C, Tun-kyi A, et al. Plasmacytoid predendritic cells initiate psoriasis through interferon-alpha production. *J Exp Med*. 2005;202(1):135-43.

2. Lande R, Gregorio J, Facchinetti V, et al. Plasmacytoid dendritic cells sense self-DNA coupled with antimicrobial peptide. *Nature*. 2007;449(7162):564-9.

3. Schmidt NW, Jin F, Lande R, et al. Liquid-crystalline ordering of antimicrobial peptide-DNA complexes controls TLR9 activation. *Nat Mater*. 2015;14(7):696-700.

4. Lande R, Botti E, Jandus C, et al. The antimicrobial peptide LL37 is a T cell autoantigen in psoriasis. *Nat Mater*. 2014;5:5621.

5. Conrad C, Di domizio J, Mylonas A, et al. TNF blockade induces a dysregulated type I interferon response without autoimmunity in paradoxical psoriasis. *Nat Commun*. 2018;9(1):25.

IL-36 pathway dysregulation in pustular psoriasis and psoriasis vulgaris

IPC Director Hervé Bachelez, MD, PhD, of Saint Louis University Hospital, Paris, France, discussed the scientific studies supporting the functional role and potential therapeutic pathway of interleukin (IL)-36 in psoriasis.

All pustular psoriasis variants are molecularly similar and are seemingly monogenic, supporting an autoinflammatory nature.[1] On chromosome 2 in the IL-1 family cluster, IL-36RN codes for IL-36 receptor antagonist (IL-36Ra).[2] The IL-36 receptor (IL-36R) is expressed strongly on many cells; in pustular phenotypes, the keratinocytes, as well as innate and adaptive immune cells, are the likely targets.[3]

The balance between IL-36 agonists and antagonists is critical, and IL-36 aberrancies lead to unregulated inflammation. Genetic mutation screening shows the prevalence of IL-36RN mutations is much higher in generalized pustular psoriasis (GPP) than palmoplantar pustulosis (PPP), with still some uncertainty about the pathogenicity of IL-36RN heterozygous mutations in pustular variants.[4] In transgenic mice, increased IL-36α agonist skin expression favors psoriasis-like inflammation and combination with a IL-36RN gene knock-out (+/- then -/-) caused increasing severity in skin inflammation with GPP-like features.[5] In "deficiency of the IL-36Ra" (DITRA) studies, a homozygous missense IL-36RN mutation, L27P, showed zero IL-36Ra protein expression via Western blotting,[6] while other mutations lead to reduced protein and/or functionality, usually found in PPP, while another missense mutation, V2F, impaired IL-36RN cleavage and IL36Ra biological activity, leading to neutrophilic skin influx and GPP.[7]

Psoriasis vulgaris (PV) and generalized pustular psoriasis (GPP) are genetically different but some striking gene similarities do exist, and upregulated IL-36 genes appear in both.[8,9] Notably, in PV-mouse models, treating with anti-IL36 receptor monoclonal antibody (anti-Rp2) in xenografted mice[10] and invalidation by knock-out of IL-36 receptor in the imiquimod mouse model[11] prevented cutaneous inflammation.

Though pustular phenotypes are severe and debilitating, targeted IL-36 therapies appear promising. In a recent proof-of-concept phase 1 study, 7 patients with acute GPP received 1 single infusion of spesolimab (anti-IL-36R humanized monoclonal antibody), with dramatic response via reduction in Generalized Pustular Psoriasis Area and Severity Index (GPPASI) by 79.8% by week 4 in all patients, which was sustained for 20 weeks. This first-in-human-disease-published study paves the way for ongoing phase 2 studies in different forms of pustular psoriasis.

REFERENCES

1. Marian AJ. Molecular genetic studies of complex phenotypes. *Transl Res*. 2012;159(2):64-79.

2. Marrakchi S, Guigue P, Renshaw BR, et al. Interleukin-36-receptor antagonist deficiency and generalized pustular psoriasis. *N Engl J Med*. 2011;365(7):620-8.

3. Lian LH, Milora KA, Manupipatpong KK, Jensen LE. The double-stranded RNA analogue polyinosinic-polycytidylic acid induces keratinocyte pyroptosis and release of IL-36γ. *J Invest Dermatol*. 2012;132(5):1346-53.

4. Twelves S, Mostafa A, Dand N, et al. Clinical and genetic differences between pustular psoriasis subtypes. *J Allergy Clin Immunol*. 2019;143(3):1021-1026.

5. Blumberg H, Dinh H, Trueblood ES, et al. Opposing activities of two novel members of the IL-1 ligand family regulate skin inflammation. *J Exp Med*. 2007;204(11):2603-14.

6. Tauber M, Bal E, Pei XY, et al. IL36RN Mutations Affect Protein Expression and Function: A Basis for Genotype-Phenotype Correlation in Pustular Diseases. *J Invest Dermatol*. 2016;136(9):1811-1819.

7. Bal E, Lim AC, Shen M, et al. Mutation in IL36RN impairs the processing and regulatory function of the interleukin-36-receptor antagonist and is associated with DITRA syndrome. *Exp Dermatol*. 2017;

8. Swindell WR, Remmer HA, Sarkar MK, et al. Proteogenomic analysis of psoriasis reveals discordant and concordant changes in mRNA and protein abundance. *Genome Med*. 2015;7(1):86.

9. Mahil SK, Catapano M, Di meglio P, et al. An analysis of IL-36 signature genes and individuals with knockout mutations validates IL-36 as a psoriasis therapeutic target. *Sci Transl Med*. 2017;9(411)

10. Johnston A, Xing X, Guzman AM, et al. IL-1F5, -F6, -F8, and -F9: a novel IL-1 family signaling system that is active in psoriasis and promotes keratinocyte antimicrobial peptide expression. *J Immunol*. 2011;186(4):2613-22.

11. Rabeony H, Pohin M, Vasseur P, et al. IMQ-induced skin inflammation in mice is dependent on IL-1R1 and MyD88 signaling but independent of the NLRP3 inflammasome. *Eur J Immunol*. 2015;45(10):2847-57.

AP1S3 and CARD14 deregulation in psoriasis and psoriasis-like disorders

Geneticist Francesca Capon, PhD, Guy's Hospital, London, United Kingdom, presented her research on 2 gene alleles conferring risk for pustular psoriasis variants.

Genetic analyses of rare forms of psoriasis provide important insights into the biology of the disease, even if the number of patients harboring mutations is small.

Though not highly penetrant, Adaptor Related Protein Complex 1 Subunit Sigma 3 (AP1S3, encoding a subunit of the AP1 complex) alleles carry substantial increase in pustular psoriasis risk, with increased frequency of F4C and R33W alleles in cases compared to controls.[1] Dr. Capon's lab studied 2 sisters, 1 with severe and 1 with mild phenotype, with shared IL36RN mutation. The severely affected sister also carried an AP1S3 allele mutation, suggesting AP1S3 can affect the phenotypic expression of the IL36RN mutation.[2] Caspase recruitment family member 14 (CARD14) is abundant in keratinocytes and promotes NF-kB activation in response to decoiling by inflammatory stimuli. Gain-of-function (GoF) CARD14 mutations, causing constitutive NFKB activation, are implicated in psoriasis vulgaris, familial pityriasis rubra pilaris, and generalized pustular psoriasis. These activating mutations all map near the "coiled-coil inactivating region," and they all reduce free cytoplasmic CARD14 and increase insoluble aggregates that mediate NF-kB.[3-5]

Loss-of-function (LoF) mutations manifest quite differently. Dr. Capon's group analyzed CARD14 sequence in 160 unrelated cases of palmoplantar psoriasis (PPP), revealing 9 rare, non-synonymous, likely damaging variants with deleterious potential (p = 0.0006), and 2 variants of deleterious potential (E442K, R682W) with increased frequency in individuals with PPP (p= 0.05). Dissimilar to GoF variants, these LoF variants dispersed across the entire length of the gene. Two variants (positions 591 and 597) were in close proximity to an LoF variant (593) causing atopic dermatitis, further suggesting palmar plantar pustulosis variants are LoF.[6]

REFERENCES

1. Setta-Kaffetzi N, Simpson MA, Navarini AA, et al. AP1S3 mutations are associated with pustular psoriasis and impaired Toll-like receptor 3 trafficking. *Am J Hum Genet*. 2014;94(5):790-7.

2. Mahil SK, Twelves S, Farkas K, et al. AP1S3 Mutations Cause Skin Autoinflammation by Disrupting Keratinocyte Autophagy and Up-Regulating IL-36 Production. *J Invest Dermatol*. 2016;136(11):2251-2259.

3. Jordan CT, Cao L, Roberson ED, et al. PSORS2 is due to mutations in CARD14. *Am J Hum Genet*. 2012;90(5):784-95.

4. Fuchs-telem D, Sarig O, Van steensel MA, et al. Familial pityriasis rubra pilaris is caused by mutations in CARD14. *Am J Hum Genet*. 2012;91(1):163-70.

5. Berki DM, Liu L, Choon SE, et al. Activating CARD14 Mutations Are Associated with Generalized Pustular Psoriasis but Rarely Account for Familial Recurrence in Psoriasis Vulgaris. *J Invest Dermatol*. 2015;135(12):2964-2970.

6. Peled A, Sarig O, Sun G, et al. Loss-of-function mutations in caspase recruitment domain-containing protein 14 (CARD14) are associated with a severe variant of atopic dermatitis. *J Allergy Clin Immunol*. 2019;143(1):173-181.e10.

IPC SYMPOSIUM POSTER PRESENTATIONS

A selective tyrosine kinase 2 inhibitor, BMS-986165, decreases the transcriptional signature of Th17 , Interleukin-12, and interferon pathways in skin of psoriasis: results from a phase 2 trial

Ian Catlett, PhD, Bristol-Myers Squibb, Princeton, New Jersey, United States

- Psoriasis is dependent upon the IL-23/Th17 pathway and is thought to be initiated through plasmacytoid dendritic cell activation and induction of Type 1 interferons (IFNs).
- BMS-986165 is an oral, selective tyrosine kinase 2 (TYK2) inhibitor that binds the pseudokinase domain (not the conserved kinase domain as in JAK inhibitors), blocking signal transduction of IL-23, IL-12, and Type 1 IFNs in cellular assays.

- In this randomized, controlled, dose-ranging phase 2 trial in 267 patients with moderate to severe psoriasis, all BMS-986165 dose groups (except 3 mg every other day) achieved superiority vs placebo in the patients achieving PASI-75 after 12 weeks; 3 mg every other day 9.1%, 3 mg daily 39%, 3 mg BID 69%, 6 mg BID 67%, and 12 mg daily 75%, vs placebo 7% (all with $p < 0.001$).
- In an optional substudy (n = 37), lesional vs non-lesional biopsies identified significant changes in post-treatment differentially expressed genes (DEGs), and transcriptomic analysis showed BMS-986165 treatment decreased IL-23/Th17 and IFN pathway markers.
- In summary, BMS-986165 has promising efficacy and a distinct selectivity and transcription signature profile, warranting further investigation.

CARD14 variants are associated with palmar plantar pustulosis

Athanasios Niaouris, MSc, King's College London, United Kingdom

- Caspase recruitment domain containing protein 14 (CARD14) is an adaptor protein that mediates NF-kB signaling in keratinocytes. Gain-of-function variants have been reported to cause psoriasis vulgaris and generalized pustular psoriasis.
- The group investigated the involvement of CARD14 in palmar plantar pustulosis (PPP) by analyzing CARD14 changes in 160 PPP cases via whole-exome profiles (n = 103) or Sanger sequencing in the CARD14 region (n = 57).
- Eleven (11) rare likely-deleterious variants were identified, and a burden test found a significant association between the changes and PPP (odds ratio: 2.5, 95% CI 1.39 to 4.65; $p = 0.0023$).
- Single-marker analysis uncovered a low-frequency allele with deleterious potential (E422K) that occurred more frequently in cases compared to controls (OR 1.7; 95% CI 1.07 to 2.69; $p = 0.025$).
- The variants were distributed across the entire gene length and mapped outside of the known gain-of-function mutation hotspot termed 'coiled-coil'.
- These findings support involvement of CARD14 in the pathogenesis of PPP, and suggest that risk alleles may act through loss-of-function mechanisms.

Circulating microRNAs in extracellular vesicles from plasma as potential biomarkers for psoriatic arthritis in patients with psoriasis

Lorenzo Pasquali, PhD candidate, Karolinska University Hospital, Stockholm, Sweden

- Psoriatic arthritis (PsA) is a challenging diagnosis that develops in 30% of patients with psoriasis, and currently there are no reliable molecular markers for PsA.
- MicroRNAs (miRNA; short noncoding regulatory RNAs) are present in circulation packaged into extracellular vesicles (EVs) and have been proposed as biomarkers for various diseases.
- Plasma samples were obtained from both patients with cutaneous-only psoriasis (PsC) and PsA with a 10-year disease duration.
- In the discovery cohort (PsC n = 15, PsA n = 14), RNA sequencing identified 19 significant differentially-expressed plasma EV-miRNAs between PsA and PsC. In the validation-phase (PsC = 29, PsA n = 28), 41 selected EV-miRNAs demonstrated significantly lower levels of plasma EV let-7b-5p and miR30e-5P via qPCR array.
- Decreased miRNA levels were associated with the presence of PsA; ROC analysis revealed an AUC of 0.68 (95% CI 0.53-0.83) for let-7b-5p and 0.69 (95% CI 0.55-0.84) for mi-R-30e-5p.
- In summary, circulating EV-microRNAs may serve as biomarkers for arthritis in patients with psoriasis.

Distinct gene expression signatures differentiate clinical response to ustekinumab compared to adalimumab in psoriasis

Ashley Rider, MSc, Newcastle University, Newcastle Upon Tyne, United Kingdom

- This study aimed to identify gene expression signatures predicting response to 2 commonly prescribed biologics, adalimumab (TNF-α inhibitor) and ustekinumab (IL-12/23 inhibitor).
- Bulk RNAseq analysis was performed on skin biopsies of lesional and nonlesional skin of 82 psoriasis patients initiating treatment with adalimumab or ustekinumab at baseline, 1 week, and 12 weeks. Clinical response was defined by percentage reduction in PASI at week 12 compared to baseline (ΔPASI).
- Differentially expressed genes (DEGs) were identified, principal component analysis showed that tissue > time > PASI were

main drivers of transcriptome variation, and ingenuity pathway analysis exhibited common regulatory signals in both drug cohorts.

- Downregulation of the NF-κB and p38 pathways showed stronger associations to absolute PASI with adalimumab, compared to the ustekinumab. Downregulation of interferon (IFN) signaling at baseline was strongly associated with ΔPASI with ustekinumab, but not adalimumab. Downregulation of IFN signaling at weeks 1 and 12 associated with ΔPASI in both drug cohorts.
- This study highlights the potential for biologic therapy stratification for use in psoriasis, based on gene expression at baseline and early in treatment.

miR-378a is overexpressed in psoriasis keratinocytes and potentiates IL-17A-mediated inflammatory responses

Enikö Pivarcsi Sonkoly, MD, PhD, Karolinska Institutet, Stockholm, Sweden

- The Th17-produced cytokine IL-17 is central to psoriasis pathogenesis. IL-17 targets keratinocytes (KCs) and induces further inflammatory pathways.
- This study identified small-RNAs in KCs from lesional and non lesional skin in psoriasis patients using next-generation RNA sequencing. mi-R378a was found to be differentially expressed in psoriasis KCs and was significantly upregulated in lesional KCs.
- qPCR expression analysis from cultured primary human KCs showed that IL-17A, but not other cytokines, significantly induced miR-378a expression.
- The NF-κB pathway inhibitor BAY 11-7082 prevented induction of miR-378a by IL-17A, implying that miR-378a is regulated through the NF-κB pathway.
- Overexpression of miR-378a in primary KCs potentiated IL-17A-mediated induction of inflammatory mediators in keratinocytes, such as CCL20, IL-8, and hBD2.
- The findings suggest that upregulation of miR-378a in lesional KCs enhances their inflammatory response to IL-17A, thereby amplifying IL-17A-mediated inflammation. Inhibiting mi-R378a may have therapeutic potential in psoriasis.

Treatment with spesolimab, an anti-interleukin-36 receptor antibody, in patients with generalized pustular psoriasis, is associated with the downregulation of biomarkers linked to innate, Th1/17 and neutrophilic pathways

Christian Thoma, MD, Boehringer Ingelheim International GmbH, Biberach, Germany

- Generalized pustular psoriasis (GPP) is a rare life-threatening disease characterized by recurrent, diffuse, pustular rashes with a strong genetic linkage to the IL-36 pathway.
- In this phase 1, proof-of-concept trial, the anti-IL36R monoclonal antibody spesolimab (BI-655130) was administered to 7 GPP patients with moderate to-severe flares as a single, open-label intravenous dose of 10mg/kg.
- Spesolimab treatment resulted in rapid and sustained clinical improvement; by week 4, all 7 patients achieved GPP Physician Global Assessment (GPPGA) score of 0 or 1 (clear or almost clear), and mean percent improvement from baseline in the Generalized Pustular Psoriasis Area and Severity Index (GPPASI) was 79.8%. Both scores were maintained at 20 weeks.
- Analysis of blood and lesional skin biomarkers revealed strong downregulation of neutrophil-focused pathogenic pathways of GPP patients after treatment.
- No serious adverse events were observed. Further clinical investigation is required to determine the clinical efficacy, duration of effect, and adverse events associated with the drug.

References: 1. ILUMYA™ [package insert]. Princeton, NJ: Sun Pharmaceuticals, Inc. **2.** Data on File. Sun Pharmaceutical Industries, Inc. **3.** Rigopoulos D, Ioannides D, Chaidemenos G, et al. Patient preference study for different characteristics of systemic psoriasis treatments (Protimisis). *Dermatol Ther*. 2018;31(3):e12592.

Brief Summary of Prescribing Information for ILUMYA™ (tildrakizumab-asmn)
ILUMYA™ (tildrakizumab-asmn) injection, for subcutaneous use
See package insert for full Prescribing Information

INDICATIONS AND USAGE ILUMYA™ is indicated for the treatment of adults with moderate-to-severe plaque psoriasis who are candidates for systemic therapy or phototherapy.

CONTRAINDICATIONS
ILUMYA is contraindicated in patients with a previous serious hypersensitivity reaction to tildrakizumab or to any of the excipients *[see Warnings and Precautions]*.

WARNINGS AND PRECAUTIONS
Hypersensitivity: Cases of angioedema and urticaria occurred in ILUMYA treated subjects in clinical trials. If a serious hypersensitivity reaction occurs, discontinue ILUMYA immediately and initiate appropriate therapy *[see Adverse Reactions]*.

Infections: ILUMYA may increase the risk of infection. Although infections were slightly more common in the ILUMYA group (23%), the difference in frequency of infections between the ILUMYA group and the placebo group was less than 1% during the placebo-controlled period. However, subjects with active infections or a history of recurrent infections were not included in clinical trials. Upper respiratory infections occurred more frequently in the ILUMYA group than in the placebo group *[see Adverse Reactions]*.

The rates of serious infections for the ILUMYA group and the placebo group were ≤0.3%. Treatment with ILUMYA should not be initiated in patients with any clinically important active infection until the infection resolves or is adequately treated.

In patients with a chronic infection or a history of recurrent infection, consider the risks and benefits prior to prescribing ILUMYA. Instruct patients to seek medical help if signs or symptoms of clinically important chronic or acute infection occur. If a patient develops a clinically important or serious infection or is not responding to standard therapy, monitor the patient closely and consider discontinuation of ILUMYA until the infection resolves *[see Adverse Reactions]*.

Pretreatment Evaluation for Tuberculosis: Evaluate patients for tuberculosis (TB) infection prior to initiating treatment with ILUMYA. Initiate treatment of latent TB prior to administering ILUMYA. In clinical trials, of 55 subjects with latent TB who were concurrently treated with ILUMYA and appropriate TB prophylaxis, no subjects developed active TB (during the mean follow-up of 56.5 weeks). One other subject developed TB while receiving ILUMYA. Monitor patients for signs and symptoms of active TB during and after ILUMYA treatment. Consider anti-TB therapy prior to initiation of ILUMYA in patients with a past history of latent or active TB in whom an adequate course of treatment cannot be confirmed. Do not administer ILUMYA to patients with active TB infection.

Immunizations: Prior to initiating therapy with ILUMYA, consider completion of all age appropriate immunizations according to current immunization guidelines. Avoid the use of live vaccines in patients treated with ILUMYA. No data are available on the response to live or inactive vaccines.

ADVERSE REACTIONS
The following serious adverse reactions are discussed elsewhere in the labeling:
Hypersensitivity Reactions *[see Warnings and Precautions]*
Infections *[see Warnings and Precautions]*

Clinical Trial Experience
Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in the clinical trials of a drug cannot be directly compared to rates in the clinical trials of another drug and may not reflect the rates observed in practice.

In clinical trials, a total of 1994 subjects with plaque psoriasis were treated with ILUMYA, of which 1083 subjects were treated with ILUMYA 100 mg. Of these, 672 subjects were exposed for at least 12 months, 587 for 18 months, and 469 for 24 months.

Data from three placebo-controlled trials (Trials 1, 2, and 3) in 705 subjects (mean age 46 years, 71% males, 81% white) were pooled to evaluate the safety of ILUMYA (100 mg administered subcutaneously at Weeks 0 and 4, followed by every 12 weeks [Q12W]) *[see Clinical Studies]*.

Placebo-Controlled Period (Weeks 0-16 of Trial 1 and Weeks 0-12 of Trials 2 and 3)
In the placebo-controlled period of Trials 1, 2, and 3 in the 100 mg group, adverse events occurred in 48.2% of subjects in the ILUMYA group compared to 53.8% of subjects in the placebo group. The rates of serious adverse events were 1.4% in the ILUMYA group and 1.7% in the placebo group.

Table 1 summarizes the adverse reactions that occurred at a rate of at least 1% and at a higher rate in the ILUMYA group than in the placebo group.

Table 1: Adverse Reactions Occurring in ≥1% of Subjects in the ILUMYA Group and More Frequently than in the Placebo Group in the Plaque Psoriasis Trials 1, 2, and 3

Adverse Reaction	ILUMYA 100 mg (N=705) N (%)	Placebo (N=355) N (%)
Upper respiratory infections*	98 (14)	41 (12)
Injection site reactions†	24 (3)	7 (2)
Diarrhea	13 (2)	5 (1)

* Upper respiratory infections include nasopharyngitis, upper respiratory tract infection, viral upper respiratory tract infection, and pharyngitis.

† Injection site reactions include injection site urticaria, pruritus, pain, reaction, erythema, inflammation, edema, swelling, bruising, hematoma, and hemorrhage.

During the placebo-controlled period of Trials 1, 2, and 3, adverse reactions that occurred at rates less than 1% but greater than 0.1% in the ILUMYA group and at a higher rate than in the placebo group included dizziness and pain in extremity.

Specific Adverse Reactions
Hypersensitivity Reactions
Cases of angioedema and urticaria occurred in ILUMYA-treated subjects in clinical trials *[see Warnings and Precautions]*.

Infections
Infections were slightly more common in the ILUMYA group. The difference in frequency of infections between the ILUMYA group (23%) and the placebo group was less than 1% during the placebo-controlled period. The most common (≥1%) infections were upper respiratory infections. The rates of severe infections for the ILUMYA group and the placebo group were ≤0.3%.

Safety Through Week 52/64
Through Week 52 (Trials 1 and 3) and Week 64 (Trial 2), no new adverse reactions were identified with ILUMYA use and the frequency of the adverse reactions was similar to that observed during the placebo-controlled period.

Immunogenicity
As with all therapeutic proteins there is the potential for immunogenicity. The detection of antibody formation is highly dependent on the sensitivity and specificity of the assay. Additionally, the observed incidence of antibody (including neutralizing antibody) positivity in an assay may be influenced by several factors including assay methodology, sample handling, timing of sample collection, concomitant medications, and underlying disease. For these reasons, comparison of incidence of antibodies to tildrakizumab in the studies described below with the incidences of antibodies in other studies or to other products may be misleading.

Up to Week 64, approximately 6.5% of subjects treated with ILUMYA 100 mg developed antibodies to tildrakizumab. Of the subjects who developed antibodies to tildrakizumab, approximately 40% (2.5% of all subjects receiving ILUMYA) had antibodies that were classified as neutralizing. Development of neutralizing antibodies to tildrakizumab was associated with lower serum tildrakizumab concentrations and reduced efficacy.

DRUG INTERACTIONS
Live Vaccinations
Avoid use of live vaccines in patients treated with ILUMYA *[see Warnings and Precautions]*.

USE IN SPECIFIC POPULATIONS
Pregnancy: Risk Summary
Limited available data with ILUMYA use in pregnant women are insufficient to inform a drug associated risk of adverse developmental outcomes. Human IgG is known to cross the placental barrier; therefore, ILUMYA may be transferred from the mother to the fetus. An embryofetal developmental study conducted with tildrakizumab in pregnant monkeys revealed no treatment-related effects to the developing fetus when tildrakizumab was administered subcutaneously during organogenesis to near parturition at doses up to 159 times the maximum recommended human dose (MRHD). When dosing was continued until parturition, a small increase in neonatal death was observed at 59 times the MRHD *[see Data]*. The clinical significance of this nonclinical finding is unknown.

All pregnancies have a background risk of birth defect, loss, or other adverse outcomes. The background risk of major birth defects and miscarriage for the indicated population is unknown. In the U.S. general population, the estimated background risk of major birth defects and miscarriage in clinically recognized pregnancies is 2-4% and 15-20%, respectively.

Data: *Animal Data*
In an embryofetal developmental study, subcutaneous doses up to 300 mg/kg tildrakizumab were administered to pregnant cynomolgus monkeys once every two weeks during organogenesis to gestation day 118 (22 days from parturition). No maternal or embryofetal toxicities were observed at doses up to 300 mg/kg (159 times the MRHD of 100 mg, based on AUC comparison). Tildrakizumab crossed the placenta in monkeys.

In a pre- and postnatal developmental study, subcutaneous doses up to 100 mg/kg tildrakizumab were administered to pregnant cynomolgus monkeys once every two weeks from gestation day 50 to parturition. Neonatal deaths occurred in the offspring of one control monkey, two monkeys at 10 mg/kg dose (6 times the MRHD based on AUC comparison), and four monkeys at 100 mg/kg dose (59 times the MRHD based on AUC comparison). The clinical significance of these nonclinical findings is unknown. No tildrakizumab-related adverse effects were noted in the remaining infants from birth through 6 months of age.

Lactation: Risk Summary
There are no data on the presence of tildrakizumab in human milk, the effects on the breastfed infant, or the effects on milk production. Human IgG is known to be present in human milk. Tildrakizumab was detected in the milk of monkeys *[see Data]*.

The developmental and health benefits of breastfeeding should be considered along with the mother's clinical need for ILUMYA and any potential adverse effects on the breastfed child from ILUMYA or from the underlying maternal condition.

Pediatric Use: Safety and effectiveness of ILUMYA in pediatric patients (<18 years of age) have not been established.

Geriatric Use: A total of 1083 subjects were exposed to ILUMYA 100 mg during Phase 2 and 3 trials. A total of 92 subjects were 65 years or older, and 17 subjects were 75 years or older. Although no differences in safety or efficacy were observed between older and younger subjects, the number of subjects aged 65 and over is not sufficient to determine whether they respond differently from younger subjects.

OVERDOSAGE: In the event of overdosage, monitor the patient for any signs or symptoms of adverse reactions and administer appropriate symptomatic treatment immediately.

PATIENT COUNSELING INFORMATION: Advise the patient and/or caregiver to read the FDA-approved patient labeling (Medication Guide).

Instruct patients and/or caregivers to read the Medication Guide before starting ILUMYA therapy and to reread the Medication Guide each time the prescription is renewed. Advise patients of the potential benefits and risks of ILUMYA.

Hypersensitivity
Advise patients to seek immediate medical attention if they experience any symptoms of serious hypersensitivity reactions *[see Warnings and Precautions]*.

Infections
Instruct patients of the importance of communicating any history of infections to the doctor and contacting their doctor if they develop any symptoms of infection *[see Warnings and Precautions]*.

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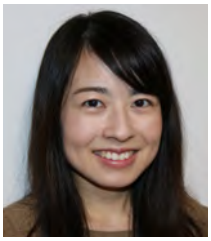
SUN PHARMA

SYMPOSIUM REPORT

Dissecting psoriasis: Mechanistic studies in pustular and plaque psoriasis

A SCIENTIFIC SYMPOSIUM PRESENTED BY IPC AT THE 2019 JAPANESE SOCIETY FOR INVESTIGATIVE DERMATOLOGY (JSID) ANNUAL MEETING

By Kana Masuda-Kuroki, MD



Dr. Masuda-Kuroki is a clinical fellow in the Tokyo Medical University Hospital dermatology department in Japan. She obtained her medical degree from the Ehime University School of Medicine in Ehime, Japan, in 2011 and a PhD in dermatology from Ehime University's Graduate School of Medicine in 2019.

Researchers have made significant advances in recent years in understanding the mechanisms and genetics of psoriasis. That was the focus of a symposium presented by IPC's Research Committee at the Japanese Society for Investigative Dermatology (JSID) annual meeting in Aomori, Japan, in early November. Discussions explored mechanistic models, epidemiological data, genetic studies, and stratified medicine using a multi-omic approach.

Co-chairs for the program, "Dissecting Psoriasis: Mechanistic Studies in Pustular and Plaque Psoriasis" were IPC Board President Professor Jonathan Barker, St John's Institute of Dermatology, King's College, London, and IPC Board Member Professor Chris Griffiths, University of Manchester, United Kingdom. The symposium featured 5 faculty presentations providing additional insights into disease mechanisms that contribute to psoriasis and psoriasis-related diseases.

Generalized pustular psoriasis genetic model

IPC Board Member Dr. Hervé Bachelez, Saint Louis University Hospital, Paris, France, began the symposium with a discussion of the immunogenetic studies on generalized pustular psoriasis (GPP). He stated that GPP and psoriasis vulgaris are genetically different.

The generalized pustular psoriasis genetic model is unlike that of psoriasis vulgaris. GPP has a complex phenotype similar to cardiac hypertrophy, which Dr. Bachelez used as an example of a complex phenotype, as well as various other potential determinants of phenotypic expression of cardiac hypertrophy, such as genetics, genomics, and external environmental factors as reported by Marian AJ et al.[1]

The pioneering identification of homozygous or composite heterozygous loss-of-function mutations of the IL36RN gene in generalized pustular psoriasis by Marrakchi et al[2] and Onoufriadis et al[3] unveiled the key pathogenic role of the deregulation of the Interleukin (IL) -36 pathway in GPP, due to impairment of the IL-36 receptor antagonist (IL-36RA) structure and function. Jordan et al[4] and then Sugiura et al[5] demonstrated that gain-of-function mutations of the CARD14 gene, such as c.526G>C (p.Asp176His), may also cause generalized pustular psoriasis, with psoriasis vulgaris, in the Japanese cohort. Setta-Kaffetzi et al reported AP1S3, is the gene targeted by causal abnormalities in pustular psoriasis.[6] Furthermore, Garlanda et al demonstrated the IL-36 pathway as a new key actor in innate immune skin responses.[7]

Identification of causal genetic abnormalities allows a better stratification of patients and the recognition of genotype-phenotype correlations. Twelves et al demonstrated that IL36RN mutations are more frequent in GPP and acrodermatitis continua of Hallopeau (ACH) than in those with palmoplantar pustulosis (PPP) and impacts on the age of disease onset.[8] Furthermore, Tauber et al reported that IL36RN mutations differently impact IL36Ra protein expression and function, which ultimately affects disease severity.[9]

Recently, functional genetics and proteomics studies about the human six-transmembrane epithelial antigen of the prostate (STEAP) protein family have been reported. STEAP1 and STEAP4 co-localize with IL36-γ and correlate with IL-1 family. Bal et al reported that missense mutation of IL36RN, encoding immature IL36RA, leads to GPP and DITRA (deficiency of the IL-36 receptor [IL-36R] antagonist) skin disease, showing that the cleavage step of the immature into the bioactive form is mandatory for the homeostasis of the IL-36 pathway.[10]

On the other hand, although IL36RN is not mutated in psoriasis vulgaris patients, the IL-36 pathway is deregulated in psoriasis skin lesions, suggesting that IL-36 might play a proinflammatory role across the different psoriasis subtypes, whatever is the genetic background.

The genetic investigations of an orphan, "extreme" phenotypic variant of psoriatic disease spectrum has already led to groundbreaking therapeutic innovative studies. Likewise, 8 years after the founder publication of the first identification of a causal abnormality in GPP, Bachelez et al reported in 2019 in the same journal that spesolimab, a monoclonal antibody against IL-36R, reduces the severity of GPP through phase 1 study in acute GPP.[11]

In summary, generalized pustular psoriasis is an informative model for the skin immune system, and pustular psoriasis and psoriasis vulgaris are genetically different.

Pathomechanisms in palmoplantar pustulosis

Dr. Masamoto Murakami, dermatology associate professor, Ehime University Graduate School of Medicine, Japan, presented informative palmoplantar pustulosis studies and questioned whether PPP is a psoriasis-related disease or a localized type of pustular psoriasis.

Palmoplantar pustulosis (PPP) has the following phenotypes: vesicle, pustule with scale, and erythema. The disease concept of PPP was first reported in 1930. Barber's palmoplantar pustulosis (PPP) is a form of localized pustular psoriasis, affecting the palmar and plantar surfaces.[12] In 1934, Andrews et al reported several cases that presented recalcitrant pustules on palms and soles.[13] The next year, Andrews et al named these eruptions "pustular bacterids of the hands and feet."[14] Now this condition is regarded as a psoriasis-related disease or a localized type of pustular psoriasis in Western countries. But in Japan, several reports consider it to be a distinct entity and that co-existence of PPP and psoriasis is rare.[15] Therefore, PPP is called "palmoplantar pustulosis" in Japan, but "palmoplantar psoriasis" outside of Japan.

Dr. Murakami reported on various studies on the mechanisms of PPP. He observed that PPP vesicles are first composed in the acrosyringium and contain the sweat antimicrobial peptides hCAP-18/LL-37 and dermcidin.[16] Furthermore, the level of IL-8 mRNA decreased significantly upon stimulation of PPP vesicles, with depletion of endogenous hCAP-18/LL-37 by affinity chromatography (dep-PPP-VF).[17] These reports suggest that PPP-VF contains the proteinase required for LL-37 processing and also may directly upregulate IL-8 in lesional keratinocytes, in turn contributing to the subsequent inflammation of PPP lesional skin. In his report, Dr. Murakami showed that TLN-58, which is an additional hCAP18 processing form, was found in the lesional vesicles of PPP.[18] This additional form could be involved in the continued inflammation in PPP lesions.

In closing, Dr. Murakami demonstrated abnormal scale formation with PPP vesicle/pustule. Kaneko et al reported over-expression of kallikrein (KLK) related peptidases in palmoplantar pustulosis.[19] Dr. Murakami summarized that the PPP mechanism on acrosyringium might be related to the LL37, IL-8, and over-expression of KLK.

Autoinflammatory keratinization disorders

Dr. Kazumitsu Sugiura, dermatology professor, Fujita Health University, Toyoake, Japan, discussed diseases associated with autoinflammatory keratinization disorders, deficiency of interleukin 36 receptor antagonist, CARD14-mediated psoriasis familial keratosis lichenoides chronica and gene mutations.

Autoinflammatory keratinization disorders (AIKD) include deficiency of interleukin 36 receptor antagonist (DITRA), CARD14-mediated psoriasis (CAMPS), and familial keratosis lichenoides chronica (FKLC).[20]

Caused by IL36RN mutation, DITRA is associated with generalized pustular psoriasis (GPP) and impetigo. Dr. Sugiura observed DITRA in impetigo herpesiform,[21] varicella-zoster-virus-associated GPP with heterozygous IL36RN mutation,[22] and amoxicillin-induced GPP in monozygotic twins.[23] Therefore, DITRA is a life-threatening monogenic autoinflammatory disease caused by loss-of-function mutations in the IL36RN gene.

CARD14-mediated psoriasis (CAMPS) is caused by CARD14 mutation. CARD14 is considered to activate NFkB (nuclear factor kappa-light-chain-enhancer of activated B cells). Dr. Sugiura reported CARD14 variant c.526G>C (p.Asp176His) is a significant risk factor for GPP with psoriasis vulgaris.[5] Berki et al and Mossner et al reported that p.Asp176His variant is also associated with GPP and pityriasis rubra pilaris (PRP).[24,25]

Griffiths et al first suggested that PRP can be classified into 5 types that differ from each other on the basis of clinical features, age of onset, and prognosis.[26] Recently, Takeuchi et al reported PRP type V is an autoinflammatory keratinization disorder by CARD14 mutations.[27] Mellet et al demonstrated that CARD14 gain-of-function causes psoriasis-like eruption.[28]

Dr. Sugiura's group also reported that familial keratosis lichenoides chronica (FKLC) is caused by NLRP1 mutation, which activates inflammasome to secrete IL-1b and IL-18. Dr. Sugiura concluded that GPP, PRP, and lichen planus are included in autoinflammatory keratinization disorders, and that these disorders include DITRA, CAMPS, and FKLC. In the future, a greater number of inflammatory skin diseases that have unknown mechanisms may be also included in AIKD.

Genetics of plaque psoriasis and implications for stratification

IPC President Professor Jonathan Barker discussed studies that demonstrated a relationship between genetics and psoriasis.

Studying the genetic architecture of a disease such as psoriasis makes it possible to understand disease susceptibility, identify key primary biological pathways (causal biology) (genome-wide association studies [GWAS] of IL-23, exome array of TYK2), predict disease trajectories (risk factors for psoriatic arthritis, causal association with obesity), and, when combined with other '-omic' analyses, lead to stratification of disease by phenotype and outcome (IL-36RN and GPP, HLA 06:02, and biologic outcome).

Heritability accounts for 60-70% risk of psoriasis. In genetic studies, Caucasian and Chinese Hans have been most studied. There is significant overlap, but also some differences. HLA-C 06:02 (HLA-Cw6), is the major genetic risk factor for psoriasis vulgaris with a genetic effect greater than all other loci combined.[29]

Genomewide association studies translate pathobiology to therapeutics. Dand et al demonstrated that variants within IFIH1 (encoding an innate antiviral receptor, MDA5) and TYK2 (encoding a Janus kinase) play significant roles in type I interferon (IFN) and IL-23 production and signaling.[30]

Bowes et al reported HLA-C*06:02 is not associated with psoriatic arthritis.[31] Furthermore, Patrick et al introduced a computational pipeline for predicting psoriatic arthritis among psoriasis patients using data from 6 cohorts with >7,000 genotyped psoriatic arthritis and psoriasis vulgaris patients without arthritis.[32] Potential genetic differences between psoriasis and psoriatic arthritis are postulated to be in regulatory elements.[30]

Recent studies reveal association between body mass index (BMI) and risk of psoriasis. Budu-Aggrey et al provided evidence that higher BMI leads to a higher risk of psoriasis.[33] Moreover, Ogawa et al identified a causal link for obesity and risk of psoriasis.[34] These studies support the prioritization of therapies and lifestyle interventions aimed at controlling weight for the prevention or treatment of this skin disease.

Genetic study can also provide valuable data in target validation. Cook et al discussed the results of a comprehensive longitudinal review of small-molecule drug projects to establish a framework based on the 5 most important technical determinants of project success and pipeline quality.[35] Drug targets with genetic evidence of involvement in disease biology had a two-fold increase chance of success.

Stratifying outcome: A multi-omic approach

IPC Board Member Professor Christopher Griffiths presented the stratifying outcome of a multi-omic approach to various phenotypes of psoriasis.

In the United Kingdom, psoriasis affects about 2% of the population, and the onset age is before 40 in most cases. Almost 55% of cases of early-onset psoriasis are associated with HLA Cw 0602. There are important comorbidities, including psoriatic arthritis (30%), depression (30%), inflammatory bowel disease, cardiovascular diseases, and obesity.

Various biologics have been developed and used for psoriasis, including anti-IL-12/23p40 (ustekinumab), anti-IL-23p19 (tildrakizumab, guselkumab and risankizumab), anti-IL-17A (secukinumab and ixekizumab), anti-IL-17R (brodalumab), and a variety that target tumor necrosis factor, such as etanercept, infliximab and adalimumab. In the United Kingdom, apart from infliximab, these are used equally as first-line treatments after conventional therapy failure or unsuitability.

Stratified medicine is based on identifying subgroups of patients with distinct mechanisms of disease (disease endotype) or particular responses to treatments (drug response endotype). This method allows researchers to identify and develop treatments that are effective for particular groups of patients. Stratified medicine aims to take trial-and-error out of treatment and make it more targeted. Ultimately, it will ensure that the right patient gets the right treatment at the right time.[36]

Wilkinson et al reported that adalimumab levels in the blood early in the course of treatment predict response at 6 months in psoriasis.[37] Moreover, Tsakok et al reported that early ustekinumab levels predict response in psoriasis.[38] Dand et al demonstrated HLA-Cw6+ve psoriasis patients have a faster and greater Psoriasis Area and Severity Index (PASI) 90 response to ustekinumab compared to those who are HLA-Cw6-ve.[39]

The British Association of Dermatologists' Biologics and Immunomodulators Register (BADBIR) is a long-term pharmacovigilance register of patients with psoriasis in 164 dermatology departments in the United Kingdom and Ireland who are treated with biologics, small molecules, or conventional systemic therapies. It has close to 19,000 registrations of whom a third have donated DNA and/or serial serum samples. Recent work using machine learning — latent class mixed modeling — has identified 4 trajectories of response to biologics using BADBIR data.[40-43]

In closing, Dr. Griffiths introduced a framework for multi-omic prediction of treatment response to biologics therapy for psoriasis.[44] The study provides both an analytical framework and empirical basis to estimate power for larger studies, specifically the ongoing United Kingdom Psoriasis Stratification to Optimise Relevant Therapy (PSORT) academic-industrial consortium. PSORT is using clinical, genetic, and immune biomarkers to attempt to predict the response of patients with psoriasis to biologic therapies.

REFERENCES

1. Marian AJ. Molecular genetic studies of complex phenotypes. *Transl Res*. 2012 Feb;159(2):64-79. doi: 10.1016/j.trsl.2011.08.001. Epub 2011 Aug 31. Review.

2. Marrakchi S, Guigue P, Renshaw BR, et al. Interleukin-36-receptor antagonist deficiency and generalized pustular psoriasis. *N Engl J Med*. 2011 Aug 18;365(7):620-628.

3. Onoufriadis A, Simpson MA, Pink AE, et al. Mutations in IL36RN/IL1F5 are associated with the severe episodic inflammatory skin disease known as generalized pustular psoriasis. *Am J Hum Genet*. 2011 Sep 9;89(3):432-7. doi: 10.1016/j.ajhg.2011.07.022. Epub 2011 Aug 11.

4. Jordan CT, Cao L, Roberson ED, et al. Rare and common variants in CARD14, encoding an epidermal regulator of NF-kappaB, in psoriasis. *Am J Hum Genet*. 2012 May 4;90(5):796-808. doi: 10.1016/j.ajhg.2012.03.013. Epub 2012 Apr 19.

5. Sugiura K, Muto M, Akiyama M. CARD14 c.526G>C (p.Asp176His) is a significant risk factor for generalized pustular psoriasis with psoriasis vulgaris in the Japanese cohort. *J Invest Dermatol*. 2014; 134: 1755-1757.

6. Setta-Kaffetzi N, Simpson MA, Navarini AA, et al. AP1S3 mutations are associated with pustular psoriasis and impaired Toll-like receptor 3 trafficking. *Am J Hum Genet*. 2014; 94: 790-7.

7. Garlanda C, Dinarello CA, Mantovani A. The interleukin-1 family: back to the future. *Immunity*. 2013 Dec 12;39(6): 1003-1018.

8. Twelves S, Mostafa A, Dand N, et al. Clinical and genetic differences between pustular psoriasis subtypes. *J Allergy Clin Immunol*. 2019 Mar; 143(3):1021-1026.

9. Tauber M, Bal E, Pei XY, et al. IL36RN mutations affect protein expression and vunction: a basis for genotype-phenotype correlation in pustular diseases. *J Invest Dermatol*. 2016; Sep;136(9): 1811-1819.

10. Bal E, Lim AC, Shen M, et al. Mutation in IL36RN impairs the processing and regulatory function of the interleukin-36-receptor antagonist and is associated with DITRA syndrome. *Exp Dermatol*. 2019 Oct;28(10): 1114-1117.

11. Bachelez H, Choon SE, Marrakchi S, et al. Inhibition of the interleukin-36 pathway for the treatment of generalized pustular psoriasis. *N Engl J Med*. 2019 Mar 7; 380(10):981-983.

12. Barber HW. Pustular Psoriasis. *Proc R Soc Med*. 1930 Oct 23(12): 1637.

13. Andrews G, Birkman FW, Kelly RJ. Recalcitrant pustular eruptions of the palms and soles. *Arch Dermatol Syphilol*. 1934; 29(4): 548-563.

14. Andrews G, Machacek GF. Pustular bacterids of the hands and feet. *Arch Dermatol Syphilol*. 1935;32:837-847.

15. Uehara M, Ofuji S. The morphogenesis of pustulosis palmaris et plantaris. *Arch Dermatol*. 1974 April;109(4):518-520.

16. Murakami M, Ohtake T, Horibe Y, et al. Acrosyringium is the main site of the vesicle/pustule formation in palmoplantar pustulosis. *J Invest Dermatol*. 2010 Aug;130(8):2010-2016.

17. Murakami M, Kaneko T, Nakatsuji T, et al. Vesicular LL-37 contributes to inflammation of the lesional skin of palmoplantar pustulosis. *PloS One*. 2014; 9(10):e110677. Published online 2014 Oct 16.

18. Murakami M, Kameda K, Tsumoto H, et al. TLN-58, an additional hCAP18 processing form, found in the lesion vesicle of palmoplantar pustulosis in the skin. *J Invest Dermatol*. 2017 Feb; 137(2):322-331.

19. Kaneko T, Murakami M, Kishibe M, et al. Over-expression of kallikrein related peptidases in palmoplantar pustulosis. *J Dermatol Sci*. 2012 July;67(1):73-76.

20. Akiyama M, Takeichi T, McGrath JA , Sugiura K. Autoinflammatory keratinization diseases. *J Allergy Clin Immunol*. 2017 Dec;140: 1545-1547.

21. Sugiura K, Oiso N, Iinuma S, et al. IL36RN mutations underlie impetigo herpetiformis. *J Invest Dermatol*. 2014 Sep;134(9): 2472-2474.

22. Sugiura K, Uchiyama R, Okuyama R, Akiyama M. Varicella zoster virus-associated generalized pustular psoriasis in a baby with heterozygous IL36RN mutation. *J Am Acad Dermatol*. 2014 Nov;71(5):e216-218.

23. Sugiura K, Shoda Y, Akiyama M. Generalized pustular psoriasis triggered by amoxicillin in monozygotic twins with compound heterozygous IL36RN mutations: comment on the article by Navarini et al. *J Invest Dermatol*. 2014 Feb;134: 578-579.

24. Berki DM, Liu L, Choon SE, et al. Activating CARD14 mutations are associated with generalized pustular psoriasis but rarely account for familial recurrence in psoriasis vulgaris. *J Invest Dermatol*. 2015 Dec;135: 2964-2970.

25. Mossner R, Frambach Y, Wilsmann-Theis D, et al. Palmoplantar pustular psoriasis is associated with missense mariants in CARD14, but not with loss-of-function mutations in IL36RN in European patients. *J Invest Dermatol*. 2015 Oct; 135(10):2538-2541.

26. Griffiths WA. Pityriasis rubra pilaris. *Clin Exp Dermatol*. 1980 Mar;5(1): 105-112.

27. Takeichi T, Sugiura K, Nomura T, et al. Pityriasis rubra pilaris type V as an autoinflammatory disease by CARD14 mutations. *JAMA Dermatol*. 2017 Jan 1;153(1):66-70.

28. Mellett M, Meier B, Mohanan D, et al. CARD14 gain-of-function mutation alone is sufficient to drive IL-23/IL-17-mediated psoriasiform skin inflammation in vivo. *J Invest Dermatol*. 2018 Sept;138(9):2010-2023.

29. Tsoi LC, Stuart PE, Tian C, et al. Large scale meta-analysis characterizes genetic architecture for common psoriasis associated variants. *Nat Commun*. 2017 May 23;8:15382.

30. Dand N, Mucha S, Tsoi LC, et al. Exome-wide association study reveals novel psoriasis susceptibility locus at TNFSF15 and rare protective alleles in genes contributing to type I IFN signalling. *Hum Mol Gen*. 2017 Nov 1;26(21):4301-4313.

31. Bowes J, Ashcroft , Dand N, et al. Cross-phenotype association mapping of the MHC identifies genetic variants that differentiate psoriatic arthritis from psoriasis. *Ann Rheum Dis*. 2017 Oct;76(10):1774-1779.

32. Patrick MT, Stuart PE, Raja K, et al. Genetic signature to provide robust risk assessment of psoriatic arthritis development in psoriasis patients. *Nat Commun*. 2018 Oct 9;9(1):4178.

33. Budu-Aggrey A, Brumpton B, Tyrell J, et al. Evidence of a causal relationship between body mass index and psoriasis: A mendelian randomization study. *PLoS Med*. 2019 Jan;16(1) :e1002739.

34. Ogawa K, Stuart PE, Tsoi LC, et al. A transethnic mendelian randomization study identifies causality of obesity on risk of psoriasis. *J Invest Dermatol*. 2019 Jun;139(6):1397-1400.

35. Cook D, Brown D, Alexander R, et al. Lessons learned from the fate of AstraZeneca's drug pipeline: a five-dimensional framework. *Nat Rev Drug Disc*. 2014 Jun;13(6):419-431.

36. Hood L, Friend SH. Predictive, personalized, preventive, participatory (P4) cancer medicine. *Nat Rev Clin Oncol*. 2011 Mar; 8(3):184-187.

37. Wilkinson N, Tsakok T, Dand N, et al. Defining the therapeutic range for adalimumab and predicting response in psoriasis: a multicenter prospective observational cohort study. *J Invest Dermatol*. 2019 Jan;139(1):115-123.

38. Tsakok T, Wilson N, Dand N, et al. Association of serum ustekinumab levels with clinical response in psoriasis. *JAMA Dermatol*. 2019;155(11):1235-1243.

39. Dand N, Duckworth M, Baudry D, et al. HLA-C*06:02 genotype is a predictive biomarker of biologic treatment response in psoriasis. *J Allergy Clin Immunol*. 2019 June;143(6):2120-2130.

40. Warren RB, Brnabic A, Saure D, et al. Matching-adjusted indirect comparison of efficacy in patients with moderate-to-severe plaque psoriasis treated with ixekizumab vs. secukinumab. *Br J Dermatol*. 2018 May;178(5):1064-1071.

41. Warren RB, Reich K, Langley RG, et al. Secukinumab in pregnancy: outcomes in psoriasis, psoriatic arthritis and ankylosing spondylitis from the global safety database. *Br J Dermatol*. 2018 Nov;179(5):1205-1207.

42. Yiu ZZN, Ashcroft DM, Evans I, et al. Infliximab is associated with an increased risk of serious infection in patients with psoriasis in the U.K. and Republic of Ireland: results from the British Association of Dermatologists Biologic Interventions Register (BADBIR). *Br J Dermatol*. 2019 Feb;180(2):329-337.

43. Warren RB, Marsden A, Tomenson B, et al. Identifying demographic, social and clinical predictors of biologic therapy effectiveness in psoriasis: a multicentre longitudinal cohort study. *Br J Dermatol*. 2019 May;180(5): 1069-1076.

44. Foulkes AC, Watson DS, Carr DF, et al. A framework for multi-omic prediction of treatment response to biologic therapy for psoriasis. *J Invest Dermatol*. 2019 Jan;139(1): 100-107.

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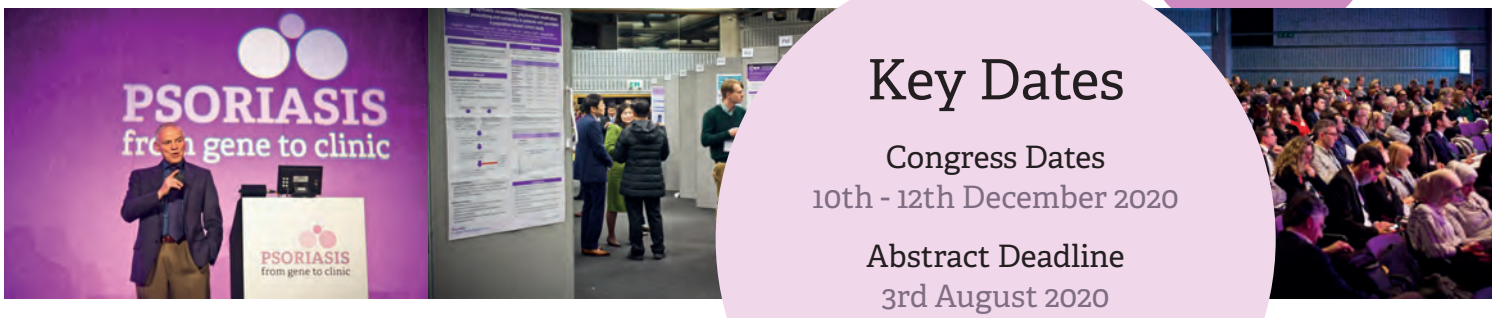

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EVENTS

IPC symposium explores challenging psoriasis cases at World Congress of Dermatology

As part of the 24th World Congress of Dermatology held in June in Milan, Italy, the IPC presented a symposium that addressed "hot topics and challenging cases in psoriasis," with a focus on pustular and pediatric psoriasis, the use of biosimilars, and treating patients in underserved areas. IPC President Jonathan Barker, St John's Institute of Dermatology, United Kingdom, served as the program's chair. Faculty for the program and topics on which they spoke were IPC councilors Hérve Bachelez, Saint Louis University Hospital, Paris, France, "Treating rare forms of psoriasis including pustular;" Lars Iversen, Aarhus University Hospital, Denmark, "Preparing for biosimilars;" Kelly Cordoro, University of California, United States, "Challenges of treating pediatric psoriasis;" and Omid Zagari, Shahid Beheshti University of Medical Sciences, Tehran, Iran, "Personalized care in underserved areas of the world." In a second part of the symposium, Professor Iversen, Dr. Cordoro, and Dr. Zagari presented challenging cases related to their respective topics: biosimilars, pediatric psoriasis, and treating the disease in underserved areas. Video lectures from this symposium are available at *bit.ly/VideoLectures*.

IPC at EADV: 'Hot topics' symposium includes disease severity, drug survival

Biosimilars, disease severity, drug survival, and systemic therapies were the main topics discussed at a satellite symposium presented by IPC during the 28th Congress of the European Academy of Dermatology and Venereology (EADV) in Madrid, Spain, in October. IPC Councilors Catherine Smith, St John's Institute of Dermatology, United Kingdom, and Bruce Strober, Central Connecticut Dermatology, United States, were the program chairs. Program faculty and their presentations were IPC councilors Lone Skov, University of Copenhagen, Denmark, "Drug survival and sequential use of biologics;" Tiago Torres, Abel Salazar Institute of Biomedical Sciences, Porto, Portugal, "The use of biosimilars in psoriasis;" and Professor Smith, "Update on methotrexate." In a second session, titled "Practical Approaches," Professors Skov and Torres, along with Dr. Robert Strohal, Hospital Feldkirch, Austria, presented and discussed challenging psoriasis cases. In a final session, Dr. Strober spoke about classifying disease severity. Find a report of the congress by 2019 IPC Fellow DeePak Balak, MD, MSC, at *bit.ly/EADV2019*. Video lectures from IPC's symposium are available at *bit.ly/VideoLectures*.

Faculty for IPC's symposium at the World Congress of Dermatology held in Milan, Italy, in June 2019 are, from left, Jonathan Barker, United Kingdom; Omid Zargari, Iran; Kelly Cordoro, United States; Hérve Bachelez, France; and Lars Iversen, Denmark.

Leading the sessions at IPC's satellite symposium at the EADV congress in October were, from left, Bruce Strober, United States; Robert Strohal, Austria; Lone Skov, Denmark; Tiago Torres, Portugal; and Catherine Smith, United Kingdom.

IPC presents Masterclasses in India and Austria

Chennai, India, and Vienna, Austria, were the locations for 2 Masterclasses presented by IPC earlier this year. Masterclasses represent IPC's commitment to expanding its global outreach and provide a comprehensive approach to treating psoriasis. They are designed for dermatologists and others who want to expand and enhance their expertise in treating this disease, particularly in underserved regions.

In Chennai, IPC experts presented lectures, panel discussions, and case-based sessions on a variety of topics, including the pathogenesis of psoriasis, new and emerging therapies, and how health care providers can advocate for their patients. Other topics included an overview of psoriasis and its comorbidities, the role of cytokines and potential targets, treatment goals, nonbiologic systemic agents, biologics, long-term psoriasis management, the complexities of diagnosis and treatment, and managing the disease and is comorbidities in women and children. IPC Councilor Murlidhar Rajagopalan, Chennai, was the program's chair. Serving as faculty were Councilors Hérve Bachelez, Paris, France, and, Alan Menter, Texas, United States, as well as Abir Saraswat, a dermatology consultant at Indushree Skin Clinic in Lucknow, India.

Designed for dermatologists who care for patients in Europe, the 2-day IPC Masterclass in Vienna, held in November, covered topics that included phenotypes and assessment of psoriasis and psoriatic arthritis; pustular psoriasis; a focus on the psoriasis comorbidities metabolic syndrome and mental health; the use of topicals, standard systemics and biolgoics; paradoxical reactions to biologics; and workshops that examined challenging

More than 2 dozen health care providers attended IPC's Masterclass in Chennai, India, in April 2019. Seated in the front row are, from left, program chair Murlidhar Rajagopalan and faculty members Alan Menter and Abir Saraswat.

Representing IPC as program chairs and faculty were, from left, IPC Chief Medical Officer Peter van de Kerkof, the Netherlands, and IPC councilors April Armstrong, United States; Georg Stingl, Vienna; and Errol Prens, the Netherlands.

psoriaisis cases. IPC Chief Medical Officer Peter van de Kerkhof of Amsterdam, the Netherlands, and IPC Councilor Georg Stingl of Vienna, were the program chairs. Faculty were IPC Councilors April Armstrong, California, United States, and Errol Prens, Rotterdam, the Netherlands.

In 2020, IPC will present its first Masterclass program in Asia during the 45th Regional Conference of Dermatology (RCD) to be held in Bangkok, Thailand, in Februrary, and in Asunción, Paraguay, in April, in conjunction with the Annual Meeting of Latin American Dermatologists (RADLA).

IPC Think Tank meets in Lisbon

More than 50 IPC councilors and board members and 25 representatives of IPC's corporate partners attended IPC's 2019 Think Tank meeting held in December in Lisbon, Portugal. The Think Tank is an annual event in which IPC councilors and corporate sponsors gather to discuss pressing global challenges in treating and understanding psoriasis. The Lisbon meeting's full-day scientific program included lectures by experts on significant psoriasis topics as they relate to IPC's updated strategic plan. IPC Councilor Jörg Prinz, Germany, delivered the session's keynote lecture on the topic, "Hunting the elusive psoriasis antigen(s)." Councilors who made presentations and the topics they addressed included: "Challenges in introducing biologics in the developing world," Mahira El Sayed, Egypt; "Biologic drug survivability," Lone Skov, Denmark; "Therapeutic drug monitoring and personalized dosing of biologics," Catherine Smith, United Kingdom; "Challenges in assessing severity and outcomes," Matthias Augustin, Germany; "Immune mechanisms in pustular forms of psoriasis," Johann Gudjonsson, United States; and "Disease severity," Bruce Strober, United States. Guest lecturer Professor Sara Brown of the University of Dundee School of

Medicine, Scotland, discussed the topic, "Are obesity and psoriasis linked? How to assess causality." IPC Board President Jonathan Barker, United Kingdom, opened the session and presented an update of the organization's strategic plan. Also attending the meeting were the recently named 2019 IPC International Fellows Romina Contreras, MD, Paraguay; Deepak MW Balak, MD, PhD, MSC, the Netherlands; and Rebecca Nguyen, MB, BS, FACD, Australia. They were introduced during the session by Board Member Claudia de la Cruz, Chile.

PROJECTS

New Global Psoriasis Atlas website offers prevalence data

Researchers, policymakers, health care providers, people who live with the disease, and anyone else interested in gaining a greater understanding of psoriasis now have a valuable, data-rich resource: the recently launched Global Psoriasis Atlas (GPA) website at *globalpsoriasisatlas.org*.

Created in 2016, the GPA is a collaboration of the IPC and 2 other leading global organizations — the International Federation of Psoriasis Associations (IFPA) and the International League of Dermatological Societies (ILDS). With the long-term goal of establishing a comprehensive database that documents the global burden of psoriasis, the GPA is gathering data that will help fill gaps in knowledge of the disease and provide a better understanding of how psoriasis occurs in different groups of people.

The new website features data on the prevalence of psoriasis in adults and children, health care statistics, and personal stories from patients with psoriasis. This information will help raise greater awareness of treatment alternatives available worldwide and provide comparisons among countries. The atlas will be updated annually, said IPC Board Member Chris Griffiths, University of Manchester, United Kingdom, who is the project's director.

Leading the organization's working groups are IPC councilors Darren Ashcroft, also of the University of Manchester, and Matthias Augustin, University Medical Center Hamburg-Eppendorf, Hamburg, Germany.

Psoriatic disease gets a voice at UN health care meeting

Psoriasis and psoriatic arthritis were among the health conditions to receive global attention at the United Nations High-Level Meeting on Universal Health Coverage that took place in New York City on September 23. Representatives from the International Federation of Psoriasis Associations (IFPA), based in Stockholm, Sweden, joined forces with more than 100 worldwide health-related organizations to call for universal access to health care. The meeting defined universal health coverage as "all people, regardless of their ability to pay, should have access to the health care they need, when and where they need it, without financial hardship."

"The achievement of universal health coverage is the primary way to reduce the burden of disease for those suffering from chronic, incurable, noncommunicable conditions, such as psoriasis and psoriatic arthritis," said IPFA's statement to the General Assembly as part of the meeting. "We strongly support the efforts to strengthen primary health care and we encourage the involvement of multiple stakeholders, including patient associations, and innovative health care solutions."

On September 24, IPFA also organized an event at the Harvard Club of New York in connection with the United Nations High Level Meeting. The session focused on health workforce and noncommunicable disease management, featuring psoriasis as an example of noncommunicable disease that needs coordination between primary and specialized care.

PUBLICATIONS

JAAD publishes IPC consensus paper on proposal to recategorize psoriasis severity

Recategorization of psoriasis severity: Delphi consensus from the International Psoriasis Council. Strober B, Ryan C, van de Kerkhof P, et al.; International Psoriasis Council Board Members and Councilors. *J Am Acad Dermatol*. 2019 Aug 16. doi: 10.1016/j.jaad.2019.08.026. [Epub ahead of print]

The prestigious *Journal of the American Academy of Dermatology (JAAD)* has published an IPC consensus paper detailing a proposed recategorization of psoriasis severity.

Previous methods of determining psoriasis severity and subsequent treatment focused on identifying patients as mild, moderate, or severe, as determined by BSA (body surface area) with active psoriasis or by PASI (Psoriasis Area and Severity Index) scores. These approaches do not readily take into account the impact of psoriasis on special areas of the body such as face, nails, scalp, hands/feet, and genitals, nor do they consider how patients have responded to topical therapies. As a result, people with psoriasis — especially those with certain mild to moderate (lower

severity) forms of the condition — are denied access to critical systemic treatments to control symptoms.

The IPC method of assessing psoriasis severity as detailed in the October 2019 *JAAD* article is a treatment-first approach that significantly simplifies the process of getting psoriasis patients on the right medication for their disease level. Rejecting the mild, moderate and severe labels used to categorize psoriasis severity, the IPC method calls for classifying patients as candidates either for topical therapy or systemic therapy. To qualify for systemic therapy, patients must meet one or more of the following criteria:

- BSA > 10%
- Psoriasis lesions on sensitive areas of the body (i.e., hands/feet, face, genitals, scalp) or
- Topical therapy failed to control symptoms

From this consensus paper, IPC intends to work with health insurance entities, health care providers, and stakeholders involved in drug development to integrate this new method of assessing psoriasis severity into standards of care for psoriasis, with the ultimate aim to increase access to care for patients worldwide.

International journal article explores IPC study linking psoriasis and mental health

Psoriasis and mental health workshop report: Exploring the links between psychosocial factors, psoriasis, neuroinflammation and cardiovascular disease risk. Kleyn CE, Talbot PS, Mehta NN, et al. *Acta Derm Venereol.* 2019 Nov 19. doi: 10.2340/00015555-3375. [Epub ahead of print]

The international peer-reviewed journal *Acta Dermato-Venereologica* has published an IPC report discussing depression as an important comorbidity of psoriasis. The report summarizes an IPC workshop held in Barcelona, Spain, focusing on the presence of depression and suicidality as well as the role of neuroinflammation in psoriasis, sleep disruption, and the impact of depression on cardiovascular disease.

The workshop featured studies and expert presentations examining the psychiatric comorbidities of psoriasis and the impact of chronic, systematic inflammation on neuro- and cardiovascular outcomes.

Among the report's conclusions:

- The association between psoriasis and depression is well established in epidemiological studies, but less well known in clinical practice. "Increased awareness and concern about effective depression management in patients with psoriasis will undoubtedly improve overall disease management."
- Further research is needed to understand how targeting the pro-inflammatory cytokines which underlie the chronic inflammation of psoriasis affects both cardiovascular events and depression.

Journals cite GPA role in 2 scientific studies

Two prestigious scientific journals — the *Journal of the European Academy of Dermatology and Venereology* (*JEADV*) and *JAMA Dermatology* — recently published 2 articles based on support provided by the Global Psoriasis Atlas (GPA), a collaboration of IPC and 2 other international dermatology organizations, the International Federation of Psoriasis Associations and the International League of Dermatological Societies.

The *JEADV* article, titled "Incidence and prevalence of psoriasis in Israel between 2011 and 2017," published in the journal's June 25, 2019 issue, acknowledged the GPA's "substantial contribution" to the administration of the study. Noting that the prevalence of psoriasis in Israel had not been previously studied, the article describes a study by Israeli researchers to determine trends in the incidence, prevalence, and mortality among patients in Israel with the disease. The article concluded that psoriasis prevalence is growing in Israel, although the incidence is stable. "Clinicians and policymakers should plan to address the growing demands in the clinical, economic and societal burden of psoriasis," the study observed.

The second article, titled "Association of psoriasis with the risk of developing or dying of cancer — a systematic review and meta-analysis," published in *JAMA Dermatology's* October 26, 2019 issue, was a systematic review and meta-analysis of the risk of cancer developing in people with psoriasis. The study concluded that those who have the disease appear to have an increased risk of cancer incidence and cancer-related mortality, and that dermatologists should be aware of this increased risk. The GPA provided funding for the study and the article's authors acknowledge the "key role played by the GPA collaborating organizations." The article is available at *bit.ly/PsoriasisCancerRisk*.

New IPC Councilors

Expanding our global network of psoriasis experts

Andrea Chiricozzi, MD
Rome, Italy

Dr. Chiricozzi is senior researcher at the Department of Translational Medicine and Surgery, Dermatology Unit, Catholic University of Rome, and a dermatologist at the Fondazione Policlinico Universitario A. Gemelli IRCCS Hospital. His scientific interests include skin immunology and inflammatory skin disorders, including psoriasis, atopic dermatitis, and hidradenitis suppurativa. In particular, he has focused on the pathophysiology underlying psoriatic plaque formation. He furthered his work on immune-mediated skin disorders at the Laboratory for Investigative Dermatology, headed by IPC Councilor Dr. James Krueger, at the Rockefeller University in New York, as a post-doctoral fellow and visiting dermatologist. Dr. Chiricozzi has been an investigator for multiple clinical trials, testing biologic therapeutics as well as new oral and topicals for inflammatory skin disorders. He was a contributing author of the recently-published Italian guidelines for the treatment of psoriasis and he has been involved in the PsoBiosimilars Registry, an Italian registry of biosimilars in psoriasis and psoriatic arthritis. He is the author of more than 100 peer-reviewed articles and 4 book chapters. He was honored with the Leo Pharma Research Silver Award in 2012.

Nejib Doss, MD
Tunis, Tunisia

Dr. Doss heads the Military Hospital of Tunis dermatology department in Tunisia. After completing medical school at the Faculté de Médecine de Tunis, he began his training in dermatology in Paris at the Hôpital Bégin. He returned to Tunis 1985, rising through academic positions and eventually becoming a full professor in 2002. Professor Doss is vice president of the International Society of Dermatology and a co-founder of the African Association of Dermatology and Venereology. He has been a member of the Tunisian Society of Dermatology and Venereology and the International Board of Psoriasis Groups network. Since 2007, he has been president of the HIV & STI Tunisian Military Prevention Programme and he belongs to the International Union against Sexually Transmitted Infections Africa Core Team. His research interests include nail diseases, psoriasis, and scabies.

Arthur Kavanaugh, MD
San Diego, California, United States

Dr. Kavanaugh is professor of Medicine at the University of California, San Diego (UCSD) School of Medicine and is the director of the Center for Innovative Therapy in the UCSD Division of Rheumatology, Allergy, and Immunology. Professor Kavanaugh's main interest has been in clinical research, particularly translational aspects of rheumatology. Although his focus has been on rheumatoid arthritis and psoriatic arthritis, he has conducted many studies in other autoimmune conditions, including systemic lupus erythematosus, ankylosing spondylitis and inflammatory bowel disease. He has helped create guidelines for the treatment and optimal care of patients with rheumatic diseases. Professor Kavanaugh helped form GRAPPA (Group for Research and Assessment of Psoriasis and Psoriatic Arthritis) and is currently on its executive committee. He has been a board member of the CORRONA (Consortium of Rheumatology Researchers of North America) registry since its inception. Professor Kavanaugh has authored more than 500 peer-reviewed scientific publications, reviews and book chapters and has served on the editorial boards of several journals. He is a fellow of the American Academy of Allergy, Asthma, and Immunology and the American College of Rheumatology.

Andrew Pink, MD
London, England, United Kingdom

Dr. Pink is a consultant dermatologist and the clinical trials lead for adult medical dermatology at St. John's Institute of Dermatology, Guy's & St. Thomas' NHS Foundation Trust, London. He is an honorary clinical

lecturer at King's College London and the honorary secretary of the St. John's Dermatological Society. His key clinical and academic interests are psoriasis and eczema. Dr. Pink received his medical training at the University of Nottingham Medical School in 2004. After completing his training, he was awarded the first National Institute of Health Research (NIHR) Academic Clinical Fellowship in dermatology at St John's Institute of Dermatology and King's College London. During his clinical dermatology training, he was awarded an MRC Clinical Research Training Fellowship to undertake and complete a PhD in the field of medical dermatology (molecular genetics of hidradenitis suppurativa), during which he received an MRC Centenary Award. He was subsequently awarded an NIHR Academic Clinical Lectureship at St John's Institute of Dermatology and King's College London prior to his consultant post. His research interests include psoriasis, eczema, and general dermatology.

IPC CONTINUING MEDICAL EDUCATION ON DEMAND

Treating to Goal: A Clear Path to Patient-Centered Psoriasis Management

Psoriasis patients and their physicians disagree about which symptoms are most important to treat. Patients report itch and other symptoms to be most bothersome while dermatologists reported location and size of skin lesions as paramount. Therefore, there is a need for greater patient-provider collaboration in setting expectations and goals around treatment and care.

In this CME program, dermatologists, a primary care physician, and a psoriasis patient discuss the management of psoriasis from all perspectives and define strategies for improving the communication of patient and physician expectations during psoriasis therapy. Discussion of the differential diagnosis, pathology, and treatment of psoriasis are also covered.

The goal of the program is to help alleviate patient frustration and help clinicians optimize skin and comorbidity-related treatment outcomes.

Learn more or start the activity at *bit.ly/Treat2Goal*

Faculty for this CMD program, from left, Paul Doghramji, Johann Gudjonsson, David Pariser, and Kathleen Gallant, discuss patient/provider communication strategies to establish psoriasis treatment goals.

EDUCATIONAL OBJECTIVES

After completing this activity, participants should be better able to:

- Recognize the most relevant symptoms for individual patients to develop appropriate personalized treatment plans
- Develop a shared decision-making strategy to guide treatment choices and measurable goals for your patients to improve outcomes
- Describe the pathogenesis of psoriasis
- Discuss the spectrum of available therapies and the evidence to support the development of personalized treatment plans
- Identify and manage comorbidities utilizing a collaborative treatment approach with other disciplines

INTENDED AUDIENCE

The target audience for this initiative includes dermatologists, primary care clinicians, nurse practitioners, physician assistants, and other clinicians who care for patients with psoriasis.

ACCREDITATION STATEMENT

This activity has been planned and implemented in accordance with the accreditation requirements and policies of the ACCME through the joint providership of The University of Chicago Pritzker School of Medicine, the International Psoriasis Council, and FACTORx Inc. The University of Chicago Pritzker School of Medicine is accredited by the ACCME to provide continuing medical education for physicians.

CREDIT

The University of Chicago designates this enduring material for a maximum of 1.0 *AMA PRA Category 1 Credit(s)*.™ Physicians should only claim credit commensurate with the extent of their participation in the activity.

This activity is supported by educational grants by AbbVie, Celgene Corporation, and Janssen Biotech Inc., and administered by Janssen Scientific Affairs LLC and Ortho Dermatologics.

Events & Resources

Increase your expertise in psoriasis treatment and care

THE INTERNATIONAL PSORIASIS COUNCIL IS PLEASED TO BRING YOU THE FOLLOWING EDUCATIONAL OPPORTUNITIES TO ADVANCE YOUR KNOWLEDGE OF TREATING PATIENTS WITH PSORIASIS:

UPCOMING IPC EVENTS

FEBRUARY 23-24, 2020
IPC Psoriasis Masterclass
Bangkok, Thailand

FEBRUARY 26, 2020
IPC Symposium
24th Regional Conference of Dermatology (RCD)
Bangkok, Thailand

MARCH 19, 2020
IPC Global Education Day Symposium
American Academy of Dermatology (AAD) Annual Meeting
Denver, Colorado

APRIL 29-30, 2020
IPC Psoriasis Masterclass
Asunción, Paraguay

MAY 3, 2020
IPC Symposium
Annual Meeting of Latin American Dermatologists (RADLA)
Asunción, Paraguay

MAY 13, 2020
IPC Symposium
Society for Investigative Dermatology (SID) Annual Meeting
Scottsdale, Arizona

IPC'S PROFESSIONAL EDUCATION & RESOURCE CENTER

ON-DEMAND WEBCASTS
IPC offers a series of webcasts presented by global leaders in dermatology to help you learn more about psoriasis.

TREATMENT GUIDELINES
A compilation of evidence-based guidelines for psoriasis diagnosis and management collected from around the world.

MEASUREMENT TOOLS
Commonly used measurement tools for psoriasis management and clinical trials.

CONGRESS COVERAGE
Reviews of psoriasis highlights from important congresses around the world.

PSORIASIS IMAGE LIBRARY
More than 500 images of different subtypes and phenotypes in psoriasis available for clinical and educational purposes.

VIDEO LECTURES
Search our library of challenging case presentations and lectures by topic and date.

Access IPC's professional education and resource centers at *psoriasiscouncil.org/education* and *psoriasiscouncil.org/tools_resources.htm*.

IPC's International Fellowship program provides young dermatologists and researchers full access to the knowledge of our network of psoriasis experts and furthers our commitment to building expertise in the field.

Learn more at *psoriasiscouncil.org/ipc_fellowship*

MEET THE 2020 IPC FELLOWS

Jacquelini Barboza da Silva, MD
Dr. Barboza da Silva is a dermatologist in private practice in Santa Cruz do Sul, Brazil. Additionally, she is an instructor at Santa Cruz University, where she is completing a master's degree studying biomarkers in psoriasis by spectroscopy. Dr. Barboza da Silva will study with Professors Darren Ashcroft and Chris Griffiths of University of Manchester in the United Kingdom.

Alvaro Gonzales-Cantero, MD, PhD
Dr. González-Cantero works as a dermatologist at the Department of Dermatology of the Ramón y Cajal University Hospital in Madrid, Spain, where he combines patient care with research. He received his PhD in psoriasis and comorbidities in 2019 at the University of Castilla la Mancha. Dr. González-Cantero will study with Dr. Joel Gelfand of the University of Pennsylvania in the United States.

Julia-Tatjana Maul, MD
Dr. Maul is a board qualified Senior Dermatologist in the Clinic for Dermatology at the University Hospital of Zürich, Switzerland. She is the principal investigator of the Swiss Dermatology Network for Targeted Therapy (SDNTT) in Psoriasis of Zürich and has contributed to the Global Psoriasis Atlas (GPA). In October 2019, Dr. Maul joined the GPA team as a medical coordinator. Dr. Maul will study with Dr. Claudia de la Cruz of Clinica Dermacross in Chile and Dr. Ricardo Romiti of the University of Sao Paulo in Brazil.

Lily Tumalad, MD, FPDS
Dr. Tumalad is the head of the psoriasis center of the Department of Dermatology at Rizal Medical Center and the head of the phototherapy unit of the Department of Dermatology at East Avenue Medical Center in Manila, Phillipines. She also serves as consultant in two Philipine government training institutions. Dr. Tumalad will study with Dr. Curdin Conrad of Lausanne University Hospital in Switzerland.

Matthew Vesely, MD, PhD
Dr. Vesely is an instructor in the Department of Dermatology at Yale University where he combines patient care with translational research in autoimmune skin diseases. He obtained his PhD in immunology studying how the immune system detects and eradicates cancers. Dr. Vesely will study with Dr. Alice Gottlieb of the Icahn School of Medicine at Mount Sinai in the United States.

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International Psoriasis Council
1034 S. Brentwood Blvd.,
Suite 600
St. Louis, MO 63117

TEL 972.861.0503
FAX 214.242.3391

PsoriasisCouncil.org

Founded in 2004, the International Psoriasis Council (IPC) is a dermatology-led, voluntary, global, nonprofit organization with a network of more than 100 psoriasis experts, thought leaders, and professionals, dedicated to improving patient care around the globe.

Through our work, we deepen the understanding of the disease and its management. We lead advancements in care by facilitating cutting-edge research, convening partners to collaborate and advocate for improved treatment, and growing capacity for psoriasis management by sharing our knowledge. Unbiased and science-based, our collective expertise and influence have a direct impact on how patients around the world are treated.

OUR VISION IS A WORLD FREE OF PSORIASIS.

We believe that psoriasis patients, no matter where they live in the world, no matter how complex their symptoms, should have access to the best care available to them, and that ultimately a world without psoriasis is possible.

OUR MISSION IS TO IMPROVE THE CARE OF PEOPLE WITH PSORIASIS WORLDWIDE THROUGH EDUCATION, RESEARCH, AND ADVOCACY.

CO-EDITORS

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WRITERS

Thomas Scharnitz, MD
Kana Masuda-Kuroki, MD

EDITORIAL STAFF

Mary Bellotti, *Editor*
Rene Choy, *Graphic Design*
Catie Coman, *Director of Communications*

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