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International Federation of Psoriasis Associations

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PEER-REVIEWED CONFERENCE REPORT

Patient Perspective

Two large studies –the 2020 UPLIFT survey of patients with psoriatic arthritis and the European PsoBarrier study in psoriasis– identified barriers to treatment and underscored the need to better manage persistent disease.

read more on PAGE 3

New Guidelines Psoriasis

The new evidence-based pan-European psoriasis guideline recommendations from EuroGuiDerm, including comorbid disease from arthritis to inflammatory bowel disease, contain detailed advice on the use of each individual drug.

read more on PAGE 13

POETYK Trial Results

The phase 3 POETYK PSO-1 and PSO-2 trials met all endpoints, demonstrating that TYK2 inhibitor deucravacitinib was effective and well-tolerated in patients with moderate-to-severe plaque psoriasis and was superior to apremilast.

read more on PAGE 17

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Contents

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MEDICOM MEDICAL PUBLISHERS

Head Office
Medicom Medical Publishers
Faas Eliaslaan 5
3742 AR Baarn
The Netherlands

Postal address
Medicom Medical Publishers
PO Box 90
3740 AB Baarn
The Netherlands

Telephone +31 85 4012 560
E-mail publishers@medicom-publishers.com

Letter from the Editor

Prof. Peter van de Kerkhof

Dear colleagues,

It is a pleasure to have been the Editor of this report on the 6th World Psoriasis and Psoriatic Arthritis. The congress is unique as it is organised by patient associations and not by an organisation of healthcare professionals. The result is a symposium that connects the various medical specialisms and healthcare providers with different disciplines involved in psoriasis care.

In this interdisciplinary symposium, important current information on gut-skin axis, cardiovascular comorbidity and arthritis were found.

The gap between patient perception and the perception of the healthcare providers has been presented in various presentations. Important is the population study UPLIFT, which is a true representation of the general population.

Disease progression is another major item. The value of patient registries as a resource for analysing long-term data remains very important.

COVID-19 has affected psoriasis care in various dimensions: the susceptibility to contract COVID-19; the effect of anti-psoriatic treatments on the course of COVID-19; and the efficacy of vaccinations during systemic anti-inflammatory treatments.

New treatments just around the corner include bimekizumab, an anti-IL-17 AF inhibitor, spesolimab, an IL-36 inhibitor, and the TYK 2 inhibitor deucravacitinib.
This report gives you an impression of the most important messages, without the ambition to be complete.

Best Regards,

Peter CM van de Kerkhof

Biography

Peter C.M. van de Kerkhof is emeritus Professor of Dermatology and immediate past chairman of the Department of Dermatology of Radboud University Nijmegen. He is currently the coordinating Medical Officer of the International Psoriasis Council and chair of the scientific advisory board of the Dutch burn association. He has been working for many years on the pathogenesis and treatment of psoriasis. He has published more than 700 publications in peer-reviewed journals and has given many presentations on invitation at international conferences. He has served as president of the ESDR, EDF, and the International Psoriasis Council, and was board member of various international societies. Current interests are pathogenesis and development of biomarkers for psoriasis; real clinical practice research; and personalised medicine.

Conflict of Interest Statement:
Consultancy services for: Celgene, Almirall, Amgen, Pfizer, Philips, AbbVie, Eli Lilly, Galderma, Novartis, Janssen Biotech, Janssen-Cilag, LEO Pharma, Sandoz, Mitsubishi Tanabe, Sandoz, Bristol Meyer Squibb, UCB, Dermavant.

Speaker services for: Celgene, Almirall, Eli Lilly, Novartis, Jansen-Cilag, LEO Pharma, Sandoz, Bristol Meyer Squibb.

Patient Perceptions and Epidemiology

Unresolved needs for patients with PsA despite growing therapeutic options

The multinational 2020 UPLIFT survey of patients with psoriatic arthritis (PsA) saw a greater proportion of patients receiving systemic treatment compared with the 2012 MAPP survey, and yet three-quarters of patients in UPLIFT considered their disease moderate-to-severe. On top of that, only half of patients reported seeing a healthcare provider in the past year. Hence, there is an unmet need to better manage persistent disease [1].

Patients with PsA experience a high disease burden and a wide range of comorbidities that negatively impact their health-related quality of life [2]. The 2012 Multinational Assessment of Psoriasis and Psoriatic Arthritis (MAPP) survey assessed the impact of psoriasis and PsA on patients [3]. MAPP results revealed a high patient-reported disease burden –measured by quality of life, work productivity, and treatment burden– and significant impact of PsA on physical function and the need for improved treatment.

2012 versus 2020

As the therapeutic landscape has evolved since the MAPP survey, the Understanding Psoriatic Disease Leveraging Insights for Treatment (UPLIFT) survey evaluated how patient perceptions and behaviours may have changed since MAPP and identified persisting areas of unmet need. UPLIFT was a multinational, online survey conducted from 2 March to 3 June 2020 in the USA, Canada, UK, France, Germany, Italy, Spain, and Japan. The MAPP survey was conducted in the same countries except for Japan. Both surveys included adults with healthcare provider-diagnosed psoriasis and/or PsA. Differences between the 2 populations included that the UPLIFT population was younger (mean age 43 vs 56 years), included more men (54% vs 40%), and was less obese (20% vs 36%) than the MAPP population [1].

Disease burden and treatment

Concerning disease burden, similar rates of dactylitis and joint involvement but higher rates of enthesitis were observed in patients with PsA in UPLIFT versus MAPP. Patients surveyed in UPLIFT had higher rates of comorbidities than patients in MAPP. The underlying reasons are not fully understood.

Considerably fewer untreated patients were observed in UPLIFT than in MAPP (17% vs 28%), but fewer patients reported seeing a healthcare provider in the past year in UPLIFT compared with MAPP. Although 78% of UPLIFT patients were receiving some form of PsA treatment, 74% characterised their PsA as moderate or severe versus 88% in MAPP [1].

Unmet need remains

Although a greater proportion of patients in the 2020 UPLIFT survey received current treatment compared with the 2012 MAPP survey, approximately three-quarters of patients in UPLIFT considered their disease moderate-to-severe. In addition, only half of patients reported seeing a healthcare provider in the past year. These results suggest that, although the number of available treatment options has increased since MAPP, an unmet need for PsA patient care remains [1].

1. Ogdie A. Changes in Patient Perceptions of Psoriatic Arthritis From 2012 to 2020: Results From the UPLIFT Survey. Abstract O5, 6th World Psoriasis & Psoriatic Arthritis Conference, 30 June–3 July 2021.
2. Gladman DD, et al. Ann Rheum Dis. 2005;64 Suppl 2(Suppl 2):ii14–7.
3. Kavanaugh A, et al. Rheumatol Ther. 2016;3:91–102.

PsoBarrier EU: Large survey evaluating quality of care in Europe

The PsoBarrier EU study was a European effort investigating over 1,300 patients with psoriasis. This study was awarded the best educational poster for furthering our understanding of how psoriasis and possibly psoriatic arthritis can be effectively treated with available measures [1]. This is one of the first international studies on barriers in psoriasis care.

A previous nationwide study demonstrated that psoriasis care continuously improved in Germany between 2004 and 2017, although some deficits persist. Few comparable studies in European countries were available. The PsoBarrier EU analysed the quality of healthcare in 4 European countries: Spain, Germany, Denmark, and Poland [2,3]. Patients were asked identical questions on a broad spectrum of issues, mainly patient-reported outcomes, but also questions about the severity of the disease.

Dr Anna Langenbruch (Universitätsklinikum Hamburg-Eppendorf, Germany) shared the results of the study concerning the long-term perspective of psoriasis and the therapeutic course in time [1]. Severity measured by PASI and quality of life measured by DLQI were highest in patients from Poland compared with the other countries, suggesting differences in healthcare between the participating countries. Nonetheless, satisfaction with the treatment was similar in Poland (65.1%) compared with Spain (68.5%), albeit lower than in Denmark (86.7%) and Spain (90.9%).

The next step will be to further analyse predictors of barriers for guideline-compliant treatment and to interpret those in the light of the respective healthcare system, and to identify needs for further action, which can be different depending on the healthcare system.

1. Langenbruch A. Quality of care and barriers to care for psoriasis in Europe – results of the PsoBarrier EU study. Poster P76, 6th World Psoriasis & Psoriatic Arthritis Conference, 30 June–3 July 2021.
2. Augustin M, et al. Arch Dermatol Res. 2016;308:389–400.
3. Langenbruch A, et al. J Eur Acad Dermatol Venereol. 2021;35:1536–42.

Bridging the gap between patients and access to psoriasis specialists

Access to medical specialists in psoriasis can be challenging. As was the case in Argentina, where the current study, awarded the 'Best patient organisation poster,' was performed [1]. Results demonstrated a gap between the number of patients in certain areas and access to medical specialists.

In 2015, the civil association for patients with psoriasis in Argentina, called AEPSO, published a survey conducted with 400 patients with psoriasis. This survey demonstrated that 38% of patients with psoriasis were diagnosed 1 year after symptom onset. This delay was 6 months to 10 years in patients with PsA. To reach a psoriasis diagnosis, patients needed to consult more than 5 dermatologists. This 2015 survey also showed that affected people tended to change dermatologists frequently because of the lack of treatment response.

The current study collected data from >500 dermatologists and rheumatologists in a database. Since 2016, there were 30,000 searches for a specialist. The database indicated that there are more dermatologists than rheumatologists. Dr Silvia Fernandez Barrio (AEPSO, Argentina) and colleagues also found that at least 7 cities have no rheumatologist, and 1 city has no dermatologist. Furthermore, they found that at least 7 cities have less than 2 dermatologists. In these areas with few or no healthcare professionals, there were 100 patient consultations. Hence, access to healthcare professionals is poor.

The observed gap between the number of patients in a certain area and the access to medical specialists can be bridged by educational programmes that aim to train dermatologists and rheumatologists in treating patients with psoriasis and psoriatic arthritis. In addition, there is a need for dermatologists and rheumatologists in some cities of Argentina.

1. Fernandez Barrio S. Correlation between patients' needs and their access to psoriasis specialists. Poster P82, 6th World Psoriasis & Psoriatic Arthritis Conference, 30 June–3 July 2021.

Psoriasis and PsA in transgender adults on hormone therapy

Feminising gender-affirming hormone therapy in transgender adults may decrease the risk of psoriasis but not psoriatic arthritis (PsA). Masculinising gender-affirming hormone therapy had no significant impact on the risk of developing psoriasis or PsA. This was found in a retrospective comparative cohort study [1].

Transgender dermatologic literature is limited; no data exists on the prevalence and risk of psoriasis and PsA in the transgender/gender-diverse populations. Ms Julia Gao (Fenway Health, MA, USA) and colleagues conducted a retrospective comparative cohort study with electronic health records of transgender/gender-diverse adults on masculinising or feminising hormone therapy and cisgender adults seen at Fenway Health between 1 August 2014 and 1 August 2020.

The sample of over 46,000 persons included approximately 1,400 adults on feminising hormone therapy, almost 1,600 adults on masculinising hormone therapy, over 25,000 cisgender men, approximately 17,000 cisgender women, 535 transmasculine adults not on gender-affirming hormone therapy, and 447 transfeminine adults not on gender-affirming hormone therapy. Of the cisgender adults, most cisgender men and over 11,000 cisgender women were not receiving exogenous hormone therapy such as testosterone replacement, hormonal birth control, or menopausal hormone replacement therapy.

Results indicated that patients on feminising hormone therapy were less likely to have psoriasis compared with

all cisgender men (OR 0.59; 95% CI 0.33–0.96; P=0.0339) and compared with cisgender men not receiving exogenous hormone therapy (OR 0.59; 95% CI 0.34–0.98; P=0.0388). Patients on masculinising hormone therapy were not at a significantly higher risk of having psoriasis compared with all cisgender women (OR 1.04; 95% CI 0.59–1.72).

No significant difference in the risk of PsA was found between patients on feminising hormone therapy compared with all cisgender men (OR 1.35; 95% CI 0.15–5.74) nor between patients on masculinising hormone therapy compared with all cisgender women (OR 1.35; 95% CI 0.15–5.74).

Transgender/gender-diverse adults on masculinising hormone therapy had a similar risk of psoriasis or PsA compared with cisgender women. In contrast, adults on feminising hormone therapy were significantly less likely to have psoriasis, but not PsA, compared with cisgender men. These findings indicate that transgender adults on gender-affirming hormone therapy are not at an increased risk of developing psoriasis or PsA.

1. Gao JL. Psoriasis and Psoriatic Arthritis in Transgender Patients on Hormone Therapy: A Retrospective Comparative Cohort Study. Abstract O4, 6th World Psoriasis & Psoriatic Arthritis Conference, 30 June–3 July 2021.

Disease Progression

Psoriasis: New disease severity classification

During a session organised by the International Psoriasis Council (IPC), Prof. Lone Skov (University of Copenhagen, Denmark), co-chair of the Psoriasis Severity Classification working group, presented the new disease classification [1]. The consensus document has recently been published [2].

Founded in 2004, the IPC (www.psoriasiscouncil.org) is a dermatologist-led, voluntary, global, non-profit organisation with a network of >100 psoriasis experts, thought leaders, and professionals, dedicated to improving patient care around the globe. Their mission is to improve the care of people with psoriasis worldwide through research, education, and advocacy.

Previous classification

To define whether or not the patient needed systemic treatment, a group of dermatologists from Europe graded psoriasis into mild and moderate-to-severe disease in 2011 [3]. Mild disease was defined as BSA ≤10, Psoriasis Area and Severity Index (PASI) ≤10, and Dermatology Life Quality Index (DLQI) ≤10, while moderate-to-severe psoriasis was defined as BSA >10 or PASI >10 and DLQI >10. Special clinical situations may change mild psoriasis to moderate-to-severe, including involvement of visible areas or severe nail involvement. However, there is no consensus on this classification because it has some limitations. Firstly, PASI and DLQI are often not used in clinical practice because they are time-consuming to measure. Furthermore, this classification does not consider the presence of areas difficult to treat with topical or special areas.

New IPC classification

Because of these limitations of the 2011 classification, the IPC recently aimed to redefine disease severity classification using a Delphi process [2]. According to the new disease severity classification, patients with psoriasis should be classified as either candidates for topical therapy or candidates for systemic therapy. The latter are patients who meet ≥1 of the following criteria: BSA >10, disease involving special areas, specifically areas that are difficult to treat with topical therapy (e.g. face, palms, soles, genitals, scalp, and nails), and failure of topical therapy.

This new classification has some limitations. Firstly, no patient-reported outcomes and no definition of failure of topical therapy are incorporated [1]. Moreover, no general dermatologists nor patients were involved in the process. Strengths include that the recommendations were patient-oriented and developed by an international group of dermatologists with expertise in psoriasis from all over the world. In addition, the proposed disease classification is simple, practical, and easy to use in daily practice. Based on this definition, whether a patient is a candidate for topical or systemic treatment is easily decided.

Future aims include demonstrating the new classification in real-world practice. "We should focus on educating regulatory bodies, clinicians, and patients on the new classification," concluded Prof. Skov.

1. Skov L. IPC's disease severity classification: What it means in the clinic. 6th World Psoriasis & Psoriatic Arthritis Conference, 30 June–3 July 2021.
2. Strober B, et al. J Am Acad Dermatol. 2020;82:117-–22.
3. Mrowietz U, et al. Arch Dermatol Res. 2011;303:1–10.

Active PsA: Biomarkers distinguish radiographic progressors from non-progressors

Patients with psoriatic arthritis (PsA) who progress to radiographic damage can potentially be discriminated from those who do not progress by 103 biomarker peptides, corresponding to 69 proteins. This has been identified using 2 complementary proteomic approaches and a combination of univariate and machine learning statistical analysis [1].

A delay in the diagnosis and treatment of patients with PsA leads to poor radiographic and functional outcomes [2]. So, identifying which patients might progress radiographically is essential. This unmet need has been recognised by the Group for Research and Assessment of Psoriasis and Psoriatic Arthritis (GRAPPA) [3]. Biomarkers for radiographic joint damage could assist in early-stage identification of patients likely to progress as well as identifying those who are progressing despite therapy.

The previous phase 3 SPIRIT-P1 trial (NCT01695239) demonstrated that treatment with the high-affinity IL-17A antagonist ixekizumab resulted in reduced progression of structural damage in patients with active PsA [4]. Nonetheless, 5–10% of patients who did progress may have benefitted from a more aggressive treatment if identified using biomarkers at baseline.

The aim of the current sub-analysis was to identify protein biomarkers that might distinguish at baseline those patients who progressed to joint damage from those who did not [1]. To this end, mass spectrometry-based proteomics was performed. Baseline serum samples were obtained from 83 participants of the SPIRIT-P1 trial. Radiographic progression was defined as those who showed a >0.5 change from baseline modified total Sharp score (mTSS) at week 24 or 52.

On univariate analysis, targeted proteomics identified 4 differentially expressed candidate peptides (P<0.01). With subsequent machine-learning random forest modelling, the top-15 candidate peptides of the previously used protein set were identified (ROC AUC of 0.85). The unbiased analysis found 74 peptides that were significantly differentially expressed between those who progressed and those who did not (P<0.01). Subsequent random forest modelling based on unbiased proteomics revealed a set of 15 proteins –distinct from the targeted set– that could distinguish progressors from non-progressors (ROC AUC of 0.94).

Baseline discrimination of progressors versus non-progressors was obtained in both discovery and targeted analysis. Peptides from the univariate and random forest models of the targeted and discovery analyses were combined to generate a list of 103 peptide candidate biomarkers of progression to joint damage in PsA.

Further work needs to verify whether the peptides within the 103 candidates can discriminate progression from non-progression and subsequently validate them using patient samples from a separate cohort.

1. Coleman O. Identification of serum protein biomarkers at baseline to distinguish radiographic progressors from non-progressors in patients with active Psoriatic Arthritis (PsA). Abstract O1, 6th World Psoriasis & Psoriatic Arthritis Conference, 30 June–3 July 2021.
2. Ocampo V, Gladman D. F1000Res. 2019;8:F1000 Faculty Rev-1665.
3. Ritchlin CT, et al. J Rheumatol. 2010;37:462-7.
4. Mease PJ, et al. Ann Rheum Dis. 2017;76:79-87.

Immune checkpoint inhibitors in patients with pre-existing psoriasis

In a recent study, treatment with immune checkpoint inhibitors (ICIs) was associated with frequent disease exacerbations in patients with pre-existing psoriasis, but flares were manageable with standard psoriasis treatment. Few patients required discontinuation of ICIs. In addition, this study revealed excellent tumour outcomes [1].

ICIs are approved to treat multiple cancers [2]. Although retrospective analyses have demonstrated acceptable safety and similar efficacy of ICIs in patients with autoimmune diseases, they are often excluded for initial trials on ICIs due to concern for immune-related adverse events (irAEs). Even though ICIs have shown acceptable safety in patients with an autoimmune disease, disease flares and irAEs may still occur. Outcomes of ICI treatment in patients with psoriasis are not well-described.

In this retrospective, multicentre, cohort study, patients with pre-existing psoriasis who received ICI treatment for cancer

were evaluated [1]. The 76 patients studied (66% men; median age 67 years) received the following ICI drugs: 67% received anti-PD-1/anti-PD-L1 antibodies, 11% anti-CTLA-4 antibodies, and 22% combination anti-PD-1/anti-CTLA-4. All patients had pre-existing psoriasis, most frequently plaque psoriasis (61%) and in some cases comorbid psoriatic arthritis (PsA; 20%). Over half of patients (54%) had received prior therapy for psoriasis, and only 2 patients (3%) were on active immunosuppression at initiation of the ICIs. With ICI treatment, 43 patients (57%) experienced a psoriasis flare. The median time from the initiation of ICI treatment to psoriasis flare was 44 days. Of the patients experiencing a flare, 23 (53%) were managed with topical therapy only. Only 5 patients (7%) needed to discontinue the ICIs due to a psoriasis flare.

Progression-free survival (PFS) and overall survival (OS) were significantly longer in patients with a psoriasis flare versus those without a flare (median PFS 39 vs 5.5 months, P=0.034; median OS not reached vs 29.3 months, P=0.045, respectively).

In this study, ICI treatment was associated with flares of pre-existing psoriasis. Most flares were manageable with topical treatment and few patients required ICI discontinuation. In addition, the occurrence of psoriasis flares was associated with improved survival. These results reveal excellent tumour outcomes, as patients who experienced disease exacerbations performed at least as well as those who did not, given the association of flares with improved PFS.

1. Halle B. Immune checkpoint inhibitors in patients with pre-existing psoriasis associated with manageable disease exacerbations and excellent tumor outcomes. Abstract O2, 6th World Psoriasis & Psoriatic Arthritis Conference, 30 June–3 July 2021.
2. Vaddepally RK, et al. Cancers (Basel). 2020;12:738.

Axial involvement is critical in psoriatic arthritis

The presence of axial involvement in patients with psoriatic arthritis (PsA) is associated with significantly worse disease status [1]. In the current study, axial involvement was identified in more than half of patients [2]. These results, awarded the best clinical poster, demonstrated that diagnostics of axial involvement are critical in clinical practice.

Dr Elena Gubar (Nasonova Research Institute of Rheumatology, Russia) and colleagues analysed disease activity and characteristics of patients with PsA with and without radiographic sacroiliitis in clinical practice.

Patients with PsA (n=385; 213 women and 172 men) according to CASPAR criteria were included. Median age was 45 years; median disease duration was 3.4 years. Patients were divided based on the presence of radiographic sacroiliitis, defined as bilateral grade ≥2 or unilateral grade ≥3:

- with radiographic sacroiliitis: n=214 (55.6%), 108 women and 106 men; and
- without radiographic sacroiliitis: n=171 (44.4%), 105 women and 66 men.

Differences were observed between these 2 groups. HLA-B27 antigen status was positive in 62 patients with radiographic sacroiliitis, compared with 26 patients without radiographic sacroiliitis (OR 1.9). Median tender joint count (TJC) was 9 in patients with radiographic sacroiliitis versus 6 in patients without radiographic sacroiliitis (P=0.02).

Disease activity was measured by Disease Activity Index for Psoriatic Arthritis (DAPSA) and Bath Ankylosing Spondylitis Disease Activity Index (BASDAI). In patients with radiographic sacroiliitis, DAPSA was higher in patients with versus without radiographic sacroiliitis (28.4 vs 20.0; P<0.05). BASDAI was 1.6 in patients with radiographic sacroiliitis versus 0, respectively (P<0.05). Leeds Enthesitis Index (LEI) was 0 in both patient groups. Dactylitis was present in 71 patients (33.2%) with radiographic sacroiliitis compared with 32 patients (18.7%) without radiographic sacroiliitis (OR 2.2). Furthermore, erosive radiographic arthritis of the feet occurred more often in patients with than without radiographic sacroiliitis (27.1% vs 17.0%; OR 1.8). The affected skin lesion area, evaluated in terms of body surface area (BSA) ≥3% was present in 120 patients with radiographic sacroiliitis and in 141 patients without (OR 0.6). Finally, the median C-reactive protein level in patients with radiographic sacroiliitis was 0.9 mg/dL, whereas in patients without radiographic sacroiliitis it was 0.8 mg/dL (P=0.03).

These results show that many differences are present between patients with and without radiographic sacroiliitis and that patients with radiographic sacroiliitis have more severe disease. Therefore, proper diagnostics of axial involvement are crucial.

1. Mease PJ, et al. J Rheumatol. 2018;45:1389–96.
2. Gubar E. Association of axial involvement with more severe disease status in psoriatic arthritis patients. Poster P6, 6th World Psoriasis & Psoriatic Arthritis Conference, 30 June–3 July 2021.

COVID-19

Psoriasis registries yield important data about COVID-19

Shortly after COVID-19 was declared a pandemic, the PsoProtect registry was set up. The patient counterpart PsoProtectMe was launched at the beginning of May. These registries yielded interesting data to inform guidelines.

"These efforts were initiated to address unmet needs in the pandemic," Dr Satveer Mahil (St John's Institute of Dermatology, UK) explained [1]. Psoriasis is a common, lifelong immune-mediated condition associated with long-term health conditions, including obesity and mental health issues.

Early in the pandemic several risk factors were shown to be associated with COVID-19-related death, such as chronic liver disease and obesity [2]. "These factors are relevant to our patients with psoriasis," said Dr Mahil. Moreover, the pathogenesis of psoriasis and COVID-19 show overlapping immune pathways [3]. Finally, psoriasis treatment affects the immune system.

Thus, it was hypothesised that in the early stage of a SARS-CoV-2 infection agents used to treat psoriasis may suppress a protective antiviral immune response. At a later stage, some patients developed an overwhelming hyperimmune response, the hyperinflammatory phase [4]. "Could it be that these drugs are protective in this later phase?"

In search of answers, 2 registries were set up with the following aims:

- PsoProtect (www.psoprotect.org): to characterise the course of COVID-19 in people with psoriasis and identify factors associated with severe COVID-19; and
- PsoProtectMe (www.psoprotectme.org): to understand experiences of people with psoriasis in the pandemic.

PsoProtect is an international registry for clinicians to report outcomes of COVID-19 in individuals with psoriasis. Outcomes can be reported through a simple case report form. PsoProtectMe is a companion global registry for people with psoriasis to self-report their experiences during the pandemic, irrespective of whether they have had COVID-19. PsoProtectMe contains optional additional questions about COVID-19 risk-mitigating behaviour such as shielding and validated screening tools evaluating depression and anxiety. The website is a global and collaborative effort.

Currently, over 1,100 clinician-reported cases of COVID-19 in patients with psoriasis are registered in PsoProtect, mainly from Europe. Approximately 4,500 people with psoriasis have completed the PsoProtectMe survey. Many countries from Europe to South America are well represented.

The first paper evaluating data from PsoProtect demonstrated that most patients with clinician-reported COVID-19 were receiving drugs that affect the immune system (71% biologics and 18% non-biologics) [5]. "In this cohort of patients treated with immunosuppressive agents, >90% fully recovered from COVID-19. In addition, risk factors for hospitalisation for COVID-19 in people with psoriasis were similar to risk factors in the general population," Dr Mahil elaborated. Patients on non-biologic immunosuppressants had an increased risk of hospitalisation for COVID-19 compared with those taking biologics (OR 2.84). This finding was also observed in other registries, particularly in a rheumatology registry and in SECURE-IBD" [6].

In a joint study by PsoProtect and the CORE-UK study groups, Dr Mahil and colleagues found that patients with inflammatory skin and joint diseases receiving biologics were performing more stringent risk-mitigating behaviour during the COVID-19 pandemic compared with those receiving standard systemic or no systemic therapy (shielding in 66%, 59%, and 59%, respectively) [7]. The greater risk-mitigating behaviour among those receiving biologics may contribute to the reported lower risk of adverse COVID-19 outcomes in this group.

In a separate analysis of this registry, Dr Mahil and others showed that a self-reported worsening of psoriasis in the COVID-19 pandemic was associated with anxiety and depression [8]. Furthermore, 19% of participants delayed or stopped their tablet or injection treatment for psoriasis during the pandemic. Delaying/stopping treatment was associated with worsening psoriasis (OR 2.9). The most common reason for delaying/stopping was concern regarding complications

related to COVID-19. Anxiety and depression were more prevalent in those who delayed/stopped medication compared with those who continued their psoriasis treatment (42.8% vs 32.4%). These outcomes contributed to the development of a statement on COVID-19 and psoriasis by the IPC [9]. This was reflected into the National Psoriasis Foundation COVID-19 Task force Guidance for the management of psoriatic disease during the pandemic [10].

1. Mahil S. Psoriasis and COVID-19 – Findings from PsoProtectMe. 6th World Psoriasis & Psoriatic Arthritis Conference, 30 June–3 July 2021.
2. Williamson EJ, et al. Nature. 2020;584:430–6.
3. Schett G, et al. Nat Rev Immunol. 2020;20:271–2.
4. Siddiqi HK, Mehra MR. J Heart Lung Transplant. 2020;39:405–7.
5. Mahil SK, et al. J Allergy Clin Immunol. 2021;147:60–71.
6. Akiyama S, et al. Ann Rheum Dis. 2020 Oct 13:annrheumdis-2020-218946.
7. Mahil SK, et al. Br J Dermatol. 2021;185:80–90.
8. Mahil SK, et al. J Eur Acad Dermatol Venereol. 2021 Jun 17. Doi: 10.1111/jdv.17450.
9. IPC Statement on COVID-19 and Psoriasis, 1 September 2020. www.psoriasiscouncil.org/blog/COVID-19-Statement.htm
10. Gelfand JM, et al. J Am Acad Dermatol. 2021;84:1254–68.

COVID-19 affects patients and care

Be aware of the impact of social distancing on patients with psoriasis. "It hits them," Prof. Peter van de Kerkhof (Radboudumc, the Netherlands) emphasised [1]. Telemedicine in the treatment of psoriasis is an important 'add-on,' but not a complete replacement.

From the start of the COVID-19 pandemic to 17 May 2020, rates increased in the general population concerning anxiety (6.33% to 50.9%), depression (14.6% to 48.3%), post-traumatic stress disorder (7% to 53.8%), psychological distress (34.43% to 38%), and stress (8.1% to 81.9%) [2]. Risk factors associated with distress measures included female gender, younger age group (≤40 years), presence of chronic and psychiatric illnesses, unemployment, student status, and frequent exposure to social media and news concerning COVID-19. "One can imagine that in patients with psoriasis, in whom the social functioning is impaired and impacted by their disease, the effect of COVID-19 on mental health will be quite severe," Prof. Van de Kerkhof added.

A postal survey in Germany among patients with psoriasis (n=205) demonstrated that 19.5% missed an appointment and about 10% changed therapy due to the pandemic [3]. Treatment alterations were encouraged by patients (50%) and physicians (40%), whereas cancellations of appointments mostly occurred at patients' request (70%). Changes in treatment and appointments were associated with higher psoriasis severity scores and more frequent disease aggravations. "So, not only on the mental aspect but also on the physical aspect of psoriasis, COVID-19 has had its impact," Prof. Van de Kerkhof concluded.

Telemedicine

Telemedicine may provide an opportunity to guarantee adequate treatment of psoriasis during the pandemic. A US survey was sent out to patients who attended telehealth appointments during the COVID-19 pandemic [4]. Out of 894 invitations sent, 168 patients completed this survey. Respondents most commonly liked telemedicine because of time efficiency (81.1%), not requiring transportation (74.2%), and maintaining social distancing (73.6). On the other hand, the most common reasons respondents did not like telemedicine were due to lack of physical touch with the doctor (26.8%) and the feeling they received an inadequate assessment (15.7%) because the doctor had not really seen their skin. Few patients reported that they were unlikely to undertake another telemedicine visit (9.94%) or recommend a telemedicine visit to others (6.92%).

Because the regulations for telemedicine were not always optimal during the COVID-19 pandemic, authors from France and Italy published a call to action and suggested a framework for telemedicine in healthcare [5]. Their first recommendation was to integrate telemedicine into international and national guidelines for public health. Secondly, the definition of national regulations and funding of frameworks for telemedicine should be optimised. Thirdly, they advised that a communication toolkit should exist to inform and educate the population on the adequate use of telemedicine.

A controlled trial (NCT02358135) randomised adults with psoriasis to online care (n=148) or in-person care (n=148) [6]. Between-group differences in the Psoriasis Area and Severity Index (PASI) score and body surface area (BSA) were within prespecified equivalence margins. "So, these methods of care can be performed quite well," concluded Prof. Van de Kerkhof.

There are some difficulties with telemedicine. Firstly, special regions are either embarrassing for the patient or difficult to visualise, such as lesions in the genital area or on the elbow or scalp. Also, the inspection of the entire body surface is difficult with telemedicine. In-person consultation provides the best empathic interaction. Investigation of the joint, tendinitis, and dactylitis, as well as screening for uveitis, inflammatory bowel disease, and auto-immune disease is difficult via the internet.

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Vaccination feasible in people with psoriatic disease

When the first SARS-CoV-2 vaccines were registered, there was particularly discussion about the RNA-based vaccines [1]. In the general population, antibodies have been shown to develop after 2 vaccination steps, independent of the age of the vaccinated people [2,3]. Whether patients with chronic inflammatory diseases are sufficiently protected remained a matter of debate, as well as the potential differences between patients receiving conventional disease-modifying drugs or biologics.

A large international trial showed that SARS-CoV-2 mRNA vaccines lead to the development of antibodies in immunosuppressed patients without considerable side effects or induction of disease flares [2]. These early data were reassuring because they demonstrated that patients with psoriasis and psoriatic arthritis (PsA), even under treatment, will develop a high level of neutralising antibodies and/or protective antibodies against SARS-CoV-2 vaccination during therapy. This study showed no major difference between healthy adults and patients concerning adverse events after vaccination. Fever was more often seen in the healthy group (13.5%) compared with the patient group (0%).

EuroGuiDerm Guideline

The EuroGuiDerm Guideline for the systemic treatment of psoriasis vulgaris recommends vaccinating people with psoriatic disease with the approved vaccines [4]. "Until now, there is no scientific reason to deviate from this first recommendation," argued Prof. Ulrich Mrowietz (University Medical Centre Schleswig-Holstein, Germany) [5].

The second guideline recommendation is that psoriasis treatment with any approved medication should not be interrupted during the phase of vaccination. However, immunosuppressive drugs may be shortly interrupted because the antibody response might be ameliorated by taking these drugs. According to currently available data, other drugs do not seem to cause any problem in combination with a COVID-19 vaccination.

Thirdly, the EuroGuiDerm Guideline stated that full protection from vaccination is not guaranteed for every person. Prof. Mrowietz advises recommending patients taking immunosuppressive drugs to continue with the common measures for disease prevention, such as wearing masks and keeping distance from other people, particularly those who have not been vaccinated yet. The last recommendation is that people with psoriasis should be receiving other vaccines, such as against influenza and *pneumococci*.

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3. Anderson EJ, et al. N Engl J Med. 2020;383:2427–38.
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5. Mrowietz U. COVID-19: Vaccination against SARS-CoV-2 in people with psoriatic disease. 6th World Psoriasis & Psoriatic Arthritis Conference, 30 June–3 July 2021.

Low COVID-19 risk for patients with psoriasis on biologic treatment

Patients with moderate-to-severe psoriasis treated with a biologic drug have a similar or possibly lower risk of contracting COVID-19 compared with the general population (0.3% vs 1.8%) [1]. This was found in a multicentre cohort study from Canada, awarded the 'Best young researcher poster' at the WPPAC Congress. These findings can guide physicians in continuing biologic therapy during the pandemic.

The COVID-19 pandemic has underlined an urgent need for adequate treatment, especially for people living with psoriatic disease and other chronic illnesses. During these uncertain times, many patients have been inquiring whether they should interrupt their treatment.

Previously, Dr Jorge Georgakopoulos (University of Toronto, Canada) and colleagues demonstrated that very few patients (1.1%) discontinued biologic therapy due to concerns regarding COVID-19 complications [2]. Around the same time, the European and American dermatology guidelines were published, which recommend continuing biologic therapy in patients who have not tested positive for or exhibited signs and/or symptoms of COVID-19. If these signs and symptoms are present or a patient is SARS-CoV-2-positive, the advice is to postpone biologic therapy.

The current multicentre, retrospective cohort study evaluated adult and paediatric patients treated with a biologic for moderate-to-severe psoriasis since the onset of the global pandemic [1]. Of 2,647 patients on biologic therapy who met the inclusion criteria, only 9 patients (0.3%) had a confirmed

SARS-CoV-2 infection. Symptoms of COVID-19 were present in 6 of these patients (67%); 3 patients (33%) were asymptomatic carriers. Of the 9 infected patients, 6 (67%) discontinued biologic therapy due to COVID-19.

These results suggest that interrupting biologic treatment should be reserved for clinically unwell patients because symptoms for COVID-19-positive patients with psoriasis on a biologic were mild and no patients required oxygenation or hospitalisation.

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Pathogenesis and the Gut-Skin Axis

Psoriasis: Disrupted gut-skin axis

An evolving field is the impact of microbiota and the intestinal barrier on the pathophysiology of chronic inflammatory diseases, including psoriasis and psoriatic arthritis. Psoriasis contributes to the disruption of the intestinal barrier integrity and to the translocation of bacterial metabolites. This can activate the inflammatory response, leading to the exacerbation of skin lesions.

Increasing evidence from experimental and clinical studies suggests an important role for the interaction between an altered intestinal microbiome (dysbiosis), intestinal barrier damage, and the immune system in the pathogenesis of psoriasis. These findings triggered research towards the gut-skin axis.

Dr Mariusz Sikora (Medical University of Warsaw, Poland) and colleagues studied the influence of the disease activity of psoriasis on the intestinal barrier permeability and the blood concentration of bacterial metabolites and its clinical implications, such as the presence of gastrointestinal symptoms and psoriasis comorbidities [1].

Patients with mild-to-severe plaque psoriasis (n=120) were included. Intestinal barrier integrity was assessed using serum concentrations of claudin-3, a modulator of intestinal tight junctions, and with intestinal fatty acid-binding protein, a marker of enterocyte damage. The levels of these markers were significantly higher in patients with psoriasis compared with healthy controls ($P<0.001$ and $P<0.05$, respectively).

The concentration of the gut microbiota-associated metabolites trimethylamine N-oxide (TMAO) and indoxyl sulphate were measured with high-performance liquid chromatography. The concentration of TMAO positively correlated with the cardiovascular risk, calculated according to the Framingham and QRISK-2 scales ($r=0.679$; $P<0.05$). Translocation of bacterial metabolites through an altered intestinal barrier in psoriasis is a potential mechanism linking gut dysbiosis to increased cardiovascular risk.

Further research on the intestinal barrier is needed to get a better understanding of the impact this may have on skin lesions. Potential treatments that are impacting gut microbiota, such as faecal transplantation, probiotics, prebiotics, antibiotics, and molecules affecting intestinal barrier permeability are being intensively studied as therapies that can potentially break the vicious circle affecting the disrupted gut-skin axis in patients with psoriasis.

1. Sikora M. Intestinal barrier and gut microbiota-derived metabolites in the pathophysiology of psoriasis. Poster P58, 6th World Psoriasis & Psoriatic Arthritis Conference, 30 June–3 July 2021.

Psoriasis associated with increased duodenum inflammation

The duodenum of patients with psoriasis is characterised by subclinical inflammation. In half of patients, the gut mucosa had an increased permeability. This study, which was awarded the best scientific poster, fits well into the discussion about the gut-skin axis and the importance of the microbiome in psoriasis and psoriatic arthritis (PsA).

Psoriasis has a known association with inflammatory bowel disease (IBD) in terms of comorbidity, with a similar clinical course and some overlap in genotype. Even patients with psoriasis who do not have IBD are more likely to suffer from

gastrointestinal symptoms. Studies from the 1990s showed increased numbers of eosinophilic granulocytes and mast cells in the duodenal mucosa of patients with psoriasis. In ulcerative colitis, these 2 cell types are implicated in increased intestinal permeability. Therefore, Prof. Maria Lampinen (Uppsala University, Sweden) and colleagues aimed to investigate the role of these cell types in patients with psoriasis [1].

The current study included 18 patients with psoriasis and 15 healthy controls. None of the participants had any gastrointestinal diagnosis. Biopsy samples were collected both from the duodenum and from the sigmoid colon. No visible inflammation was observed in the intestine of the patients, nor did the pathologist see any signs of damage.

The expression of several types of immune cells was assessed with immunohistochemistry and flow cytometry. Interestingly, not only were increased numbers of eosinophils and mast cells found, but also increased numbers of proinflammatory macrophages and cytotoxic CD8-positive T cells, which had increased expression of the activation marker CD69. Eosinophils were also activated, with increased expression of CD66b, a marker for degranulation.

These results suggest that, even in the absence of apparent inflammation, the intestinal immune cells in patients with psoriasis have an increased potential for inflammatory responses.

1. Lampinen M. Subclinical inflammation in the duodenum with increased numbers of activated immune cells in patients with mild to moderate psoriasis. Poster P17, 6th World Psoriasis & Psoriatic Arthritis Conference, 30 June–3 July 2021.

Whole-exome sequencing to study the underlying pathogenesis of psoriasis

Using laser-capture microdissection and subsequent whole-genome sequencing, Mr Sigurgeir Olafsson (University of Cambridge, UK) and colleagues were able to analyse skin biopsies from many patients with psoriasis vulgaris [1]. This technique of whole-exome sequencing will improve understanding of the underlying pathogenesis of psoriasis vulgaris.

Somatic mutations may contribute to the pathogenesis of complex diseases. Also, chronic inflammation can affect disease progression. Although the hyperproliferation of keratinocytes is associated with the disease status of psoriasis, no differences have been observed in the clonal composition of lesional and non-lesional epidermis. The current study aimed to investigate these differences.

In this study, laser-capture microdissection was used to isolate 140 small samples of epidermis from 16 patient donors. Afterwards, these samples were assessed by whole-exome sequencing. In previous studies, hundreds of oncogenic mutations have been found in each square centimetre of skin.

Using a special method called dNdScv, 4 genes were identified that are potentially involved in psoriasis vulgaris. One of these genes, *GXYLT1*, has not been identified in previous studies. In samples from 1 patient who had previously been treated with psoralens plus UVA, thousands of mutations per exome were found. These findings suggested psoralens plus UVA treatment to be highly mutagenic, causing a characteristic mutational signature.

This study describes the clonal structure, mutation burden, and positive selection operating in lesional and non-lesional skin biopsies from patients with psoriasis. In this preliminary data, differences associated with psoriasis were not readily apparent.

Mr Olafsson and colleagues plan to sequence approximately 1,200 exomes from 110–120 patients as part of this project. They will compare lesional and non-lesional skins in terms of their mutation burden, clonal structure, mutagen activity, and selection landscape.

1. Olafsson S. Whole-exome sequencing of hundreds of biopsies reveals the somatic evolutionary landscape of psoriatic skin. Poster P52, 6th World Psoriasis & Psoriatic Arthritis Conference, 30 June–3 July 2021.

Treatment Guidelines

Pan-European guidelines for the treatment of psoriasis and comorbid conditions

Recently, guidelines for the treatment of psoriasis have been developed under the umbrella of a new system called EuroGuiDerm, a pan-European initiative launched by the European Dermatology Forum and supported by many national dermatological societies to develop high-quality joint European guidelines [1]. Guideline coordinator Prof. Alexander Nast (Charité Universitätsmedizin Berlin, Germany) gave an excellent overview of the development and recommendations of these and previous guidelines [2].

Most recommended treatments in the EuroGuiDerm guidelines are quite familiar [1]. "We still have the traditional treatments (i.e. acitretin, ciclosporin, fumarates, and methotrexate) as first-line. Some patients bypass the first-line treatments, going directly into other treatment options, especially in severe cases if treatment success cannot be expected with the conventional drugs," Prof. Nast explained.

Efficacy compared

A network meta-analysis, which was used as an evidence basis for the guidelines, provided estimates of all pairwise intervention comparisons that are connected within a network, including those that have never been directly compared in randomised controlled trials, the latter being referred to as indirect evidence [3]. "There are some pronounced differences in the efficacy," Prof. Nast mentioned (see Figure). Safety is more difficult to compare because different side effects cannot be grouped easily.

The guidelines contain detailed advice on the use of each individual drug. Important factors to consider are lab controls, adverse drug reactions, special considerations during treatment, contraindications, and drug interactions.

Management of PsA

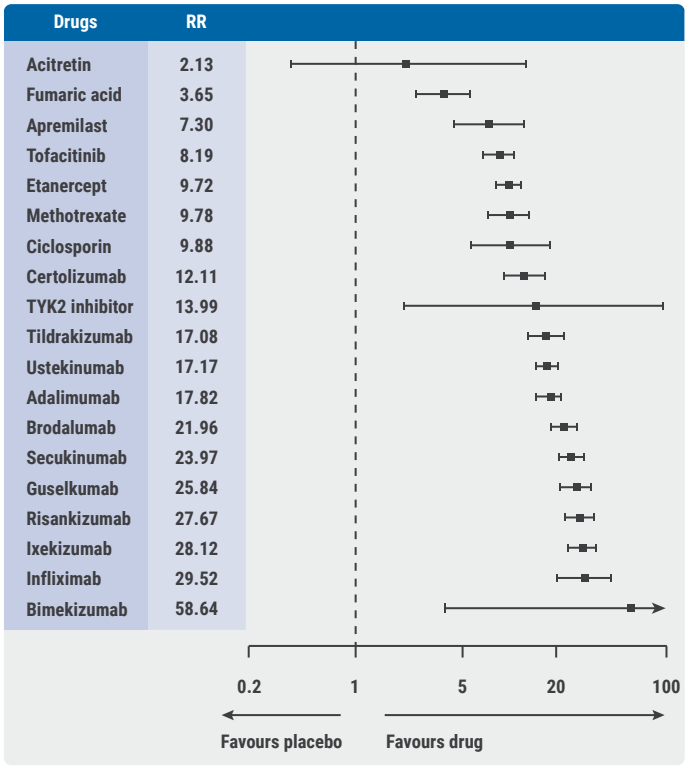
How should patients with psoriasis and concomitant psoriatic arthritis (PsA) be managed? The guidelines recommend starting a conventional synthetic DMARD (preferably methotrexate) early to prevent disease progression and erosive destruction of joints for patients with moderate-to-severe psoriasis and peripheral active joint involvement despite the usage of NSAIDs. Alternatively, glucocorticoid site injections in case of poor prognosis due to polyarthritis, increased inflammatory markers and erosive changes, and extra-articular musculoskeletal manifestations.

For inadequately responding patients after ≥1 synthetic DMARD, the use of biological DMARDs is recommended as monotherapy or in combination with synthetic DMARDs. Concerning efficacy for patients with PsA, a subsequent systematic review was published [4]. "The differences are much less pronounced compared with the treatment of plaque-type psoriasis," Prof. Nast explained. Taken together in a decision aid, methotrexate is first-line treatment of psoriasis with joint involvement. "If this does not work, biologics should be considered next."

Management of comorbid IBD

How should patients with psoriasis with comorbid inflammatory bowel disease (IBD) be managed? "This is a

Figure: PASI 90: Relative effects from the network meta-analysis against placebo [3]



patient group where we have to be careful," Prof. Nast stressed. IL-17 blockers are not strongly recommended. Ustekinumab is a better option. The choice after that is anti-IL-23. "If you need a cheaper option or an oral treatment, we also give guidance on that, with methotrexate being preferred for Crohn's disease and ciclosporin for ulcerative colitis," Prof. Nast concluded.

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Psoriatic arthritis: Guidelines and best practice

In recent years, many treatment options for patients with psoriatic arthritis (PsA) have become available, in addition to the traditional adjunctive drugs and DMARDs. These include biologic agents, targeted synthetic DMARDs, JAK inhibitors, PDE4 inhibitors, and many agents in development [1].

Prof. Philip Mease (Swedish Medical Center, WA, USA) discussed several new drugs on the block, with a focus on drugs that have recently been approved or will be approved in the near future, including IL-17 blockers, IL-23 blockers, and JAK inhibitors [2,3]. Results from the phase 2b BE ACTIVE study (NCT02969525) on IL-17A/F blocker bimekizumab and the phase 3 PATERA study (NCT03598751) on IL-17A blocker netakimab are promising [4,5]. "We see good musculoskeletal and skin responses with these medications," Prof. Mease mentioned, "with a safety profile similar to other IL-17 inhibitors." Another monoclonal antibody in development is izokibep (ABY-035), a unique bispecific, small molecule potently binding IL-17A and albumin.

IL-23 blockers that are approved for psoriasis and in the pipeline for psoriatic arthritis include risankizumab and tildrakizumab. The IL-23 blocker guselkumab has been approved for both psoriasis and psoriatic arthritis. Unlike the rapid effect observed with some biologics, these drugs may take up to 24 weeks to get a full response. The JAK1 inhibitor upadacitinib and the oral, selective TYK2 inhibitor deucravacitinib have shown promise as well [6,7]. "These new drugs show efficacy and are relatively safe for use in this patient group. Taken together, all treatments we are now able to work with for PsA have the capability of getting a patient in low disease activity or remission, which is a treatment target for us," Prof. Mease concluded.

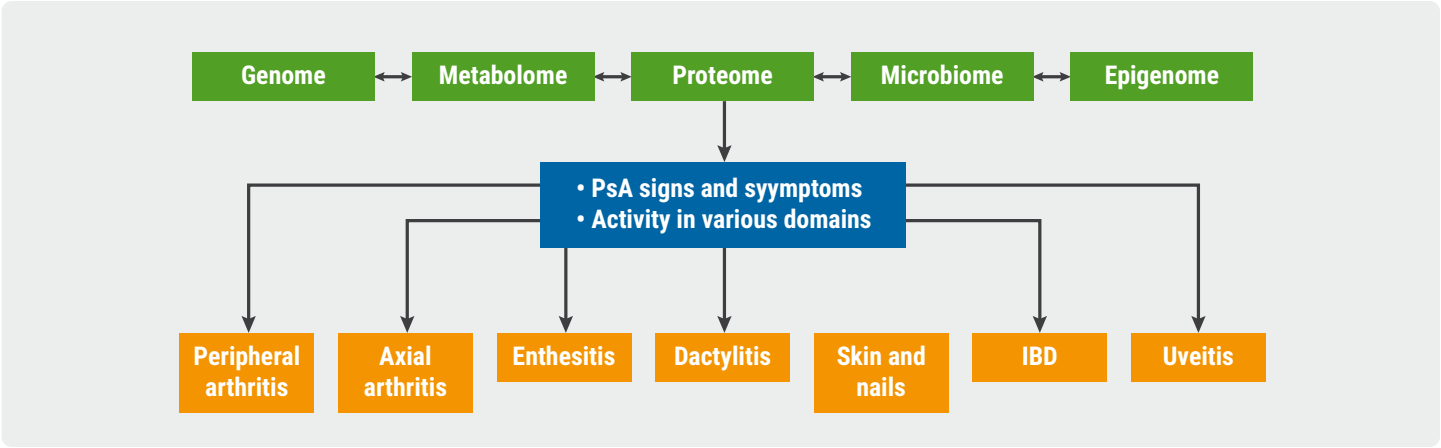
Heterogeneous pathogenesis and treatment

"A frequently asked question is how to use all these new agents to optimise care for our patients. That is part of the rationale for the creation of treatment recommendations and guidelines," Prof. Arthur Kavanaugh (University of California, USA) explained. Management of PsA can be challenging due to its heterogeneity. "We need to choose the treatment that offers the best improvement to the patient across all the affected domains (see Figure)."

Guidelines since 2009

In 2009, the Group for Research and Assessment of Psoriasis and Psoriatic Arthritis (GRAPPA) published treatment recommendations [9]. The disease was divided into different domains. "Various therapies will work to different extents for different domains specifically. Relatively few choices were available back then, but I think the overall schema is still reasonable," explained Prof. Kavanaugh.

Figure: Putative immunopathogenesis of PsA [8]



In the last years, these and other guidelines were regularly updated. In 2018, the guidelines of the American College of Rheumatology (ACR) and the National Psoriasis Foundation (NPF) for the treatment of PsA [10]. One year later, the most recent joint guidelines of the American Academy of Dermatology (AAD) and the NPF was published [11]. In 2019, the EULAR developed recommendations for the treatment of PsA [12].

"The 3rd edition of GRAPPA's treatment recommendations are a work in progress" [13]. In this version, comorbidities have been broken down into comorbidities and associated conditions. These are important for the choice of treatment for an individual patient.

Interpretations, unmet needs, and future directions

Prof. Kurt de Vlam (UZ Leuven, Belgium) emphasised that these new drugs are a "tremendous improvement for our patients," but added that not all treatment classes are effective across all key domains of PsA [14].

Prof. Kilian Eyerich (Karolinska Institute, Sweden) and Dr Laura Coates (University of Oxford, UK) discussed unmet needs in the treatment of PsA from a dermatology and rheumatology point of view, respectively. These include the lack of predictive tools, the relatively better treatment outcomes on skin lesions compared with joint problems of PsA, and the need for personalised medicine in PsA. "We still do not know definitively which drug should be given to which patient," Dr Coates acknowledged.

In the future, Prof. Kavanaugh expects that there will be drugs with new mechanisms of action, combination therapy with different DMARDs and biological DMARDs, and targeted therapy based on cellular and clinical phenotypes. "It is an exciting time for the treatment of PsA, for clinicians and hopefully also for patients."

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Cardiovascular Comorbidities

Patients with PsA have a higher cardiovascular risk

Cardiovascular (CV) comorbidities are a large problem for patients with psoriatic diseases. A cross-sectional, observational, comparative study from Mexico, awarded the *Nature Reviews Rheumatology* poster prize, discussed a practical solution to try and improve the calculation of the CV risk [1].

Due to a higher prevalence of CV risk factors and disease-related characteristics such as systemic inflammation, patients with psoriatic arthritis (PsA) have a higher risk of developing a CV event than the general population. Although multiple algorithms exist that can estimate the CV risk for the general population, no such algorithm exists for patients with PsA. Existing algorithms underestimate the real CV risk of patients with PsA. This could be attributed to the fact that these algorithms do not include disease characteristics that can affect the CV prognosis of patients with PsA. Therefore, a carotid ultrasound should be done to correctly classify the CV risk of patients with PsA and identify those who would benefit from an opportune treatment.

The current cross-sectional, observational, comparative study included 75 patients (aged 40–75 years) who fulfilled the 2006 CASPAR criteria and 75 controls without PsA matched by age, sex, and comorbidities. The results were presented by Dr Natalia Guajardo-Jauregui (Autonomous University of Nuevo León, Mexico).

CV risk was evaluated according to 6 CV risk algorithms: Framingham Risk Score (FRS)-lipids, FRS-BMI, American College of Cardiology and American Heart Association Risk Algorithm (ASCVD), Systemic Coronary Risk Evaluation (SCORE), QRISK3, and Reynolds Risk Score (RRS).

Age and sex were similar in the 2 groups. The mean age was 54 years and 57.3% were women in both groups. The results indicated that the presence of carotid plaque was more prevalent in patients with PsA compared with healthy controls: 44.0% versus 26.7% (P=0.026). When comparing the CV risk reclassification to a higher risk category, a difference was found in 5/6 CV algorithms.

A CV risk reclassification to a higher risk category after carotid ultrasound and presence of carotid plaque was more prevalent in patients with PsA than in controls. Performing a carotid ultrasound as part of the CV evaluation of these patients is essential, argued Dr Guajardo-Jauregui, for CV risk algorithms are insufficient to identify patients who would benefit from an opportune treatment.

1. Guajardo-Jauregui N. Cardiovascular risk reclassification according to traditional cardiovascular risk algorithms and a carotid ultrasound in Psoriatic Arthritis patients. Poster P9, 6th World Psoriasis & Psoriatic Arthritis Conference, 30 June–3 July 2021.

Potential role of inflammation in cardiovascular comorbidity

Systemic inflammation appears to play a role in psoriasis comorbidities. However, the magnitude of this effect remains unclear. Bias and residual confounding are major limiting factors in many existing studies in patients with psoriasis. Dr Alexander Egeberg (Herlev and Gentofte Hospital, Denmark) discussed the association between psoriasis and cardiovascular comorbidities.

Systemic inflammation in psoriasis shows similarities with the inflammation observed in cardiovascular disease, specifically related to atherosclerosis; for example, the role of the IL-23/Th17 pathway [1,2]. "An interesting question is whether we can prevent this by treatment of psoriasis," Prof. Egeberg suggested.

Negative studies

The CANTOS study (NCT01327846) evaluated whether the treatment of inflammation, independent of psoriatic disease, could lower the risk of cardiovascular disease [3]. Approximately 10,000 patients with a high cardiovascular risk were randomised to either canakinumab, a therapeutic monoclonal antibody targeting IL-1β, or placebo. After 5 years, a small effect was observed (HR 0.86; P=0.031).

The phase 3 CIRT trial (NCT01594333) was a similar study that randomised patients with high cardiovascular risk to either low-dose methotrexate or placebo [4]. This study was terminated early because no trend or effect was observed after 4 years (HR 1.01; P=0.91). "So, treatment with methotrexate in patients without inflammatory disease does not appear to reduce the cardiovascular risk," Prof. Egeberg argued.

In patients with psoriasis, treatment with either placebo, the TNF inhibitor adalimumab, or phototherapy showed no difference in cardiovascular risk or reduction of cardiovascular inflammation [5].

True effect or bias?

Dr Egeberg subsequently emphasised that we should be aware of the question whether this is a true effect or bias. "Even if there is an effect, it may be insignificant." Although statins were associated with reduced risk of all-cause mortality, the number needed to treat (NNT) was 250 after 1–6 years. "Now, assume that biologics are equally as cardioprotective as statins, what we need to know is not only the NNT but also the number needed to harm," Prof. Egeberg stressed [6,7]. Data on the effect of established psoriasis therapies remains inconclusive. Even if there is a benefit of established psoriasis therapies, the NNT would be high, and the risk-benefit ratio favours established cardiovascular risk reduction strategies.

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New Treatments

Psoriasis: New treatments and current pipeline

In the last few years, new treatment options have been developed based on new insights into the pathophysiology of psoriasis.

In the pathophysiology of psoriasis, dendritic cells are thought to orchestrate and steer the inflammatory process via the release of cytokines [1,2]. One of these prominent cytokines is IL-23, which stimulates T cells. Upregulation of IL-17 is viewed as a central element. In the presence of tumour necrosis factor (TNF), IL-17 is the strongest activator of keratinocyte function. Cytokines produced by keratinocytes signal back to T cells and dendritic cells. "This vicious circle is viewed to contribute to the chronicity of the disease," Prof. Kristian Reich (Dermatologikum Hamburg, Germany) explained.

Recently, Prof. Reich and colleagues showed that IL-23 is produced by inflammatory monocytes; not by dendritic cells [3]. In addition, TNF is produced by dendritic cells, and IL-17 by T cells. It becomes increasingly clear that both IL-17A and IL-17F have a pro-inflammatory role in the pathogenesis of psoriasis [4]. "But they don't come from the same cells" Prof. Reich added. "There is evidence that more types of innate immune cells, such as γδ T cells, type 3 innate lymphoid cells, and neutrophils, synthesise IL-17, and that this process is not controlled by IL-23."

Targeted therapies

These insights are important as "one of the new treatment modalities we now get – in addition to the existing IL-17A blockers – are molecules that also block IL-17F," Prof. Reich elaborated. Previous research demonstrated that IL-17A was absent in healthy skin but upregulated in psoriasis, while IL-17F is present in normal skin and upregulated in psoriasis, likely contributing to inflammation [5]. To normalise both IL-17A and IL-17F in psoriasis, IL-17A and IL-17F should be downregulated in different degrees.

A head-to-head trial, recently published in the *New England Journal of Medicine*, showed that bimekizumab (anti-IL-17A/F) resulted in significantly higher Psoriasis Area and Severity Index (PASI) scores compared with secukinumab (anti-IL-17A) in plaque psoriasis [6]. Furthermore, results recently published in *The Lancet* on the IL-17A/F nanobody sonelokimab were "impressive," according to Prof. Reich [7]. Interestingly, *Candida* rates in phase 2 studies showed dramatic differences: 13.4% with bimekizumab and only 5.2% with sonelokimab [8,9]. "Obviously, the nanobody has a more differentially inhibitory effect and is likely blocking IL-17A more than IL-17F," Prof. Reich concluded.

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Selective TYK2 inhibitor effective in moderate-to-severe plaque psoriasis

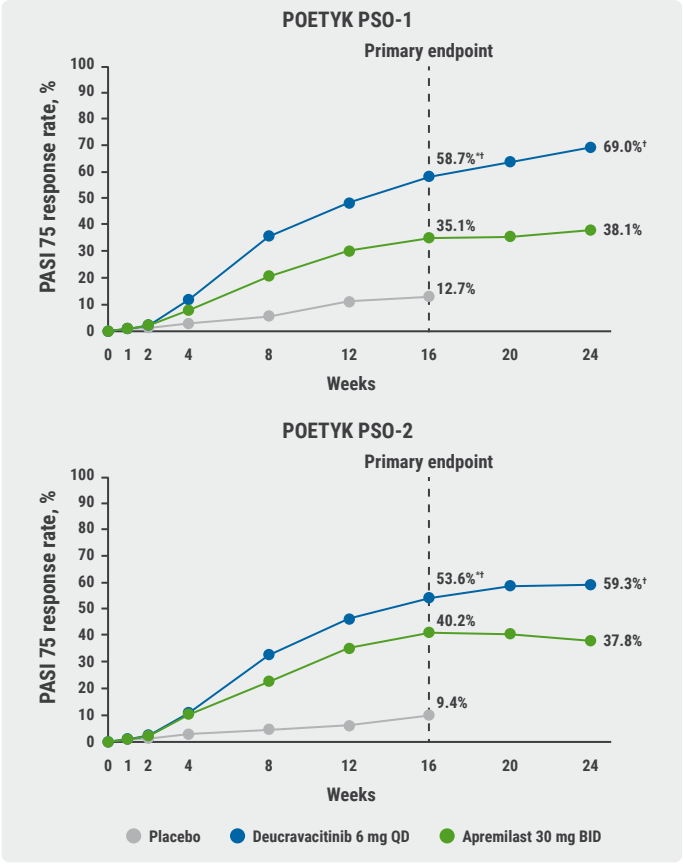
Based on the findings of the phase 3 POETYK PSO-1 and PSO-2 trials, deucravacitinib, a once-daily, oral, selective tyrosine kinase (TYK)2 inhibitor, has the potential to become an efficacious and well-tolerated treatment of choice for patients with moderate-to-severe plaque psoriasis [1].

TYK2 is an intracellular kinase that mediates IL-23, IL-12, and type 1 interferon signalling in the pathogenesis of psoriasis. Deucravacitinib has a unique mechanism of action distinct from JAK1/2/3 inhibitors. It achieves a high degree of selectivity by uniquely binding to the TYK2 regulatory domain, rather than to the active domain of TYK2, which is structurally distinct from the regulatory domains of JAK1/2/3 [2]. Deucravacitinib previously demonstrated efficacy and tolerability in phase 2 trials in patients with moderate-to-severe plaque psoriasis and active psoriatic arthritis [3,4].

POETYK PSO-1 (NCT03624127) and PSO-2 (NCT03611751) were two phase 3, double-blind, 52-week trials that randomised patients with moderate-to-severe plaque psoriasis (BSA ≥10%, PASI ≥12, sPGA ≥3) to placebo, deucravacitinib 6 mg once daily, or apremilast 30 mg twice daily. POETYK PSO-1 included 666 patients and POETYK PSO-2 included 1,020 patients [1].

The co-primary endpoints, PASI 75 and sPGA 0/1 response versus placebo at week 16, were achieved in both trials. In addition, statistical significance was met for deucravacitinib versus placebo and apremilast for multiple ranked secondary endpoints. Significantly greater proportions of patients in the deucravacitinib versus placebo and apremilast arms achieved PASI 75 and sPGA 0/1 responses at week 16. Deucravacitinib responses increased beyond week 16 and were also superior to apremilast at week 24 in both trials (P<0.0001 for all comparisons; see Figure).

Figure: PASI 75 response rates of POETYK PSO-1 and POETYK PSO-2 [1]



*P<0.0001 vs placebo; †P<0.0001 vs apremilast.

PASI, Psoriasis Area Severity Index; QD, once daily; BID, twice daily.

During the 16-week, placebo-controlled periods, the most common adverse events (AEs) were nasopharyngitis, upper respiratory tract infections, headache, diarrhoea, and nausea. Overall AEs, serious AEs, and AEs leading to discontinuation were similar across the 3 groups. No clinically meaningful changes were observed in laboratory parameters during the 2 trials. Deucravacitinib was well tolerated and had a similar safety profile in both trials.

Based on these findings deucravacitinib has the potential to become an efficacious and well-tolerated treatment of choice for patients with moderate-to-severe plaque psoriasis.

1. Armstrong A. Deucravacitinib, an Oral, Selective Tyrosine Kinase 2 (TYK2) Inhibitor, Compared With Placebo and Apremilast in Moderate to Severe Plaque Psoriasis: Efficacy and Safety Results From the Phase 3 POETYK PSO-1 and POETYK PSO-2 Trials. Abstract O6, 6th World Psoriasis & Psoriatic Arthritis Conference, 30 June–3 July 2021.
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4. Mease PJ, et al. ACR 2020, 5–9 November.

Rapid pustule and skin clearance with IL-36 receptor inhibitor spesolimab

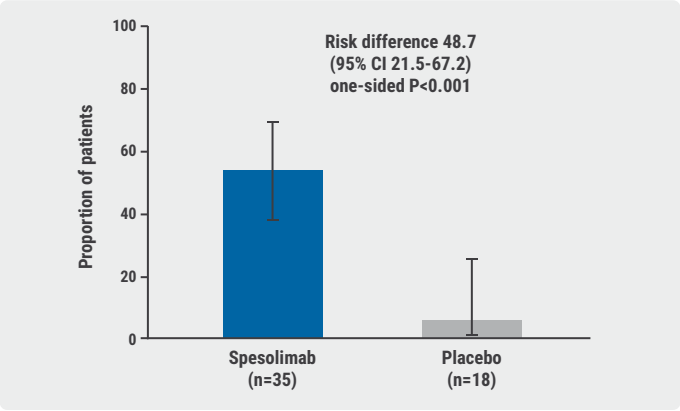
The first randomised, placebo-controlled trial in patients with generalised pustular psoriasis (GPP) demonstrated that IL-36 receptor inhibition with spesolimab resulted in rapid improvements in signs and symptoms of flares versus placebo, with sustained effects and a favourable benefit-risk profile [1].

GPP is a rare, potentially life-threatening, multisystemic autoinflammatory disease characterised by widespread recurrent flares of sterile pustules on the skin. Dysregulation of the IL-36 pathway appears to be central in its pathogenesis [2]. Currently, no therapies have been approved for flares of GPP in the USA or Europe.

In a previous phase 1 study (NCT02978690), a single intravenous dose of spesolimab resulted in rapid pustule clearance in patients with GPP [3]. The subsequent phase 2 Effisayil 1 study (NCT03782792) was a 12-week, double-blind, randomised, placebo-controlled trial including 53 patients with a flare of GPP that evaluated the efficacy and safety of spesolimab. The results were shared by Prof. Hervé Bachelez (Hôpital Saint-Louis, France).

A GPP Physician Global Assessment (GPPGA) pustulation subscore of 0 (i.e. pustule clearance) at week 1 was achieved by 54.3% of patients receiving spesolimab versus 5.6% receiving placebo (one-sided P=0.0004; see Figure) [1]. These results were sustained throughout the 12-week study. A GPPGA score of 0/1 (clear/almost clear) at week 1 was achieved by 42.9% of patients receiving spesolimab versus 11.1% receiving placebo (one-sided P=0.012).

Figure: GPPGA pustulation subscore of 0 at week 1 [1]



CI, confidence interval; GPPGA, generalised pustular psoriasis Physician Global Assessment.

At week 4, 45.7% of patients receiving spesolimab achieved a 75% improvement in GPP Area and Severity Index (GPPASI) versus 11.1% receiving placebo (risk difference 34.6; one-sided P=0.008). In addition, patients receiving spesolimab reported greater reductions in pain visual analogue scale (VAS; P=0.001) at week 4 versus patients receiving placebo.

The overall safety profile of spesolimab was acceptable. Most adverse events were mild to moderate and similar between both study arms. Non-serious infections rates were higher in the spesolimab group (34.3%) compared with the placebo group (5.6%), with no patterns in pathogen or affected organs.

Spesolimab treatment of flares of GPP was associated with rapid pustule and skin clearance within 1 week and was sustained through 12 weeks. These findings support spesolimab as a potential therapeutic option for patients with GPP flares. Long-term administration of spesolimab is being evaluated as a subcutaneous formulation in an ongoing 5-year, open-label extension study in the Effisayil 2 study (NCT04399837).

1. Bachelez H, et al. Effisayil 1: A multicenter, randomized, double-blind, placebo-controlled study to evaluate the efficacy, safety, and tolerability of spesolimab in patients with a generalized pustular psoriasis flare. Abstract O3, 6th World Psoriasis & Psoriatic Arthritis Conference, 30 June–3 July 2021.
2. Gooderham MJ, et al. Expert Rev Clin Immunol. 2019;15:907–19.
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