



**IPC**

INTERNATIONAL  
PSORIASIS  
COUNCIL

SEPTEMBER 2021

**A report from the  
50th Anniversary ESDR Annual Meeting**

By Thomas Sharnitz, MD

**FOCUS ON PSORIASIS**

# INTRODUCTION

The European Society for Dermatological Research (ESDR) celebrated its 50th anniversary in 2021 with the initial goal to meet in person, as the COVID-19 pandemic forced the postponement of all live meetings in 2020. Despite being unable to meet in person again for this year's congress, the ESDR featured brilliant lectures for its half-a-century anniversary. Specific to psoriasis and the IPC, Chief Medical Officer Peter van de Kerkhof was honored and gave a special anniversary lecture on the evolution of psoriasis management across the past five decades.

# TABLE OF CONTENTS

## 50 Years ESDR Anniversary Lecture

- |          |   |
|----------|---|
| <b>3</b> | <b>Psoriasis</b><br>Peter van de Kerkhof, MD PhD, IPC Chief Medical Officer |
|----------|---|

## IPC Symposium: Research on SARS-CoV-2 during the COVID-19 pandemic crisis: An IPC tribute to young researchers

- |          |  |
|----------|--|
| <b>4</b> | <b>Autoantibodies to type I IFNs in patient with life-threatening COVID-19</b><br>Paul Bastard, PhD  |
| <b>6</b> | <b>B-cell responses to SARS-CoV-2 in the setting of COVID-19 infection and vaccination</b><br>Zijun Wang, MD, PhD                            |
| <b>7</b> | <b>COVID-19 infection in psoriasis patients: Lessons from real-life registries</b><br>Satveer Mahil, PhD, MRCP, IPC Councilor                |
| <b>9</b> | <b>Interactions between skin inflammatory diseases and COVID-19: Lessons from genomic epidemiology studies</b><br>Matthew Patrick, MEng, PhD |

## Pustular Psoriasis

- |           |   |
|-----------|---|
| <b>11</b> | <b>Discovery: Understanding of generalized pustular psoriasis from bench to bedside</b><br>Peter van de Kerkhof, MD, PhD, IPC Chief Medical Officer |
| <b>13</b> | <b>Innovations in generalized pustular psoriasis treatment</b><br>Jörg Prinz, MD, IPC Councilor   |
| <b>15</b> | <b>Impact of generalized pustular psoriasis: Disease burden and unmet needs</b><br>Siew Eng Choon, MBBS, FRCP, IPC Councilor                        |

## Other

- |           |   |
|-----------|---|
| <b>17</b> | <b>Mesenchymal stromal cell therapy for psoriasis</b><br>Lajos Kemeny, MD                             |
| <b>19</b> | <b>Detection and management of psoriatic arthritis: Spot the signs, act fast</b><br>Frank Behrens, MD |
| <b>21</b> | <b>New MOAs in the psoriasis pipeline</b><br>Wolf-Henning Boehncke, MD, MA, IPC Councilor             |

## **50 Years ESDR Anniversary Lecture: Psoriasis**

**Peter van de Kerkhof, MD PhD, IPC Chief Medical Officer**

Radboud University Nijmegen Medical Centre, Amsterdam, Netherlands

Dr. van de Kerkhof was honored as one of the 50th-anniversary speakers, highlighting the advances in psoriasis pathogenesis and treatment across the decades since ESDR's inception.

Much of our understanding of psoriasis from 1970-2000 focused on epidermal regulation, neutrophil migration, cytokines, and chemokines. Importantly, beginning in 1980, psoriasis began being regarded as a T cell-driven disease. T-cell significance was cemented into our understanding via the efficacy of cyclosporin and the calcineurin pathway, as well as ancillary studies showing the effectiveness of blocking IL-2 in psoriasis.

In the first decade of the new century, the Th1/Th2 paradigm was important in understanding both psoriasis and atopic dermatitis. Psoriasis was regarded as a Th1 disease, with the release of inflammatory mediators such as IFN $\gamma$ , TNF- $\alpha$ , and IL-2/12/23. Conversely, atopic dermatitis is a disease of the Th2 pathway with mediators including IL-4/13.

Research in the 2000s has provided many remarkable findings. The immunological synapse/interaction of MHC complexes to T-cell receptor antigen presentation was elucidated, with drugs such as alefacept and efalizumab emerging. Simultaneously, the roles of dendritic cells autoantigens such as LL-37 were defined.

Additionally, the paramount IL-23/Th17 pathway was further described, leading to targeted biologic treatments with truly unparalleled results. Additional studies also found additional IL-17-releasing mediators such as innate lymphocytes,  $\gamma\delta$  T cells, NK and NKT cells, neutrophils, and mast cells, found to contribute to psoriasis pathogenesis.

Further noteworthy discoveries included candidate causal genes from selected disease-associated loci, psoriasis explained as a disease of a branching innate and acquired immunity, and pathogenesis-based biologics with European Medicines Agency registration providing for a long term, effective, safe treatment of psoriasis.

Most recently, small molecule development targeting the JAK pathway TYK2 (deucravacitinib), phosphodiesterase-4 (oral apremilast and topical roflumilast), and a topical aryl hydrocarbon receptor modulating agent (tapinarof) shows great promise and will offer important new alternative therapies to patients.

Dr. van de Kerkhof finished his compelling lecture describing the critical shift over 50 years from psoriasis as a 'skin-only disease' to vital recognition of its systemic inflammatory nature. He believes this outlook represents the future of psoriasis research and management, in which our goals will reach beyond PASI to treat and prevent the vast array of psoriasis comorbidities.

## IPC SYMPOSIUM

### Autoantibodies against type I IFNs in patient with life-threatening COVID-19

Paul Bastard, PhD

The Rockefeller University, New York, New York, United States

Though most individuals' risk of life-threatening (critical) COVID-19 is low, it increases with epidemiologic risk factors such as age and male sex. However, substantial interindividual variability remains. Dr. Bastard and The COVID Human Genetic Effort studied > 10,000 patients with asymptomatic/mild and severe/critical COVID-19 focusing on Type 1 interferons (IFNs), which trigger potent anti-viral responses and are implicated in other severe infections. In critical COVID-19, they found that 2-3% of patients harbored Type1-IFN gene mutations.<sup>1</sup> Other studies found strong enrichment in damaging loss-of-function mutations in TLR7 (essential in IFN-signaling) in > 1% of men with critical COVID under 60 years old. It appears that in a small proportion of young patients, inborn errors of Type1-IFN immunity may cause critical COVID-19.<sup>2</sup>

In an international cohort (n = 987), Dr. Bastard's group found high titers of pre-existing neutralizing autoantibodies to Type1-IFNs in 10.2% of patients with critical COVID-19. Of these, 94% were men, and 50% were > 65 years of age. No asymptomatic controls, and only 0.3% of healthy controls had such autoantibodies. More sensitive testing at lower concentrations found IFN-autoantibodies in critical (15%) and severe (8%) COVID-19, versus controls (1%), suggesting high risk but incomplete penetrance.<sup>3</sup>

Moreover, autoantibodies to IFN- $\alpha$ 2 neutralized all 13 alpha-IFNs, but not those against IFN- $\Omega$  only. Autoantibodies against *both* IFN-  $\alpha$ 2 and IFN- $\Omega$  appear to underly a striking increase in critical covid (ref image). At least 1% of patients with essential COVID had antibodies blocking only IFN- $\beta$ , suggesting IFN- $\beta$  deficiency alone can also cause critical COVID-19. Overall, impaired type 1 IFN immunity in patients with critical COVID-19 was seen in > 20% of elderly patients and >20% of COVID-19 deaths.<sup>3</sup>

#### Key points:

- Type 1 IFNs appear to be essential for protective immunity against SARS-CoV-2; inborn errors or autoantibodies to type 1 IFNs place individuals at risk for life-threatening/critical COVID-19.
- Autoantibodies neutralizing type 1 IFNs underlie at least 15% of critical COVID-19 cases, > 20% of cases in patients older than 80 years old, and > 20% in patients who died of COVID-19.

#### References:

1. Zhang Q, Bastard P, Liu Z, et al. Inborn errors of type I IFN immunity in patients with life-threatening COVID-19. *Science*. 2020;370(6515):eabd4570.
2. Asano T, Boisson B, Onodi F, et al. X-linked recessive TLR7 deficiency in ~1% of men under 60 years old with life-threatening COVID-19. *Science Immunology*. 2021;6(62):eabl4348.
3. Bastard P, Rosen LB, Zhang Q, et al. Autoantibodies against type I IFNs in patients with life-threatening COVID-19. *Science*. 2020;370(6515):eabd4585.

## Risk of critical COVID-19 pneumonia in patients with auto-Abs when compared with that of asymptomatic/mild infection

Anti-type I IFN auto-Ab positive (amount of type I IFN neutralized, in plasma diluted 1/10)	Proportion of critical patients with neutralizing auto-Abs	OR [95% CI]	P-value
anti-IFN- $\alpha$ 2 and anti-IFN- $\omega$ auto-Abs (10 ng/mL)	5.6%	67 [4-1109]	7.8x10 <sup>-13</sup>
anti-IFN- $\alpha$ 2 and/or anti-IFN- $\omega$ auto-Abs (10 ng/mL)	9.8%	17 [7-45]	< 10 <sup>-13</sup>
anti-IFN- $\alpha$ 2 auto-Abs (10 ng/mL)	9%	45 [9-225]	< 10 <sup>-13</sup>
anti-IFN- $\alpha$ 2 auto-Abs only (10 ng/mL)	3.4%	21 [4-107]	1.8x10 <sup>-09</sup>
anti-IFN- $\omega$ auto-Abs (10 ng/mL)	6.4%	13 [4-38]	1.4x10 <sup>-12</sup>
anti-IFN- $\omega$ auto-Abs only (10 ng/mL)	0.8%	3 [0.9-10]	0.057
anti-IFN- $\alpha$ 2 and anti-IFN- $\omega$ auto-Abs (100 pg/mL)	7.1%	54 [11-275]	< 10 <sup>-13</sup>
anti-IFN- $\alpha$ 2 and/or anti-IFN- $\omega$ auto-Abs (100 pg/mL)	13.6%	13 [8-21]	< 10 <sup>-13</sup>
anti-IFN- $\alpha$ 2 auto-Abs (100 pg/mL)	10%	23 [10-55]	< 10 <sup>-13</sup>
anti-IFN- $\alpha$ 2 auto-Abs only (100 pg/mL)	2.9%	10 [3-26]	2.8x10 <sup>-09</sup>
anti-IFN- $\omega$ auto-Abs (100 pg/mL)	10.7%	13 [7-23]	< 10 <sup>-13</sup>
anti-IFN- $\omega$ auto-Abs only (100 pg/mL)	3.6%	6 [3-12]	3.9x10 <sup>-10</sup>
anti-IFN- $\beta$ auto-Abs (10 ng/mL)	1.3%	8 [2-36]	1.7x10 <sup>-3</sup>
anti-IFN- $\beta$ auto-Abs only (10 ng/mL)	0.96%	5 [1-25]	0.043
anti-IFN- $\beta$ auto-Abs (10 ng/mL) and, anti-IFN- $\alpha$ 2 and/or anti-IFN- $\omega$ auto-Abs (100 pg/mL)	0.34%	16 [0.5-497]	0.018
anti-IFN- $\beta$ (10 ng/mL) and, anti-IFN- $\alpha$ 2 and anti-IFN- $\omega$ auto-	0.98%	16 [0.5-509]	0.019

## IPC SYMPOSIUM

### B-cell responses to SARS-CoV-2 in the setting of COVID-19 infection and vaccination

Zijun Wang, MD, PhD

Rockefeller University, New York, New York, United States

SARS-CoV-2 to date has caused > 120 million infections and > 2.65 million global deaths. Dr. Wang's group recruited convalescent individuals to study polyclonal and monoclonal B-cell and antibody responses to SARS-CoV-2 post-infection. Prior post-infection studies characterized antibody response at three months,<sup>1</sup> and found the evolution of antibody immunity after six months.<sup>2</sup>

From February 8 to March 26, 2021, they studied 63 convalescent individuals, of whom 41% were mRNA vaccinated. Of those returning for the 12-month follow-up, only 10% had been hospitalized, and the remainder had relatively mild initial infections. Though 40% had persistent long-term symptoms, this was not associated with disease severity, duration, or vaccination status.

Those unvaccinated individuals maintained most of their anti-RBD IgM (103%), IgG (82%), and IgA (72%) titers between 6 and 12 months after infection (all  $p < 0.0001$ ). Those vaccinated also maintained levels of all three isotypes but strikingly displayed a near 5-fold increase in IgG titers than the non-vaccinated. Regardless of vaccination status, the anti-nuclear capsid antibody titers decrease between 6 and 12 months.<sup>3</sup> This suggests persistent humoral immunity is different in each individual, and anti-RBD is superior to an anti-nuclear capsid antibody response.

Using HIV-1 pseudotyped with SARS-CoV-2 spike protein, they measured neutralizing activity. From 6 to 12 months after infection, they found that the geometric mean half-maximal neutralizing titer (NT50) for those unvaccinated was not significantly different, but in vaccinated individuals found dramatic ~50-fold higher NT50 than unvaccinated individuals. This correlated with anti-RBD IgG antibodies but not anti-nuclear capsid titers.

#### Key points:

- Approximately 10% of convalescent patients were hospitalized for SARS-CoV-2 infection.
- Regardless of vaccination status, neutralizing antibody titers remain relatively unchanged between 6 and 12 months after infection. However, vaccination boosts these significantly and immensely.

#### References:

1. Robbani DF, Gaebler C, Muecksch F, et al. Convergent antibody responses to SARS-CoV-2 in convalescent individuals. *Nature*. 2020;584(7821):437-442.
2. Gaebler C, Wang Z, Lorenzi JCC, et al. Evolution of antibody immunity to SARS-CoV-2. *Nature*. 2021;591(7851):639-644.
3. Wang Z, Muecksch F, Schaefer-Babajew D, et al. Naturally enhanced neutralizing breadth against SARS-CoV-2 one year after infection. *Nature*. 2021;595(7867):426-431.

## IPC SYMPOSIUM

### COVID-19 infection in psoriasis patients: Lessons from real-life registries

Satveer Mahil, PhD, MRCP, IPC Councilor

St John's Institute of Dermatology, Guy's and St Thomas' NHS Foundation Trust, London, England, United Kingdom

[https://www.jacionline.org/article/S0091-6749\(20\)31413-5/fulltext](https://www.jacionline.org/article/S0091-6749(20)31413-5/fulltext)

During the COVID-19 pandemic, psoriasis patients are faced with many uncertainties.<sup>1</sup> However, the infection risk attributed to psoriasis alone or with treatments remains uncertain. Global registries such as PsoProtect (clinician reporting) and PsoProtectMe (patient reporting) were created to clarify the associations between the COVID-19 pandemic and psoriasis.

In the latest dataset from PsoProtect (n = 1205), most patients were receiving systemic therapy (70% biologics, 17% non-biologics), and > 90% fully recovered from COVID-19. Hospitalization rates were higher with non-biologics compared with biologics (OR 2.37, 95% CI 1.5-3.76), and these rates align with rheumatologic registry data.<sup>2</sup>

Stratified significant risk factors were similar in psoriasis and the general population, including male sex (OR 1.83; 1.22-2.73), older age (OR 1.47 per 10 years; 1.24-1.73), non-white ethnicity (OR 2.38; 1.39-4.06), and comorbidities of hypertension (OR 1.81, 1.18-2.78), chronic liver disease (OR 2.48; 1.37-4.48), and chronic lung disease (OR 2.50; 1.41-4.42).<sup>3</sup>

PsoProtect and similar registry data compared the impact of TNF- $\alpha$  inhibitors (TNFi) on immunomodulatory drugs. Using pooled cross-analysis (n = 6,077) this dataset found increase risks of: azathioprine/6-mercaptopurine [AZA/6MP] monotherapy (OR 1.84; 1.30-2.61), methotrexate monotherapy (OR 2.0; 1.57-2.56), TNFi combined with AZA/6MP (OR 1.74; 1.17-2.58), JAK inhibitor monotherapy (OR 1.82; 1.21-2.73).<sup>3</sup> Limitations include risk-mitigating behavior by those on biologics,<sup>4</sup> lack of causality and denominator data, and selection bias.

During the pandemic, PsoProtectMe data shows that 43% of patients report worsening disease, which frequently leads to worsening depression and anxiety. 18% report non-adherence due to concerns of therapy-related COVID-19 complications associated with subsequent worsening disease (OR 2.90, CI 2.31-3.63).

#### Key points:

- Most cases reported to PsoProtect fully recovered from infection. Biologic monotherapy is associated with a reduced risk of hospitalization. Risk factors are similar in psoriasis and the general population.
- The COVID-19 pandemic may cause non-adherence and worsening psoriasis, which is associated with poor mental health. Concerns about immunosuppressant risks of COVID-19 primarily drive non-adherence.

#### References:

1. Williamson EJ, Walker AJ, Bhaskaran K, et al. Factors associated with COVID-19-related death using OpenSAFELY. *Nature*. 2020;584(7821):430-436.

2. Mahil SK, Yates M, Langan SM, et al. Risk-mitigating behaviours in people with inflammatory skin and joint disease during the COVID-19 pandemic differ by treatment type: A cross-sectional patient survey. *Br J Dermatol.* 2021;185(1):80-90.
3. Mahil SK, Dand N, Mason KJ, et al. Factors associated with adverse COVID-19 outcomes in patients with psoriasis-insights from a global registry-based study. *J Allergy Clin Immunol.* 2021;147(1):60-71.
4. Mahil SK, Yates M, Langan SM, et al. Risk-mitigating behaviours in people with inflammatory skin and joint disease during the COVID-19 pandemic differ by treatment type: a cross-sectional patient survey. *Br J Dermatol.* 2021;185(1):80-90.

## IPC SYMPOSIUM

### Interactions between skin inflammatory diseases and COVID-19: Lessons from genomic epidemiology studies

Matthew Patrick, Meng, PhD

University of Michigan, Department of Dermatology, Ann Arbor, Michigan, United States

Inflammatory skin disease makes patients more susceptible to infections. Prior studies show severe psoriasis increases the risk of infection, hospitalizations, and pneumonia.<sup>1,2</sup> Reports from around the world suggest that psoriasis patients may be at greater risk from COVID-19 psoriasis. Interestingly, SARS-Cov-2 binds to ACE2<sup>3</sup> in the lung epithelia, and ACE2 is upregulated in psoriasis lesions.

Dr. Patrick's group conducted an extensive study (n > 435,000) across encounters in 2019/2020 with recorded age, race, sex, BMI, and socioeconomic status. 1,115 (0.25%) had COVID-19, and of these, 150 (13.5%) required mechanical ventilation.

They found having any skin condition (odds ratio 1.55, p < 0.001) increases susceptibility to infection (odds ratio 1.55, p < 0.001; psoriasis OR 1.48, p = 0.020. However, ventilation risk decreased with skin condition (OR 0.22, p < 0.001). Interestingly, history of tonsillitis or pharyngitis also demonstrated increased infection (OR 1.60, p < 0.001) but decreased ventilation (OR 0.38, p < 0.001).

Comparing differential gene expression (DEGs) using genomic analysis on 11 gene expression datasets from mild skin diseases and two SARS-CoV-2 infected cell lines, they found common upregulated genes including IL-6, IL-1B, and the most enriched TNF- $\alpha$  and IL-17C.

Shared gene expression in psoriasis and SARS-CoV-2 infected respiratory tract shows a high proportion of the genes from chromosome 1, around 1/3 of which are inside the epidermal differentiation complex (EDC) locus, which is involved in keratinocyte differentiation and molecular physiology of psoriasis and other skin diseases.

Since the EDC is an established locus for psoriasis susceptibility, they found shared genetic signals in chromosome 19 near the FUT2 gene, significant in both psoriasis and COVID-19, via genome-wide association studies (GWAS)<sup>4</sup> and supported by Trans-Disease Meta-Analysis (TDMA).

#### Key points:

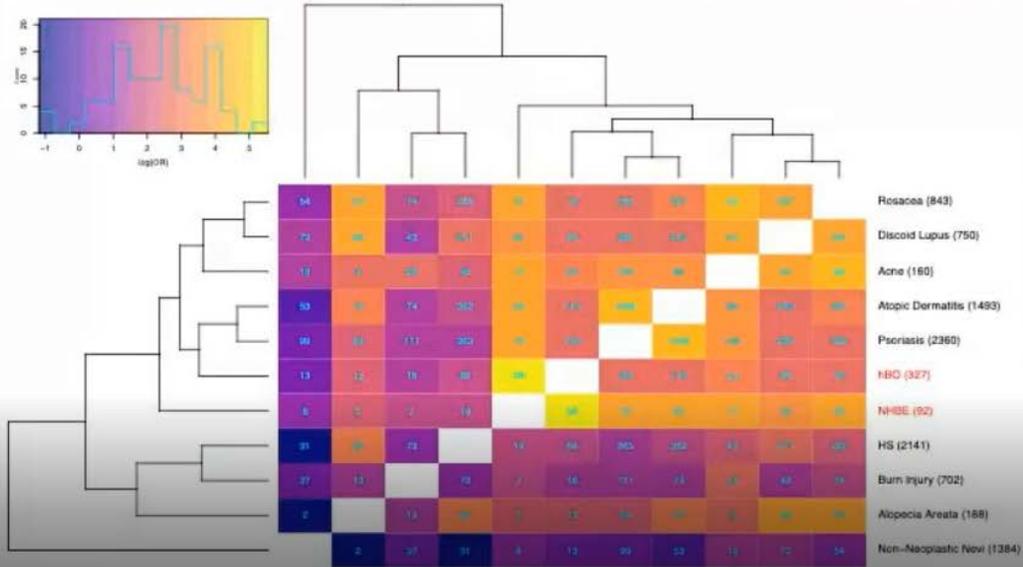
- Skin disease patients have higher rates of COVID-19 than the general population but appear to have less severe cases.
- Skin diseases and SARS-CoV-2 share upregulated genes, including IL-6, IL-1B, TNF- $\alpha$ , and IL-17C.
- Psoriasis and SARS-CoV-2 share high gene expression inside the epidermal differentiation complex (EDC) locus, involved in keratinocyte differentiation and molecular physiology of psoriasis.

#### References:

1. Yiu ZZN, Parisi R, Lunt M, et al. Risk of hospitalization and death due to infection in people with psoriasis: a population-based cohort study using the Clinical Practice Research Datalink. *Br J Dermatol.* 2021;184(1):78-86.

2. Takeshita J, Shin DB, Ogdie A, Gelfand JM. Risk of serious infection, opportunistic infection, and herpes zoster among patients with psoriasis in the United Kingdom. *J Invest Dermatol.* 2018;138(8):1726-1735.
3. Wrapp Daniel, Wang Nianshuang, Corbett Kizzmekia S., et al. Cryo-EM structure of the 2019-nCoV spike in the prefusion conformation. *Science.* 2020;367(6483):1260-1263.
4. Wrapp Daniel, Wang Nianshuang, Corbett Kizzmekia S., et al. Cryo-EM structure of the 2019-nCoV spike in the prefusion conformation. *Science.* 2020;367(6483):1260-1263.

## Enrichment of Shared Upregulated Genes



Rosacea, DLE,  
acne, AD and  
psoriasis share  
more genes  
with COVID-19

Screen Recording (9-22-2021 11-33-46 AM)

## PUSTULAR PSORIASIS

### Discovery: Understanding of generalized pustular psoriasis from bench to bedside

Peter van de Kerkhof, MD, PhD, IPC Chief Medical Officer

Radboud University Nijmegen Medical Centre, Amsterdam, The Netherlands

Generalized pustular psoriasis (GPP) is an autoinflammatory condition first described in 1910. Recently, a substantial body of evidence supports the principal role of the IL-36 pathway in GPP pathophysiology.<sup>1</sup> Though not all patients have identifiable genetic mutations, nearly 50% of GPP patients carry some variant in IL36RN, CARD14, or AP1S3.<sup>1-3</sup>

GPP is distinct from plaque psoriasis phenotypically, genetically, morphologically, in histopathology, disease course, and effective treatments.<sup>4</sup> In 2017, the European Rare and Severe Psoriasis Expert Network (ERASPEN) published a consensus classification of clinical phenotypes in pustular psoriasis. GPP consists of the classic morphology of primary sterile pustules on non-acral skin, can occur with or without systemic inflammation or psoriasis vulgaris, and can be either relapsing or persistent.<sup>5</sup>

Under normal conditions, IL-36R signaling leads to a balanced and regulated inflammatory response, with both agonist and antagonist binding. Dysregulation leads to pathology; damaged keratinocytes release high levels of IL-36, resulting in chemokine overexpression, neutrophil infiltration, and dendritic cell recruitment with a subsequent proinflammatory response. Neutrophil proteases activate IL-36, leading to an autocrine agonist activation storm with upregulated IL-36R signaling.<sup>1</sup>

With critical therapeutic implications, GPP patients respond to IL-36R inhibition irrespective of genetic mutations. In a Phase I trial of seven patients, four of whom did not carry mutations, IL-36 inhibition provided rapid and sustained response via reduction in Generalized Pustular Psoriasis Area and Severity Index (GPPASI) by 80% by week four in all patients.<sup>6</sup> This suggests the IL-36 pathway may play a pathogenic role among GPP patients across different genetic backgrounds.

#### Key points:

- GPP is phenotypically, genetically, and clinically distinct from plaque psoriasis, and much evidence supports the central role of the IL-36 pathway in GPP pathophysiology.
- Further research to explicate the GPP pathogenesis could produce effective treatment options.

#### References:

1. Marrakchi S, Guigue P, Renshaw BR, et al. Interleukin-36–receptor antagonist deficiency and generalized pustular psoriasis. *New England Journal of Medicine*. 2011;365(7):620-628.
2. 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.
3. Bachelez H. Pustular psoriasis and related pustular skin diseases. *Br J Dermatol*. 2018;178(3):614-618.
4. Johnston A, Xing X, Wolterink L, et al. IL-1 and IL-36 are dominant cytokines in generalized pustular psoriasis. *J Allergy Clin Immunol*. 2017;140(1):109-120.

5. Navarini AA, Burden AD, Capon F, et al. European consensus statement on phenotypes of pustular psoriasis. *J Eur Acad Dermatol Venereol.* 2017;31(11):1792-1799.
6. Bachelez H, Choon S-E, Marrakchi S, et al. Inhibition of the interleukin-36 pathway for the treatment of generalized pustular psoriasis. *New England Journal of Medicine.* 2019;380(10):981-983.

## PUSTULAR PSORIASIS

### Innovations in generalized pustular psoriasis treatment

Jörg Prinz, MD, IPC Councilor

Ludwig-Maximilians University, Munich, Germany

Identifying the role of the IL-36 pathway in the pathophysiology of generalized pustular psoriasis (GPP) has led to the development of two IL-36R antibody antagonists IFN- $\Omega$  currently in clinical trials: imsidolimab and spesolimab.

The Generalized Pustular Psoriasis Physician Global Assessment (GPPGA) uses pustules, erythema, and scaling/crusting, each ranked 0 (clear) to 4 (severe), and the averaged is calculated to give the overall score. The GPP pustulation sub score only assesses pustulation.<sup>1</sup>

Imsidolimab recently completed a 16-week phase 2 trial of 8 adults with moderate-to-severe GPP across with 75% (n = 6) achieving the primary endpoint of Clinical Global Impression improvement.<sup>2</sup> Phase 3 trials are planned for the near future, with a primary endpoint of GPPGA score clear (0) or almost clear (1) at four weeks.

A Phase 1 study of spesolimab showed a rapid response in GPPGA (0,1). Preliminary results of the international phase 2 study “Effisayil-1” of 53 adults with mild-to-moderate GPP and BSA  $\geq$ 5% were recently reported. At week 1, 54.3% of subjects receiving spesolimab vs 5.6% placebo achieved *primary endpoint* of GPPGA pustulation score of 0 (no visible pustules); risk difference 48.7, 95% CI 21.5-67.2,  $p < 0.001$ . Though not significant, also found 42.9% in treatment arm vs 11.1% placebo achieved the *secondary endpoint* GPPGA total score  $\leq$  1 (clear/almost clear); risk difference 31.7, 95% CI 2.2-52.7,  $p = 0.12$ .<sup>3</sup>

Adverse events (AEs) were generally comparable between both arms at week one but increased in the treatment arm by week twelve. Severe AEs occurred in two patients in the treatment arm at week one and six by week twelve, but none in placebo. No deaths or AEs requiring discontinuation of treatment were observed.<sup>4</sup>

#### Key points:

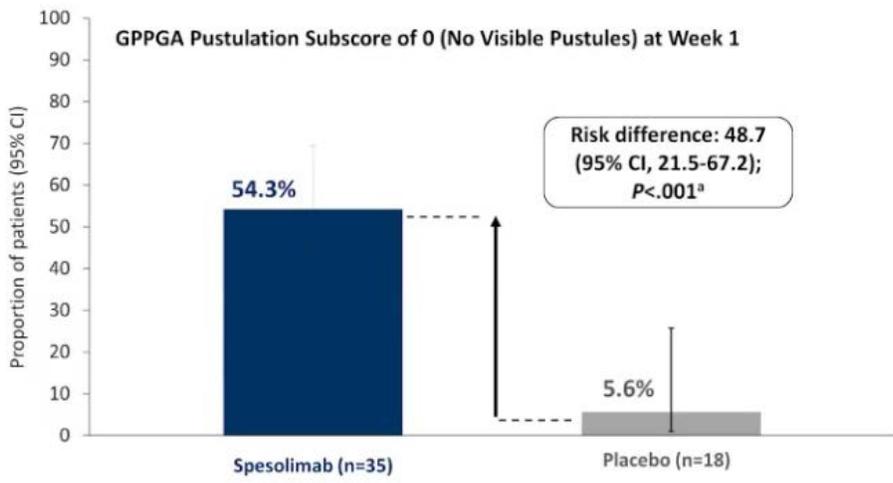
- IL-36 is a key cytokine in GPP. Blockade of the IL-36 receptor signaling, central to the pathogenesis of GPP, is a novel, targeted therapeutic approach.
- Spesolimab and imsidolimab are IL-36R antagonists, and early data suggest promising results using these medications in GPP independent of IL-36RN mutation status.

#### References:

1. Choon et al. Presented at AAD VMX April 23-25 2021 Virtual Conference.
2. ANAPTYSBIO. (n.d.). ANAPTYSBIO Reports positive topline data from GALLOP Phase 2 Clinical Trial of imsidolimab in moderate-to-severe generalized pustular psoriasis (GPP). [Press release]. Accessed October 3, 2021, from <https://ir.anaptysbio.com/news-releases/news-release-details/anaptysbio-reports-positive-topline-data-gallop-phase-2-clinical>

- 3. Bachelez H, et al. EADV 2018, Late-breaking news D3T01.1E. Inhibition of the Interleukin-36 Pathway for the Treatment of Generalized Pustular Psoriasis
- 4. Bachelet et al. Presented at WPPAC Conference June 30-July 3, 2021. Stockholm, Sweden. Poster 35129.

### Primary Endpoint: Rapid Pustular Clearance With Spesolimab in Treatment of GPP Flares



Any use of SOC or OL spesolimab at day 8 represents nonresponse  
NRI: nonresponse imputation for missing values

### Improvements in Skin Were Observed Within 1 Week of Receiving Spesolimab and Sustained Through 12 Weeks

	Baseline	Day 3 post spesolimab	Week 1 post spesolimab	Week 12 post spesolimab	
<b>Patient 1</b> <i>IL36RN-</i> randomised to spesolimab					
GPPGA:					
Pustulation subscore	4	0	0	0	
Total score	3	2	1	2	
	Screening	Baseline	Week 1 post placebo	Week 2 1 week post OL spesolimab	Week 12 11 weeks post OL spesolimab
<b>Patient 2</b> <i>IL36RN+</i> randomised to placebo; received OL spesolimab on Day 8					

## PUSTULAR PSORIASIS

### Impact of generalized pustular psoriasis: Disease burden and unmet needs

Siew Eng Choon, MBBS, FRCP, IPC Councilor

Jeffrey Cheah School of Medicine and Health Sciences, Monash University, Johor Bahru, Malaysia

GPP is a rare and severe autoinflammatory disease with a highly variable reported prevalence. GPP is characterized by recurrent, widespread erythema with numerous sterile pustules, typically accompanied by high fevers, malaise, fatigue, joint pains, and lab abnormalities.<sup>1-3</sup>

GPP has a high clinical burden and impact on quality of life, with significant distressful pain, itch, and fatigue. Additionally, comorbidities are highly prevalent and more frequently seen than in psoriasis vulgaris; a retrospective cohort study found 64.4% of GPP patients had  $\geq 1$  comorbidity, and another study found 32% suffered from anxiety and depression.<sup>4, 5, 7</sup>

The international healthcare burden of GPP is striking. Germany has had 250-300 admissions per year since 2011., and in the USA, GPP patients had higher rates of inpatient visits (23% vs 10%) and more emergency department visits (41% vs 23%) than psoriasis vulgaris.

GPP is also potentially life-threatening, largely due to complications including sepsis (most common), renal, hepatic, respiratory, and cardiac failure.<sup>6, 8</sup> In a large French study (n = 569), 25% of GPP patients were admitted to the ICU during flares, 2.6% died within four weeks of their last flare, and all-cause mortality was 24.4% through the study period.<sup>2, 7, 8</sup> A recent study from Japan (n = 1516) of GPP-associated hospitalization found 4.2% total mortality, with highest mortality from systemic corticosteroids monotherapy at 9.1%, vs 1.0% for biologics and 3.7% for oral agents (P < 0.001).<sup>9</sup>

Unfortunately, to date, we lack high-quality evidence to guide GPP treatment, and treatment often provides an inadequate response. A retrospective study by Dr. Choon showed that despite systemic therapy, 32% of patients still had  $\geq 2$  annual flares, and 28% had persistent/recalcitrant GPP.<sup>10, 11</sup>

#### Key points:

- GPP is rare but potentially life-threatening and has huge impacts on physical and mental health
- There are crucial unmet needs in both robust evidence and effective treatments at this time.

#### References:

1. Augey F, Renaudier P, Nicolas J-F. Generalized pustular psoriasis (Zumbusch): a French epidemiological survey. *Eur J Dermatol*. 2006;16(6):669-673.
2. Kharawala S, Golembesky AK, Bohn RL, Esser D. The clinical, humanistic, and economic burden of generalized pustular psoriasis: a structured review. *Expert Rev Clin Immunol*. 2020;16(3):239-252.
3. Bachelez H. Pustular psoriasis: the dawn of a new era. *Acta Derm Venereol*. 2020;100(3):adv00034.
4. Choon SE, et al. AAD 2021. Poster 26590.
5. Strober B, et al. AAD 2021. Poster 26588.

6. Choon SE, Lai NM, Mohammad NA, Nanu NM, Tey KE, Chew SF. Clinical profile, morbidity, and outcome of adult-onset generalized pustular psoriasis: analysis of 102 cases seen in a tertiary hospital in Johor, Malaysia. *Int J Dermatol.* 2014;53(6):676-684.
7. Kotowsky N, et al. Maui Derm 2020. Abstract R20-2784.
8. Bachelez H, et al. AAD 2021. Poster 26591.
9. Miyachi H, Konishi T, Kumazawa R, et al. Treatments and outcomes of generalized pustular psoriasis: A cohort of 1516 patients in a nationwide inpatient database in Japan. *Journal of the American Academy of Dermatology.* 2021;0(0).
10. Strober B, Kotowsky N, Medeiros R, et al. Unmet medical needs in the treatment and management of generalized pustular psoriasis flares: Evidence from a survey of corona registry dermatologists. *Dermatol Ther (Heidelb).* 2021;11(2):529-541.
11. Robinson A, Voorhees ASV, Hsu S, et al. Treatment of pustular psoriasis: from the medical board of the national psoriasis foundation. *Journal of the American Academy of Dermatology.* 2012;67(2):279-288.

## GPP Is Associated With Comorbidities That May Greatly Affect QOL

Retrospective Study of 102 Patients With GPP<sup>1</sup>

**64.4%**

had ≥1 comorbidity

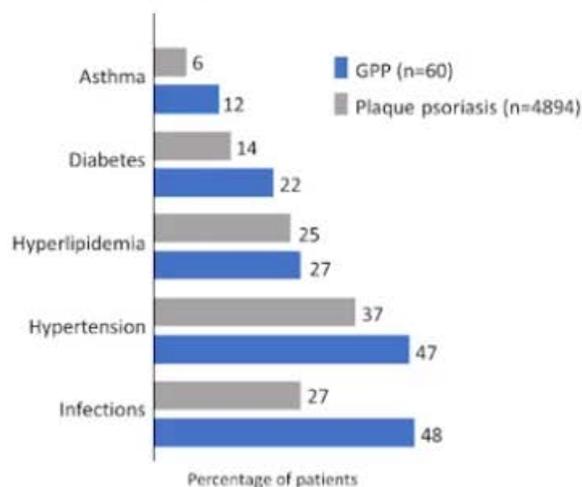
Most commonly:  
Hypertension  
Hyperlipidemia  
Diabetes mellitus

Retrospective Cohort Study of Patients With  
GPP and PsO<sup>3</sup>

**32%**

of patients with GPP had  
anxiety and depression  
vs <18% of  
patients with PsO

Cross-Sectional Study From the CorEvitas  
Psoriasis Registry<sup>2</sup>: Common Comorbidities



1. Choon SE, et al. *Int J Dermatol.* 2014;53(6):676-684. 2. Strober B, et al. AAD 2021. Poster 26588. 3. Kotowsky N, et al. Maui Derm 2020. Abstract R20-2784.  
Copyright © 2021 Springer Nature International GmbH. All rights reserved. SC-CRP-08348 Date of preparation July 2021

## OTHER

### Mesenchymal stromal cell therapy for psoriasis

**Lajos Kemeny, MD**

HCEMM-USZ Skin Research Group, University of Szeged, Szeged, Hungary

Psoriasis is multifactorial with a complex interplay between genetic, epigenetic, immune, and environmental factors. Biological therapies have transformed treatment, but no therapy is curative, and some patients cannot obtain control. There is promising data for stem cell therapy used to significantly improve, or even clear, psoriasis.

Though we have limited data for both autologous and allogeneic hematopoietic stem cell transplantation (HSCT) in psoriasis, case reports describing psoriasis resolution (or drastic improvement) for both HSCT types exist.<sup>1-3</sup>

Similar to HSCT, isolation and systemic administration of multipotent mesenchymal stromal/stem cells (MSCs) have therapeutic promise for autoimmune conditions, including psoriasis, but data remains limited. Fortunately, there are nine current clinical trials studying MSC therapy in autoimmune diseases.

MSCs exist in many tissues, are highly immunomodulatory, are easily accessible, and are relatively easy to isolate and maintain in tissue culture. MSCs inhibit activation of Th17 cells and reduce IL-17, convert Th17 cells into Tregs, and also reduce Tregs, inhibit Th1 and Th17 proliferation, and inhibit maturation and activation of dendritic cell precursors.<sup>4</sup>

Though adipose-derived MSCs (AD-MSC) are often preferred due to ease of collection, proliferative capacity, and survival, different types of MSCs can be obtained and systemically administered. Case reports of AD-MSCs include two patients with a reduction in disease severity from PASI ~25 to < 10, with the durable response across seven months.<sup>5</sup>

Complete, durable clearance after MSC therapy has also been seen in umbilical-derived MSCs therapy in 2 patients, gingival MSCs therapy in 1 patient, and <sup>6,7</sup> stromal vascular fraction (mix of AD-MSC and other cells) in a patient with severe, recalcitrant psoriasis.

#### Key points:

- Mesenchymal stromal/stem cells (MSCs) are highly immunomodulatory and can be harvested and systemically administered to patients who autoimmune diseases.
- MSC therapy offers a promising future option for patients with recalcitrant or severe psoriasis, and trials are underway to further study and perfect this technique for use in psoriasis.

#### References:

1. Masszi T, Farkas A, Remenyi P, et al. Ten-year remission of psoriasis after allogeneic but not autologous bone marrow transplantation. *DRM*. 2006;212(1):88-89.
2. Snowden JA, Badoglio M, Alexander T. The rise of autologous HCT for autoimmune diseases: what is behind it and what does it mean for the future of treatment? An update on behalf of the EBMT Autoimmune Diseases Working Party. *Expert Rev Clin Immunol*. 2019;15(10):981-985.

3. Chen W, Ren G, Zuo K, Huang X. Complete remission of both immunoglobulin light chain amyloidosis and psoriasis after autologous hematopoietic stem cell transplantation. *Medicine (Baltimore)*. 2018;97(50):e13589.
4. Veréb Z, Mázló A, Szabó A, et al. Vessel wall-derived mesenchymal stromal cells share similar differentiation potential and immunomodulatory properties with bone marrow-derived stromal cells. *Stem Cells Int*. 2020;2020:8847038.
5. De Jesus MM, Santiago JS, Trinidad CV, et al. Autologous adipose-derived mesenchymal stromal cells for the treatment of psoriasis vulgaris and psoriatic arthritis: a case report. *Cell Transplant*. 2016;25(11):2063-2069.
6. Chen H, Niu J-W, Ning H-M, et al. Treatment of psoriasis with mesenchymal stem cells. *Am J Med*. 2016;129(3):e13-14.
7. Wang SG, Hsu NC, Wang SM, Wang FN. Successful treatment of plaque psoriasis with allogeneic gingival mesenchymal stem cells: a case study. *Case Rep Dermatol Med*. 2020;2020:4617520.

## OTHER

### Detection and management of psoriatic arthritis: Spot the signs, act fast

Frank Behrens, MD

Goethe University, Frankfurt am Main, Germany

Psoriatic arthritis (PsA) is a common manifestation of psoriasis and leads to significantly worse quality of life (QOL) scores and daily work impairment, the skin-limited disease. Mortality rates in both psoriasis and psoriatic arthritis (PsA) are also elevated compared to the general population,<sup>1</sup> and despite overall temporal improvements and the advent of biologics, the gap remains.

Dermatologists can assist in early PsA diagnosis by screening for stiffness, pain at rest, and edema. Upon referral, Rheumatologists provide definitive diagnoses and can employ rapid imaging such as ultrasound, which can detect *early* signs of PsA (unlike x-ray).

Though 70% of patients with PsA show skin psoriasis 7-12 years prior to diagnosis, early diagnosis remains<sup>2</sup> challenging as PsA exists on a continuum. PsA risk factors include nail psoriasis (roughly 3-fold increase), high BMI, severe skin disease, smoking, and 1st-degree relatives with PsA. Serum biomarkers such as CXCL10 exist, but we need to develop more sensitive biomarkers are needed. Since the IL-23/IL-17 axis drives the PsA, we ideally will develop biomarkers to detect these changes early to prevent further joint damage.<sup>3</sup>

Promising data for IL-23 inhibition exists, as patients on guselkumab (GUS) obtained high ACR20 responses at week 24 (59% for GUS q4weeks, 52% for GUS q8weeks, vs 22% placebo), improving at week 52 (73%, 60%, and 56% with placebo crossover to GUS, respectively) and week 100 (75.9%, 73.8%, and 68.3% respectively).<sup>4</sup> Patients with prior inadequate response to TNF-blockers had similar results through 24 weeks.<sup>5</sup> QOL was also significantly improved. Risankizumab<sup>6</sup> produced similar results (51.3% vs 26.5% placebo at 24 weeks), with high PASI-90 response (55.0% vs 10.2% placebo).

#### Key points:

- Early detection of PsA is crucial to slow progression and joint damage. Screening for joint stiffness, edema, nail changes, and resting pain can be early clues. Future serum biomarkers may assist in early detection.
- IL-23 inhibition shows great promise in treating PsA, including in those who failed other therapies.

#### References:

1. Trends in mortality and cause-specific mortality among patients with psoriasis and psoriatic arthritis in Ontario, Canada. *Journal of the American Academy of Dermatology*. 2021;84(5):1302-1309.
2. Savage L, Tinazzi I, Zabotti A, Laws PM, Wittmann M, McGonagle D. Defining pre-clinical psoriatic arthritis in an integrated dermato-rheumatology environment. *J Clin Med*. 2020;9(10): E3262.
3. Scher JU, Ogdie A, Merola JF, Ritchlin C. Preventing psoriatic arthritis: focusing on patients with psoriasis at increased risk of transition. *Nat Rev Rheumatol*. 2019;15(3):153-166.
4. McInnes, I et al. Poster presented at EULAR 2021. Abstract POS 1027

5. Coates, LC et al. Oral presentation at EULAR 2021; abstract OP0230.
6. Ostar A, et al. Oral presentation at EULAR 2021; abstract OP0228

## New MOAs in the psoriasis pipeline

**Wolf-Henning Boehncke, MD, MA, IPC Councilor**

Hospital Universitaire de Geneve, Geneva, Switzerland

Professor Boehncke focused on novel treatment targets in the plaque psoriasis pipeline, including those targeting ROR- $\gamma$ , A3AR, Tyk2, and the newly approved IL-17A/F medications.

ROR- $\gamma$  is a transcription factor that regulates the transcription of genes encoding the crucial IL-17A and IL-17F. Inverse agonists can reduce cytokine expression via blocking this 'master regulator.' In Phase 2 studies, GSK2981278 effectively blocked IL-17 induction and reduced various cytokine levels (IL-17A/F, IL-22, IL-23p19) in subjects' skin biopsies.<sup>1</sup>

The drug piclidenoson targets the A3 Adenosine receptor (A3AR), which is overexpressed in psoriatic skin lesions, to reduce its expression. In a Phase 2 trial, piclidenoson showed linear, significant mean PASI improvement from ~20 to ~10 (vs 2 for placebo) across 12 weeks, and also reduction in A3AR mRNA.<sup>2, 3</sup>

TYK2 is a member of the JAK family linked to downstream IL-23 and IL-12 signaling and type 1 interferons (IFN). Expression of Tyk2 in dendritic cells is required for gene transcription and subsequent IL-23 production.<sup>4</sup> Two pivotal Phase 3 studies of the TYK2 inhibitor deucravacitinib display PASI-75 responses of 59%/54% (week 16) and 69%/59% (week 24), significantly superior to apremilast (35%/40% and 38%/38%,<sup>5</sup> respectively). Interestingly, GWAS studies found have a high expression of TYK2 linked to life-threatening COVID-19 illness; therefore, TYK2 may represent a therapeutic target.<sup>6</sup>

Bimekizumab and sonelokimab, drugs targeting *both IL-17A and IL-17F*, show impressive clinical improvement compared to only IL-17A inhibition. In a Phase 2b trial, subjects receiving sonelokimab achieved IGA0/1 in 88%, PASI-90 in 77%, and PASI-100 in 33% (vs 77%, 64%, and 28% for secukinumab, respectively).<sup>7</sup> Similarly, the selective inhibitor bimekizumab exhibited PASI-100 response in 74% (q4weeks) and 66% (q8weeks) vs 46.2% for secukinumab, durably across 48 weeks.<sup>8</sup>

### Key points:

- Fortunately, the psoriasis pipeline has many exciting new drugs targeting new mechanisms of action.
- Notably, TYK2 inhibition with deucravacitinib shows superior clinical efficacy to apremilast, and similarly, the IL-17A and F inhibitors sonelokimab and bimekizumab display superior efficacy to established IL-17A inhibitors.

### References

1. Smith SH, Peredo CE, Takeda Y, et al. Development of a topical treatment for psoriasis targeting rory: From bench to skin. *PLOS ONE*. 2016;11(2):e0147979.
2. Cohen S, Barer F, Itzhak I, Silverman MH, Fishman P. Inhibition of il-17 and il-23 in human keratinocytes by the a3 adenosine receptor agonist piclidenoson. *J Immunol Res*. 2018;2018:2310970.
3. David M, Akerman L, Ziv M, et al. Treatment of plaque-type psoriasis with oral CF101: data from an exploratory randomized phase 2 clinical trial. *Journal of the European Academy of Dermatology and Venereology*. 2012;26(3):361-367.

4. Nogueira M, Puig L, Torres T. Jak inhibitors for treatment of psoriasis: Focus on selective tyk2 inhibitors. *Drugs*. 2020;80(4):341-352.
5. Armstrong A. Efficacy and safety of deucravacitinib, an oral, selective tyrosine kinase 2 (TYK2) inhibitor, compared with placebo and apremilast in moderate to severe plaque psoriasis: results from the phase 3 POETYK PSO-1 POETYK PSO-2 studies. Presented at: American Academy of Dermatology Virtual Meeting Experience 2021; April 23-25,2020; virtual.
6. Pairo-Castineira E, Clohisey S, Klaric L, et al. Genetic mechanisms of critical illness in COVID-19. *Nature*. 2021;591(7848):92-98.
7. IL17A/F nanobody sonelokimab in patients with plaque psoriasis: a multicentre, randomised, placebo-controlled, phase 2b study. *The Lancet*. 2021;397(10284):1564-1575.
8. Reich K, Warren RB, Lebwohl M, et al. Bimekizumab versus secukinumab in plaque psoriasis. *New England Journal of Medicine*. 2021;385(2):142-152.

Want to watch IPC's symposium  
in full? Available now!

**Research on SARS-CoV-2 during the COVID-19  
pandemic crisis: An IPC tribute to young researchers**