Medicom International Conference Series in Dermatology

Psoriasis from Gene to Clinic 2021

British Association of Dermatologists

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PEER-REVIEWED CONFERENCE REPORT

New Link Between Psoriasis and Cancer

A large population-based cohort study from Denmark, England, Israel, and Taiwan showed that psoriasis, especially severe disease, is linked to a higher cancer risk overall and in specific sites.

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IL-36 in GPP Lesions

In the Effisayil 1 trial, differential expression of IL-36 was identified in lesional compared with non-lesional skin of patients with generalised pustular psoriasis, which normalised after spesolimab treatment.

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New Biomarker Predicts Ustekinumab Response?

IL-23 induced STAT3 nuclear translocation in MAIT cells could serve as a biomarker for ustekinumab response. Will this assay offer future guidance for ustekinumab therapy?

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Editor Prof. Peter van de Kerkhof, Radboudumc, the Netherlands

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Letter from the Editor

Prof. Peter van de Kerkhof

Dear colleagues,

Psoriasis from Gene to Clinic is a congress for Dermatologists with a special interest in psoriasis, which is organised once every 3 years. For the meeting in December 2021, the expectation was an in-person congress. For dermatologists from outside the UK, travelling to London was a challenge, which resulted in a hybrid congress with life communications in the UK and virtual presentations and audience in the rest of the world.

Also, this congress of psoriasis from gene to clinic brought innovations in discussion. Psoriasis is a showcase of translational medicine with pathogenesis-based treatments and biomarkers in development.

New information was reported on genetic markers and their relevance to the treatment of psoriasis. The information on comorbidities was not only limited to psoriatic arthritis and metabolic syndrome and cardiovascular. New information on the association between psoriasis and cancers was reported.
IL-36 signalling and IL-36 inhibition as a therapeutic principle is an innovation in the treatment of generalised pustular psoriasis.

The long-term management of psoriasis with biologics is enriched by real practice studies. In particular, early active intervention and dosage reduction in patients on maintenance treatment are areas of interest.

Last but not least, new information was communicated on COVID-19 and psoriasis, in particular related to the treatment of psoriasis.

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.

Genes in Psoriasis and Psoriatic Arthritis

HLA-C*06:02-positive patients on ustekinumab show higher drug survival in a real-world scenario

A real-world analysis of the BADBIR registry showed that human leukocyte antigen (HLA)-C*06:02 status is a predictive biomarker of drug survival for ustekinumab and perhaps adalimumab but not for etanercept or secukinumab. In contrast, no association was found between drug survival and HLA-C*06:02 status of patients who discontinued treatment due to adverse events.

HLA-C*06:02 has been identified as the strongest psoriasis susceptibility allele, particularly associated with early-onset psoriasis and guttate lesions [1]. Clinical presentation and response to treatment in patients with psoriasis can vary considerably due to complex interactions between immune, genetic and environmental factors, and the presence of HLA-C*06:02 can be one of the factors that may influence the treatment response. In a previous phase 3 trial, patients with HLA-C*06:02 did show a slightly better response to ustekinumab [2]. However, information from larger cohorts using real-world data has been lacking.

Thus, the present study, presented by Dr Oras Alabas (University of Manchester, UK), aimed to investigate whether HLA-C*06:02 affects the discontinuation of biologics in a large cohort of psoriasis patients in the real world [3]. BADBIR is a UK pharmacovigilance register designed to assess the long-term safety of newer drugs by following a real-world population of psoriasis patients of different sex, age, ethnicity, body mass index (BMI), and comorbidities. The population consisted of patients with chronic plaque psoriasis registered to BADBIR from 2007–2020. All patients were treated with adalimumab, etanercept, secukinumab, or ustekinumab, with at least 6 months follow-up, and HLA-C*06:02 data was available for all patients. Exposure time was calculated from initiation to the discontinuation of therapy and/or was censored at the latest follow-up.

Included in the analysis were 3,199 patients, of whom 52% were HLA-C*06:02 positive. Compared with HLA-C*06:02-negative psoriasis patients, they had an earlier onset of disease (onset <40 years in 94% of HLA-C*06:02-positive vs 85% in HLA-C*06:02-negative patients; P<0.001) and were less likely to have psoriatic arthritis (21% of HLA-positive vs 29% in HLA-negative patients; P<0.001). "The HLA-C*06:02-positive patients showed a better overall drug survival on ustekinumab compared with HLA-C*06:02-negative patients (HR 0.62; 95% CI 0.44–0.87; P<0.005). The same pattern was seen in adalimumab-treated patients with non-imputed data," Dr Alabas explained. However, only the association with ustekinumab remained significant when using imputed data.

Further, HLA-C*06:02-positive patients had a 38% lower relative risk to stop treatment owing to lack of effectiveness than HLA-C*06:02-negative patients. HLA-C*06:02 status did not influence drug survival of patients discontinuing due to adverse events.

Thus, Dr Alabas concluded that HLA-C*06:02-positive patients treated with ustekinumab and maybe with adalimumab showed a lower risk of treatment discontinuation due to a lack of effectiveness in a real-world situation.

1. Chen L, Tsai TF. Br J Dermatol 2018;178:854–62.
2. Li K, et al. J Invest Dermatol 2016;136:2364–71.
3. Alabas O, et al. HLA-C*06:02 allele is associated with higher drug survival in patients with psoriasis on ustekinumab: an analysis from the British Association of Dermatologists Biologics and Immunomodulators Register (BADBIR), on behalf of the BADBIR and BSTOP. FC14, Psoriasis from Gene to Clinic 2021, 9–11 December.

Selective IL-23 inhibition normalises gene expression in active PsA

An analysis of gene expression profiles in blood of patients with active psoriatic arthritis (PsA) compared with healthy controls showed that genes related to neutrophils, monocytes, eosinophils, and macrophages are upregulated. Therapy with guselkumab starting after only 4 weeks led to a down-regulation of these genes towards a normalisation of whole blood transcriptomic signatures.

Based on the phase 3 trials results of DISCOVER-1 (NCT03162796) and DISCOVER-2 (NCT03158285), which together included over 1,000 patients with active PsA, the IL-23(p19)-blocker guselkumab has been approved for adults with moderate-to-severe psoriasis and active PsA [1,2]. Ms Michelle Miron (Janssen Research & Development, CA, USA) presented an analysis of gene expression in the blood of

patients with PsA both at baseline and through week 24 of guselkumab treatment [3]. Their gene profiles were compared with demographically matched, healthy control subjects. Whole blood transcriptome profiling by RNA sequencing was performed using the NovaSeq 6000 System. "The cohort of PsA patients selected for the whole blood RNA sequencing was chosen to be representative of the overall DISCOVER-1 and -2 population," Ms Miron explained.

The researchers found 355 upregulated genes and 314 downregulated genes in patients with PsA compared with the non-PsA control group. "Upregulated genes were associated with neutrophils, monocytes, and certain myeloid cells," Ms Mirion said. This is consistent with the published literature. Downregulated genes were not specific to cell types.

"We then asked what is happening over time," Ms Mirion continued. Therapy with guselkumab had a distinct effect on the disease-associated genes. Upregulated disease-associated genes were significantly decreased, and downregulated genes were significantly increased by guselkumab treatment versus placebo at week 4 and week 24. Changes from baseline with guselkumab showed directionality towards a normalisation of whole blood transcriptomic signatures. In contrast, there was no change in the placebo group. Moreover, in PsA patients who showed a good response to guselkumab treatment (defined as an American College of Rheumatology [ACR] 20 response), disease-associated genes were downregulated to a greater extent compared with non-responders at week 24.

These findings suggest a dysregulation of immune cell profiles in PsA. Most of these disease-associated genes can be modulated by guselkumab towards the direction of normalisation.

1. Deodhar A, et al. Lancet 2020;395:1115–25.
2. Mease P, et al. Lancet 2020;395:1126–36.
3. Miron M, et al. Guselkumab, an anti-interleukin-23p19 monoclonal antibody, modulates core psoriatic arthritis gene expression in two phase 3 clinical trials (DISCOVER-1 and -2). FC24, Psoriasis from Gene to Clinic 2021, 9–11 December.

Protective factors identified against anti-drug antibody formation to adalimumab in psoriasis

The development of anti-drug antibodies (ADA) against adalimumab is an important cause of treatment failure in patients with psoriasis. In a genome-wide association study, certain amino acid variations within the human leukocyte antigens (HLA)-DR peptide-binding groove showed to be protective against ADA formation. Thus, pre-treatment HLA-DRB1 genotyping might be a promising option for patient selection.

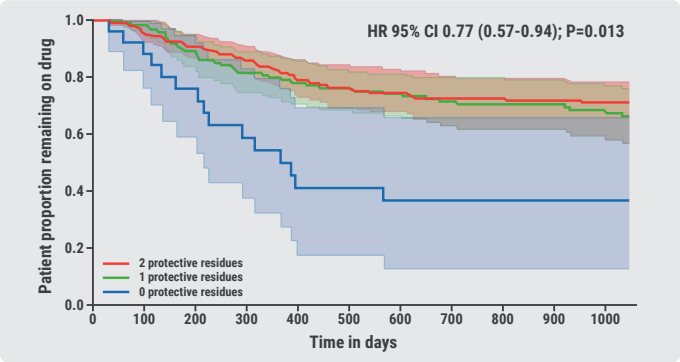
An analysis of the BADBIR registry enrolling more than 50% of patients with psoriasis in the United Kingdom revealed that the major reason for stopping biologic therapy is ineffectiveness [1]. "We know that at least some of this ineffectiveness is driven by drug immunogenicity, the ability of therapeutic proteins to trigger the development of ADA," Dr Teresa Tsakok (King's College London, UK) explained. ADA drive drug ineffectiveness by reducing levels of a functional drug. In a UK cohort, 65% of patients developed ADA over 3 years. ADA-positive patients were more than twice as likely to stop treatment compared with ADA-negative patients. Until now, it was not clear why some patients on adalimumab treatment developed ADA and some did not. "Genetic predictors of developing ADA at baseline may have clinical utility in decision making even before treatment has started, such as using a more immunogenic biologic and whether to consider co-therapy with an immunosuppressant such as methotrexate, which is known to reduce the development of ADA," Dr Tsakok suggested.

With their genome-wide association study, Dr Tsakok and her team aimed to identify genetic predictors of developing ADA in psoriasis patients on their first course of adalimumab. They used data within the BSTOP bioresource. Genotyping data was available of 1,732 patients exposed to adalimumab. The discovery cohort comprised 784 psoriasis patients with ADA data available 6–36 months after starting adalimumab. In the replication cohort, 232 patients had ADA data available of <6 months after starting adalimumab, and the treatment cohort had 716 psoriasis patients with only clinical data but no ADA data available. All in all, they measured genetic variations of single nucleotide polymorphisms in 10,917,604 samples.

In the discovery cohort, a genome-wide significant association was identified with ADA within the major histocompatibility complex (MHC). This complex is responsible for antigen presentation, which initiates the adaptive immune response. Dr Takok pointed out that the presence of tryptophan at position 9 and lysine at position 71 each conferred about 2.8-fold protection against ADA. This result was also shown in the replication cohort. Amino acid positions 9 and 71 are centrally located in the peptide-binding groove of the HLA-DR protein. "In fact, these HLA-

DR positions are well known in terms of susceptibility to immune-mediated diseases such as rheumatoid arthritis or inflammatory bowel disease, but they have not been robustly described in the context of developing an immune response against a drug," Dr Tsakok explained. An assessment of the treatment cohort underscored the clinical relevance of these findings: both HLA-DRB1 residues (position 9 and 71) were also protective against treatment failure (HR 0.73; 95% CI 0.57–0.94; P=0.013) with patients having 2 protective residues being most likely to remain on adalimumab treatment (see Figure). Thus, Dr Tsakok concluded that pre-treatment HLA-DRB1 genotyping holds the potential to direct clinical decision-making in terms of biologic selection and immunosuppressant co-therapy.

Figure: HLA-DRB1 residues 9W and 71K protect against treatment failure [2]



1. Yiu ZZN, et al. Br J Dermatol 2020;183:294–302.
2. Tsakok T, et al. Development of antidrug antibodies to adalimumab is associated with amino acid variation within the HLADRB1 peptide-binding groove. FC-15. Psoriasis form gene to clinic 2021, 9–11. December.

Comorbidity in Psoriasis

Psoriasis associated with a higher cancer risk

A large, pooled population-based cohort study from Denmark, England, Israel, and Taiwan showed that psoriasis, especially severe disease, is linked to a higher cancer risk overall and in specific sites. In addition, psoriasis was associated with several cancers beyond those currently regarded as connected.

Mr Alex Trafford (University of Manchester, UK) noted that an association between cancer and psoriasis is plausible due to the chronic inflammation in psoriasis patients [1]. Moreover, lifestyle factors like smoking and alcohol consumption are particularly prevalent in patients with psoriasis. Yet, previous studies of cancer risk in people with psoriasis have yielded inconsistent results. To evaluate the possible relationship, Mr Trafford and colleagues aimed to investigate the risk of cancer occurrence in individuals with psoriasis by analysing data from population-based health records from Denmark, England, Israel, and Taiwan. They also wanted to explore whether cancer risk is associated with psoriasis severity. "As we had no direct data, we used systemic therapy as an indicator of moderate-to-severe psoriasis," he explained.

Individuals with psoriasis from the cohort were matched with up to 6 individuals with no prior record of psoriasis based on a minimum of age, sex, and calendar time. Country-specific risks of cancer overall and site-specific cancers were analysed using Cox proportional hazards models. Patients who had cancer before were excluded from the analysis.

The analysis included 702,062 participants with psoriasis and 4,185,596 matched comparators. Age and sex were similar between countries. Patients in Denmark were older; in Taiwan, they were more likely to be men. In crude models, individuals with psoriasis (pooled HR 1.08; 95% CI 1.04–1.13) and the subgroup with moderate-to-severe psoriasis (pooled HR 1.16; 95% CI 1.04–1.28) had a slightly higher risk of cancer overall.

Further, people with psoriasis had higher risks for the following site-specific cancers: oral cavity, pharynx, oesophagus, liver, pancreas, kidney, bladder, skin (keratinocyte), Hodgkin lymphoma, non-Hodgkin lymphoma, and leukaemia. However, the risk elevation differed between cancer types, from a relatively modest 9% relative risk elevation in pancreas cancer to an almost doubled risk for Hodgkin lymphoma. "The cancer risk was exacerbated in more severe psoriasis. Moreover, additional associations for lung cancer and ovarian cancer were found in these patients," Mr Trafford said.

In summary, the study established the associated increased risk of developing cancer in psoriasis patients. Associations

generally persist, with a more pronounced risk, when limited to people with moderate-to-severe disease. The current study revealed that psoriasis is associated with several cancers, beyond those currently regarded to be linked to the condition. This should be recognised to guide optimal psoriasis care and future research.

1. Trafford AM, et al. Psoriasis and the risk of cancer development: pooled population-based cohort studies from Denmark, England, Israel and Taiwan. FC13, Psoriasis from Gene to Clinic 2021, 9–11 December.

Comorbidity and clinical features of psoriasis vary according to HLA-C*06:02 status

A British cross-sectional investigation found that HLA-C*06:02-positive patients were more likely women and younger at diagnosis of psoriasis. Genetic effects on comorbid body weight were also different between the sexes [1].

Carrying the HLA-C*06:02 allele has been linked to certain features of psoriasis, such as early onset of disease, severe disease, guttate psoriasis, and differential response to therapy with biologics in the past [2–5]. "We, therefore, set out to systematically evaluate and further characterise differences between HLA-C*06:02 positive and negative psoriasis," Dr Ravi Ramessur (King's College London, UK) said [1]. To do so, data of people with European ancestry was analysed from 2 British cross-sectional databanks: the Biomarkers of Systemic Treatment Outcomes in Psoriasis (BSTOP) and the UK Biobank [1,2]. BSTOP is an observational study of severe psoriasis containing clinical and genotype data from more than 70 dermatology centres in the UK. The UK Biobank is a population-based biomedical research resource with also genotype and clinical data from questionnaires and healthcare records. In the BSTOP cohort (n=3,767), 43.5% were women, 53.7% were HLA-C*06:02 positive, and the median age of psoriasis onset was 20 years [1]. In contrast, the respective characteristics in the UK Biobank (n=5,519) were 45.7%, 46.3%, and 29 years of age.

"The 2 stand-out observations from our study were: firstly, intriguing sex-specific differences and, secondly, an association with comorbidity," Dr Ramessur disclosed. In both datasets, HLA-C*06:02-positive participants were significantly more likely to be women and have a younger median age at onset of psoriasis (P<0.0001 for all). BSTOP also provided information on the proportion of those with a family history of psoriasis and this was considerably higher in carriers of the HLA-C*06:02 allele (60.2% vs 42.6%; P<0.0001).

Obesity and hypertension associated with negative HLA-C*06:02 status

HLA-C*06:02 negativity was also associated with higher levels of obesity in terms of waist circumference and BMI, an effect that was more pronounced in women.

Overall, comorbid cardiometabolic disease had a higher prevalence in HLA-C*06:02-negative persons with a consistent trend for traits like ischaemic hypertension, ischaemic heart disease, and dyslipidaemia in both datasets. However, only hypertension demonstrated statistical significance (P<0.0001 for both datasets).

In addition, clinical subtypes were evaluated according to status of positive or negative presence of HLA-C*06:02 in BSTOP. "We confirmed the previously established association of a high prevalence of guttate psoriasis and a lower prevalence of nail involvement in HLA-C*06:02-positive compared with HLA-C*06:02-negative psoriasis," Dr Ramessur commented.

"These findings are suggestive of a different contribution of genetic effects between the sexes and highlight the importance of considering sex stratification for future genetic analyses to help identify potential sex-specific disease mechanisms," underlined Dr Ramessur.

1. Ramessur R, et al. Differences in clinical features and comorbid burden between HLA-C*06:02 carrier groups in more than 9000 people with psoriasis. FC21, Psoriasis from Gene to Clinic 2021, 9–11 December.
2. Douroudis K, et al. J Invest Dermatol. 2021;S0022-202X(21)02473–8.
3. Fan X, et al. Acta Derm Venereol. 2007;87(4):335–340.
4. Dand N, et al. J Allergy Clin Immunol. 2019;143(6):2120–2130.
5. Gudjonsson JE, et al. J Invest Dermatol. 2006;126(4):740–745.

Psoriasis patients with cardiovascular comorbidity characterised by high systemic inflammation

A cohort study revealed that the novel biomarker systemic immune-inflammation index (SII), associated with a worse prognosis in different disease entities, was markedly elevated in psoriasis patients with concomitant cardiovascular comorbidity. There was a weak but significant correlation with the Psoriasis Area and Severity Index (PASI) but no correlation with smoking status.

"The systemic immune inflammation (SII) index is a simple calculation of neutrophils multiplied by platelets divided by lymphocytes," Dr Niamh Kearney (St. Vincent's University Hospital, Ireland) explained [1]. The SII has proven to be a promising prognostic indicator in various cancers, COVID-19

and other diseases. In patients with coronary artery disease, this index provides a better prediction of major cardiovascular events than traditional risk factors [2]. Severe psoriasis is associated with a distinct risk elevation for cardiovascular events and death. With their retrospective cohort study, Dr Kearny and her team wanted to assess whether SII is increased in psoriasis, particularly in psoriasis patients with cardiovascular comorbidities. They also aimed to quantify the SII in psoriasis and stratify it by the presence of diabetes, hypertension, dyslipidaemia, and coronary artery disease. They analysed electronic and physical records from specialty psoriasis clinics. "We looked at demographics, treatments, full blood count, and C-reactive protein results," Dr Kearney explained. Patients on methotrexate were excluded from the study.

The analysis included data from 73 patients. Most patients were on a biologic and were smokers. Dyslipidaemia was the most common comorbidity prevalent in 12.3% of patients, followed by hypertension in 11% of patients. The mean c-reactive protein (CRP) for patients with cardiovascular comorbidities was 5.01 mg/L compared with 3.53 mg/L without comorbidities (P=0.046).

The researchers found a modest correlation between the CRP concentrations and the SII (r=0.530; P<0.001), and a weak significant correlation between the PASI and SII (r=0.299; P=0.011). However, no difference was observed in smokers, ex-smokers, and never smokers. Psoriasis patients with comorbidity (i.e. diabetes, hypertension, dyslipidaemia, or coronary artery disease) had an SII of 859.74 compared with 612.04 (P=0.014) in patients without comorbidity. In the individual comorbidity analysis, only hypertension was associated with a higher CRP of 7.4 mg/L (P<0.001) and an SII of 1038.05 (P=0.004).

The limitations of the study were the small number of patients with comorbidities and the lack of imaging data to confirm the association. Despite this, the authors think that the SII might have a role in risk stratification for primary and secondary prevention in psoriasis patients.

1. Kearney N, et al. Systemic immune inflammation index as a predictor of systemic inflammatory burden and cardiovascular comorbidities in psoriasis. FC23, Psoriasis from Gene to Clinic 2021, 9–11 December.
2. Yang YL, et al. Eur J Clin Invest 2020;50:e13230.

Psoriasis Therapy: New Findings

IL-36 gene expression in GPP lesions reduced by spesolimab

Different patterns of gene expression were identified in lesional compared with non-lesional skin of patients with generalised pustular psoriasis (GPP). In the Effisayil 1 trial, various changes present in lesional skin were re-transformed after spesolimab treatment.

"It is known that the dysregulation of the IL-36 signalling pathway is involved in the GPP pathogenesis," Dr Ahmed Farag (Boehringer Ingelheim, Germany) stated. Spesolimab is a monoclonal, anti-IL-36R antibody with proven efficacy as a treatment of flaring GPP in the phase 2 Effisayil 1 trial (NCT03782792) [1,2]. This study also included a gene analysis of skin biopsies taken from lesional and non-lesional sites at different time points.

The study comprised 53 GPP patients experiencing an acute flare, who were randomised 2:1 to receive 900 mg of spesolimab or placebo once [2]. The primary endpoint of 'no visible pustules' (defined as Generalised Pustular Psoriasis Physician Global Assessment=0) at day 8 was achieved by 54.3% of the participants (one-sided P<0.001 for the risk difference vs placebo). Baseline biopsies were taken from lesional and non-lesional skin; lesional skin samples were also taken on days 8 and 57. RNA-sequencing and immunohistochemistry were performed in the skin samples.

In the gene expression analysis of the study, researchers compared baseline findings of lesional with non-lesional skin (adjusted P<0.05) and found 5,208 differentially expressed gene transcripts, of which 2,347 were upregulated and 2,861 downregulated [1]. "The lesional skin biopsies versus baseline at week 1 had 940 genes differentially expressed, reaching 2,200 genes at week 8," Dr Farag pointed out. He elaborated that there were significantly differentially expressed genes in treatment responders compared with patients who did not achieve pustular clearance at week 1.

A closer look at the top 50 differentially expressed genes in lesional and non-lesional skin revealed pronounced dissimilarities. The group of most upregulated genes included *IL-36A*, *IL-36B*, and *IL-36G*. Further, genes linked to skin inflammation (i.e. *DEFB4a*, *S100A7*, *S100A8*, *S100A9*), neutrophilic recruitment (i.e. *CXCL1*, *CXCL6*, *CXCL8*), and pro-inflammatory cytokines (i.e. IL-6, IL-19, IL-20) showed markedly different expressions when comparing lesional versus non-lesional skin. At 1 and 8 weeks after a single dose of spesolimab, many genes were modulated within the lesional skin. Primarily, significantly decreased expression was found for the before upregulated IL-36 ligands, as well as genes associated with neutrophil recruitment and mediators of inflammation.

In a particular analysis of the IL-36 pathway, an *IL-36* gene set variation analysis (GSVA), scores were significantly reduced in the spesolimab arm at day 8 (P=0.0047 for the difference to baseline) with a more robust effect at week 8 (P=0.001 for the difference to baseline). Interestingly, the researchers also found upregulation in the epidermal differentiation complex gene set. "We see increases in the GSVA score of this gene set at day 8 that was stronger at week 8, and all in all we see that this reflects spesolimab's effect on restoring skin homeostasis," Dr Farag stressed and pointed to a spesolimab-induced reversal of the lesional skin gene expression pattern that is linked to GPP.

"Pathway analysis showed that spesolimab did suppress genes involved in GPP pathogenesis and IL-36 signaling with GSVA scores also showing the decreases in the scores in the IL-36 gene set and increases in epidermal differentiation gene set after spesolimab treatment," Dr Farag summarised.

1. Farag A. Spesolimab alters the molecular profile of lesional skin in patients with generalised pustular psoriasis with a clinical response. FC4, Psoriasis from Gene to Clinic 2021, 9–11 December.
2. Bachelez H, et al. N Engl J Med 2021;385(26):2431–2440.

Inhibition of heat shock protein: A novel way to treat psoriasis?

Inhibition of heat shock protein 90 (HSP90) may emerge as a potential novel treatment target in psoriasis. In a proof-of-concept trial, therapy with RGRN-305 showed marked efficacy with an acceptable safety profile. An evaluation of gene expression showed that the agent acts by downregulating the IL-12/23 JAK/STAT signalling pathway.

HSP90 protein plays an important role in maintaining cellular protein homeostasis by acting as an intracellular molecular chaperone involved in stabilisation, correct folding, and activity of many proteins. The HSP90 inhibitor RGRN-305 is a small molecule originally developed for anti-cancer therapy. A surprising result of the first clinical RGRN-305 trial in oncology was a previously untreated psoriasis patient, who achieved complete remission of their skin manifestation [1]. Further, a xenograft mouse model showed alleviating effects on psoriatic lesions after administration of RGRN-305 [1]. This was the rationale for Dr Anne Bregnhøj (Aarhus University Hospital, Denmark) and her colleagues to evaluate the safety and efficacy of RGRN-305 in a phase 1b, proof-of-concept study in patients with plaque psoriasis [2].

In this open-label, single-arm, dose-selection study, 13 patients were treated with RGRN-305, either 250 mg or 500 mg daily RGRN-305 for 12 weeks. At week 16, 2 participants had dropped out of the study, and 6 out of 13 participants were clinical responders, defined as an improvement of the Psoriasis Area and Severity Index (PASI) of ≥50%. All responders maintained improvement until the end of the study at week 16. "The total PASI reduction was between 71% and 94%," Dr Bregnhøj said.

Histopathology and immunohistochemistry were assessed in 1 patient from the responder group. Histological evaluation showed a decreased epidermal thickness in lesional skin at week 12 with a significant reduction of T-cell infiltrates and decreased epidermal proliferation. An evaluation of gene expression revealed that key psoriasis-associated genes (e.g. *DEFB4*, *LCN2*, *S100A7A*, *IL-36A*, *CCL20*, and *CXCL8*) were present among the top 25 downregulated genes. Already at week 4, downregulation of the IL-12/23 JAK/STAT signalling pathway could be demonstrated, and thereby a pronounced suppression of IL-17A/F.

No severe adverse events were reported. A mild-to-moderate exanthematous drug-induced eruption due to study medication was experienced by 4 of the 7 patients who were treated with the higher dose, due to which 2 patients decided to stop treatment. After treatment ended. drug eruptions and psoriasis lesions resolved in all 4 patients.

Due to these encouraging results and acceptable safety, especially in the low-dose group, treatment with RGRN-305 may serve as a novel future treatment option in psoriasis.

1. Stenderup K, et al. Acta Derm Venereol 2014;94:672–6.
2. Bregnhøj A, et al. Heat shock protein 90 inhibitor RGRN-305 for oral treatment of plaque-type psoriasis: efficacy, safety and biomarker results in an open-label, proof-of-concept study. FC19, Psoriasis from Gene to Clinic 2021, 9–11 December.

Guselkumab shows highest drug survival among systemic treatments

In a comparison of 5 commonly used systemic treatments for psoriasis, guselkumab demonstrated the highest drug survival and adalimumab the lowest in a prospective cohort study from the BADBIR. If the drug was discontinued due to ineffectiveness of treatment, drug survival was also affected by prior lines of biologic therapy.

"Drug survival essentially measures the time between starting and stopping a treatment and that serves as a proxy marker for a treatment's effect," Dr Zenas Yiu (University of Manchester, UK) explained [1]. He pointed out that real-world evidence on drug survival is still inconsistent and previous study results have been limited by a lack of data on discontinuation reasons or previous biologic therapies.

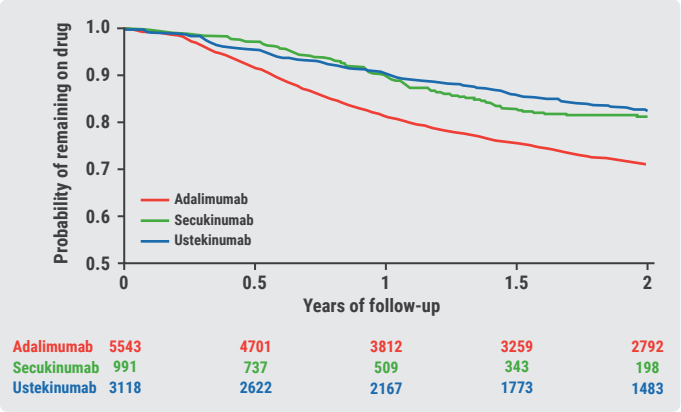
To gain more insight, a prospective cohort study was conducted using data between 2007 and 2021 from the longitudinal, pharmacovigilance registry on patients with moderate-to-severe psoriasis: the British Association of Dermatologists Biologics and Immunomodulators Register (BADBIR). "There are currently 165 recruiting centres, over 20,400 registrations and over 76,000 patient-years," Dr Yiu said.

Therapy discontinuation was defined as a treatment gap of more than 90 days. The study included data on the most widely used agents for psoriasis: adalimumab (TNF inhibition), guselkumab (IL-23 inhibition), ustekinumab (IL-12/23 inhibition), ixekizumab and secukinumab (IL-17A inhibition). Drug survival was analysed at 1 and 2 years, and flexible parametric survival models were fitted to evaluate possible effect modification by variables like age, sex, body mass index, or history of prior biologic therapy.

As the investigated drugs have been on the market for different time-spans, the number of evaluated patients differed. For example, the adalimumab cohort comprised 6,607 participants, while the ixekizumab and the guselkumab groups had 703 and 730 participants, respectively. Follow-up time also varied between 1.1 and 2.7 years, and the mean age of patients ranged from 45 to 48 years. The study participants were predominantly men. As might be expected, the rate of biologic-naïve patients was comparatively lower for the newer therapeutic agents. It extended from 74.8% in the adalimumab arm to 18.2% for ixekizumab and 23.6% for guselkumab.

The functions of drug survival were determined according to ineffectiveness or adverse events as reasons for discontinuation. "Across all of the outcomes and years, guselkumab has the highest drug survival, and adalimumab the lowest," highlighted Dr Yiu (see Figure).

Figure: Crude drug survival for discontinuation due to either ineffectiveness or adverse events [2]



At years 1 and 2, the drug survival for discontinuation due to ineffectiveness: adalimumab 0.81/0.76, secukinumab 0.86/0.75, ustekinumab 0.89/0.83, ixekizumab 0.86/0.75, and guselkumab 0.94/0.92.

The respective results for drug survival for discontinuation as a result of side effects were: adalimumab 0.91/0.88, secukinumab 0.94/0.0.90, ustekinumab 0.94/0.91, ixekizumab 0.92/0.87, and guselkumab 0.96/0.93. "You can see great drug survival for all our treatments for safety but again it demonstrates that guselkumab has higher drug survival compared with the comparators," Dr Yiu commented. He further pointed out that an effect modification was detected by previous biologic treatment history.

"Guselkumab had the highest drug survival for both effectiveness and safety out of the treatments looked at here. Previous biologic experience was an effect modifier for discontinuation due to ineffectiveness, and this reduction-effect for drug survival over treatment lines seems to be most pronounced for the IL-17A inhibitors," Dr Yiu concluded.

1. Yiu ZZN. Drug survival of guselkumab, ixekizumab, secukinumab, ustekinumab and adalimumab for psoriasis: a prospective cohort study from the British Association of Dermatologists Biologics and Immunomodulators Register (BADBIR). FC20, Psoriasis from Gene to Clinic 2021, 9–11 December.
2. Yiu ZZN, et al. Br J Dermatol 2020;182(2):294–302.

Risankizumab superior to ustekinumab in skin histopathology scores

Therapy with risankizumab produced faster histopathological improvement of psoriatic lesions and a more complete resolution of inflammation as judged by markers analysed by immunohistochemistry, as compared with ustekinumab. RNA sequencing also revealed a greater modulation of the psoriasis transcriptome by risankizumab.

The presented data compared molecular and histopathologic patterns in psoriatic skin from the phase 3 UltiMMa-1 trial (NCT02684370), a head-to-head comparison of treatment with risankizumab and ustekinumab for moderate-to-severe plaque psoriasis [1]. The 2 monoclonal antibodies bind to different subunits of IL-23: risankizumab to p19 and ustekinumab to p40, a subunit that is shared by IL-23 and IL-12 [2,3].

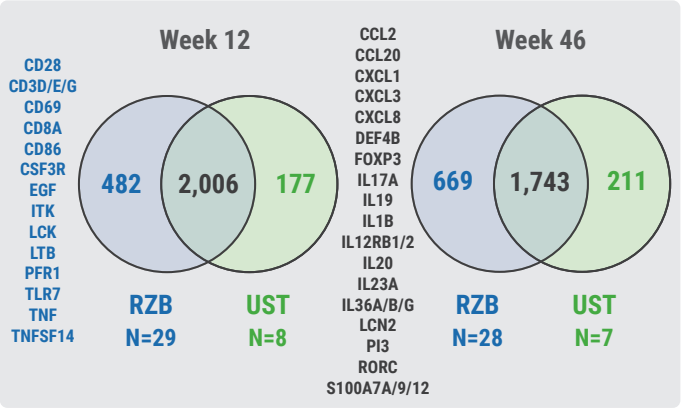
In UltiMMa-1, participants received either 150 mg of risankizumab or 45/90 mg of ustekinumab at weeks 0, 4, 16, 28, and 40 [1]. From consenting participants, skin biopsies were also obtained at baseline in lesional and non-lesional skin and at weeks 12 and 46 in lesional skin. "The analysis methods were histopathological analysis of sections stained with hematoxylin and eosin, and immunohistochemistry performed for the proliferation marker Ki67, the T-cell marker CD3, the dendritic cell markers CD11c and DC-LAMP, which stains matured dendritic cells," Dr Kathleen Smith (AbbVie Bioresearch Center, MA, USA) explained. Gene expression in the biopsies was analysed using RNA sequencing.

The 2 study arms were fairly similar in terms of mean age (53 and 51 years), body mass index (31 and 30 kg/m^2), and percentage of women (33% and 38%). However, the involved body surface area was 27.3% in the risankizumab and 18.8% in the ustekinumab group.

At weeks 12 and 46, both agents significantly decreased the number of cells positive for CD3, CD11c, DC-LAMP, and Ki67. At week 12, a difference in histopathology scores was found between risankizumab and ustekinumab treated patients. On risankizumab, 76% achieved an excellent or likely excellent improvement versus 45% on ustekinumab. "These improvements were maintained by week 46," Dr Smith further indicated.

The transcriptome analysis included participants with a Psoriasis Area Severity Index (PASI) 90 response at week 46. "We defined the psoriasis transcriptome as the 3,146 genes which were differentially expressed in lesional versus non-lesional skin at baseline," Dr Smith stated. Risankizumab therapy led to 79% changes in the transcriptome and ustekinumab in 69%, respectively. A more detailed look at transcriptome modulation at week 12 revealed that the 2 agents downregulated, for example, CCL20, FoxP3, IL-17A, IL-23A, and the IL-36 transcripts. "However, there is a large group of genes that were modified only by risankizumab and these included T-cell gene CD28, CD3, activation marker CD69, and CD 8 itself (see Figure). This supports the histological analysis where we see slightly better improvement in T-cell infiltration," Dr Smith highlighted. Treatment with risankizumab also downregulated the kinetochore metaphase signalling pathway and the role of IL-17A in psoriasis (see Figure).

Figure: Modulation of the psoriasis transcriptome on treatment with risankizumab or ustekinumab [1]



RZB, risankizumab; UST, ustekinumab.

"A higher proportion of patients treated with risankizumab experienced an excellent improvement in histopathology scores compared with patients with ustekinumab, which parallels clinical efficacy, and treatment with risankizumab modulated a greater number of psoriasis transcriptome genes, including those specifically targeting inflammation pathways compared with ustekinumab," Dr Smith concluded.

1. Smith, K. Interleukin-23 pathway inhibition by risankizumab differentially modulates the molecular profile in psoriatic skin compared with ustekinumab. FC28, Psoriasis from Gene to Clinic 2021, 9–11 December.
2. Wcisło-Dziadecka DL, et al. Adv Clin Exp Med. 2020;29(2):235–241.
3. Strober B, et al. J Eur Acad Dermatol Venereol. 2020; 34(12):2830–2838.

Tapering biologics: No alarming signs of increased anti-drug antibodies

The induction of antibody formation is one of the major concerns with tapering biologic treatments. However, a CONDOR sub-study found no signs of increased anti-body formation after dose reductions of adalimumab or ustekinumab.

In patients with long-term use of biologics and stable treatment response, the question often arises of a possible dose reduction. "In a recent questionnaire study that we performed with the International Psoriasis Council, we found that 70% of psoriasis experts already perform dose reductions," Dr Juul van den Reek (Radboud University Medical Center, the Netherlands) said [1]. The main reasons for doing so were the implicated reduction of costs (87%) and increased patient safety (43%), as well as requests by the patients themselves (41%). Those who chose not to reduce dosages were concerned about the lack of evidence (94%), psoriasis exacerbations (56%), and immunogenicity issues in terms of anti-drug antibodies (53%).

The phase 4, randomised, non-inferiority CONDOR study (NCT02602925) demonstrated that 53% of psoriasis patients with prior stable and low disease activity successfully tapered their dosage of biologic treatment with adalimumab, etanercept, or ustekinumab at 12 months. The current sub-study investigated serum drug levels and anti-drug antibodies in patients with drug reduction versus routine care and attempted to identify variables to predict successful dose tapering. The CONDOR sub-study consisted of 118 patients who either reduced dosing or continued with usual care. Blood samples were collected every 3 months, preferably at trough moments, i.e. just before administering the next dose of medication. Anti-drug antibodies were analysed for adalimumab and ustekinumab only, as antibodies for etanercept are considered rare and non-neutralising.

Interestingly, the baseline drug levels demonstrated great variance. "So, even with extremely low drug levels, some patients had very low disease activity," Dr van den Reek pointed out. In all 3 drug reduction groups, drug levels were significantly lowered compared with the usual care arms after 3 months of drug reduction. Participants in the drug reduction group on adalimumab did not develop significantly more anti-drug antibodies than those on the normal dosage of the agent (P values for group comparison 0.33–0.76 at different time-points). Of note, 1 patient had a seroconversion from anti-drug antibodies-negative to anti-drug antibodies-positive, as did 2 patients in the usual care arm.

"Looking at the results of ustekinumab, no detectable anti-drug antibodies were seen at baseline, nor throughout the study, not in the dose reduction nor the usual care group, so there is also no difference between those groups," Dr van den Reek stated. Thus, the multivariate regression set up to identify variables of prediction of successful dose reduction was inconclusive. Given the heterogeneity of baseline drug levels, no clarification could be given on how to predict beneficial dose reduction versus failure.

"Most importantly, there was no sign of increased anti-drug antibody formation, and although groups were small, based on this study, it is highly questionable whether fear for anti-drug antibody formation should be a barrier to apply dose reduction in practice," Dr van den Reek stressed in her conclusion.

1. van den Reek J. Serum drug levels and anti-drug antibodies in the context of dose tapering by interval prolongation of adalimumab, etanercept and ustekinumab in patients with psoriasis: results of the randomised controlled CONDOR trial. FC30, Psoriasis from Gene to Clinic 2021, 9–11 December.

Intermediate monocytes are possible predictors of response to secukinumab

Research on various types of cells from the myeloid lineage found that the frequency of intermediate monocytes at baseline differs significantly between responders and non-responders to psoriasis therapy with secukinumab. This could lead to the use of intermediate monocytes as a biomarker for treatment success.

Dr Jonathan Hardman-Smart (King's College London, UK) highlighted the clear need for stratification in psoriasis treatment [1]. Although the biologic armamentarium offers a wide range of drugs that have proven substantial efficacy, a lack of biomarkers exists for the prediction of treatment success. The objective of the Psoriasis Stratification to Optimise Relevant Therapy (PSORT) consortium is to identify predictors of response, which may include clinical, pharmacological, and genetic markers, as well as blood immune monitoring. For example, previous PSORT research identified an association between baseline NF-κβ signalling in type-2 dendritic cells and an absence of clinical treatment response to adalimumab [2].

Dr Hardman-Smart presented new research that enrolled 17 patients from the SIGNATURE (NCT01961609) study and evaluated immunophenotyping of psoriasis patients receiving therapy with secukinumab [1]. SIGNATURE participants had been non-responders to TNF-blockers for psoriasis. "Real-world data has shown that about 57% of patients will achieve a 90% reduction in their Psoriasis Area and Severity Index (PASI) or achieve PASI 90 by 12 months of treatment. However, this means up to 40% of patients may not respond adequately to treatment," Dr Hardman-Smart indicated.

From baseline blood samples and blood drawn after 12 weeks of secukinumab treatment, peripheral blood mononuclear cells, including myeloid cells, were isolated for further investigation. These comprised markers for plasmacytoid dendritic cells, myeloid dendritic cells, and also monocytes and subsets. Different types of monocytes express different levels of CD14 and CD16: classical monocytes are highly positive for CD14 but negative for CD16, non-classical in contrast show high levels of CD16 and low levels of CD14, while intermediate monocytes express little CD16 and much CD14. "We included these in our panel because it has recently been shown that monocytes express IL-17 receptor. Moreover, IL-17 promotes an inflammatory phenotype in monocytes and causes them to home to skin or tissue specifically," Dr Hardman-Smart stated.

Monocyte subsets: the key to secukinumab response

Overall, the rates of plasmacytoid dendritic cells, myeloid dendritic cells, and monocytes did not change in the wake of secukinumab therapy. "However, when we broke this down and looked into the monocytes subsets, we found some interesting trends in the classic monocyte population and intermediate monocyte population but not in the non-classical monocytes," Dr Hardman-Smart uncovered. Differentiating further between responders with PASI 75 and non-responders at week 12, a significant decrease was found in classical monocytes in responders together with an increase in intermediate monocytes ($P<0.01$ for both changes). This phenomenon was not seen in non-responders. Of note, responders already had a significantly higher percentage of classical and a lower rate of intermediate monocytes at baseline compared with non-responders ($P<0.01$).

But what about prediction of treatment response? "We first used a percentage relative PASI. This is a measure of an individual's residual psoriasis based on week 12, and what we found was a significant correlation with the baseline frequency of intermediate monocytes and clinical response," Dr Hardman-Smart explained. Testing the predictive validity of the baseline frequency of intermediate monocytes at a certain cut-off, the receiver operator analysis led to a sensitivity of 100%, a specificity of 83.3% and an area under the curve of 92.4% with a P-value of 0.0056. According to Dr Hardman-Smart, these are promising results.

The researchers concluded that these results suggest that the frequency of monocytes subsets before therapy may be an immune determinant of clinical response to secukinumab, which could be exploited as a predictive biomarker.

1. Hardman-Smart JA, et al. Relative frequency of monocyte subsets at baseline in psoriasis is associated with clinical outcome to secukinumab therapy. FC26, Psoriasis Gene to Clinic Congress 2021, 9-11. December.
2. Andres-Ejarque R, et al. Nat Commun. 2021;12(1):4741.

Gut microbiota of psoriasis patients: less diverse and reduced functionality

The microbiota of patients with psoriasis are less diverse compared with healthy controls. Moreover, psoriasis patients show a decreased functional richness compared with both healthy controls and healthy partners that live in the same household.

Advances in technology have led to an increased number of studies investigating the microbiome in patients with inflammatory diseases. Growing evidence supports an altered gut microbiota in patients with psoriasis. Culture-based studies have identified an increased presence of oral *Candida* in patients with psoriasis [1]. Interestingly, probiotics have been associated with a significant improvement in the severity of psoriasis but did not change microbiota [1]. "There is an association, but, according to our recently published review, the results are quite heterogeneous," Dr Tanja Todberg (University of Copenhagen, Denmark) explained [1,2]. This can in part be explained by poor study design with most studies lacking relevant inclusion criteria and baseline information [1].

To further assess microbiota in psoriasis, Dr Todberg and colleagues defined 3 different research questions: Do patients with psoriasis exhibit an aberrant gut microbial profile compared with healthy individuals? Do patients with psoriasis exhibit an aberrant gut microbial profile compared with their healthy partners that live in the same house? And is the known seasonal change of psoriasis severity associated with a shift in the composition of the gut microbiota?

The researchers collected 126 faecal samples: 53 from patients with plaque psoriasis without systemic treatment, another 52 from healthy controls matched for age, sex, body mass index (BMI), and geographical location, and 21 of the healthy cohabitants of the psoriasis patients. All participants with psoriasis had to have a Psoriasis Area Severity Index (PASI) score of ≥8, restriction of antibiotics and systemic anti-inflammatory treatment for >3 months, and a BMI <35.

Patients with diabetes or other inflammatory conditions were excluded. "We assessed patients with more severe disease to be able to see a difference. There is definitely a correlation between differences in gut microbiota and increasing severity of disease," Dr Todberg explained.

"Our psoriasis patients had moderate-to-severe disease with early-onset and a normal weight. What separated them from the control group is that they smoked significantly more, and their level of physical activity was significantly lower," Dr Todberg said. The microbial composition of the patients with psoriasis was characterised by a significantly lower richness (P=0.007) and difference in community composition (P=0.01) of metagenomic species compared with healthy controls. Moreover, the functional richness was decreased in patients with psoriasis compared with healthy controls (P=0.01) and partners (P=0.05). Interestingly, no seasonal differences were detectable in the gut microbiota.

In conclusion, the study showed that patients with psoriasis exhibit a dysbiotic taxonomic and functional gut microbiota compared with age, sex, and BMI-matched healthy controls. Despite the similar environment, a significantly lower microbial diversity was seen in patients with psoriasis compared with their partners (P=0.04). As Dr Todberg commented in the discussion, a pilot study examined the effect of adalimumab on gut microbiota in 10 psoriasis patients. Although the therapy had a very positive impact on the skin lesions, the gut microbiota stayed the same, even after 5–6 months of adalimumab therapy.

1. Todberg T, et al. Acta Derm Venereol. 2021;101(7):adv00512.
2. Todberg T, et al. Characteristics of the gut microbiota in patients with psoriasis. FC09, Psoriasis from Gene to Clinic 2021, 9–11 December.

COVID-19: What is New

DLQI scores underestimated during lockdowns?

Classic Dermatology Life Quality Index (DLQI) scores may not adequately reflect the status of patients during the pandemic. The increased numbers of 'not-relevant' responses (NRR) during this period could entail less reliable results.

The DLQI was introduced in 1994 and has since been used to determine the magnitude of effect that skin disease has on a patient's life [1,2]. Items 3–10 of the DLQI questionnaire include an NRR option. These questions comprise the influence of shopping, social/leisure activities, sex, sports, and work/studying. In some countries, reaching a certain DLQI score is a prerequisite for health insurance to render a patient with psoriasis eligible for systemic treatment [1].

"Most European countries, Ireland included, went through a series of lockdowns and we hypothesised that because people were not able to access shops, gyms, and restaurants, more 'non-relevant' responses would be ticked on DLQI questionnaires," Dr Ali Alsharqi (St. Vincent's University Hospital, Ireland) explained the study's aim [1]. Previous research had found that 38.8% of psoriasis patients generally choose an NRR at least once in their questionnaires. It was suggested that more than 1 NNR would decrease the DLQI score, and a formula was created that led to a score adjustment for NRR: the DLQI-R [3]. A second interest of the single centre, retrospective study was to evaluate potential differences in DLQI and DLQI-R during the lockdown phases of the pandemic [1].

The 52 participants all had stable disease, reflected by a Psoriasis Area Severity Index (PASI) score of ≤4. The mean age of the study subjects was 55.3 years, and 53.8% were women. Unsurprisingly in the setting of a specialist clinic, the vast majority was treated with biologics or other systemic drugs. Assessed were the most current DLQI scores obtained before lockdown restrictions and during the lockdown. The results showed similar mean disease activity before (PASI 2.16) and during lockdown (PASI 2.09). Looking at the DLQI in general, the mean scores slightly dropped with 3.13 pre-pandemic and 3.0 during the restrictions. However, mean values for NRRs increased during the lockdown (0.62 vs 1.27), and the picture changed when adjusted for these NRRs with the DLQI-R. "There was a statistically significant increase in the number

of NNRs and that corresponded to a statistically significant increase in the DLQI-R," Dr Alsharqi highlighted, pointing out that the numerical scores for interpersonal relationships, social/leisure, shopping/garden, and home were higher during lockdowns than in pre-pandemic research.

"We think it is important for clinicians to be aware of this, as they make decisions with respect to continuation or altering patient's treatments and also when it comes to data collection in registries," Dr Alsharqi summarised the findings.

1. Alsharqi A. Are we underestimating Dermatology Life Quality Index Values in the Era of COVID-19? FC12, Psoriasis Gene to Clinic 2021, 9–11. December.
2. Finlay AY, et al. Clin Exp Dermatol. 1994;19(3):210–216.
3. Rencz F, et al. J Eur Acad Dermatol Venereol. 2018;32(5):783–790.

TNF blockers likely beneficial for psoriatic patients with COVID-19

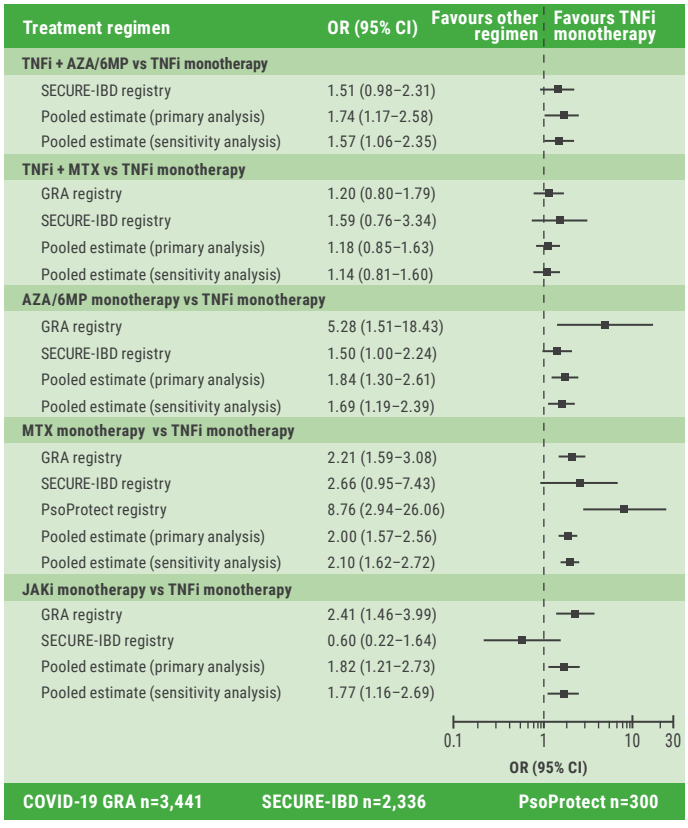
Non-biologic systemic treatment more than doubled the risk for hospitalisation and death compared with tumour necrosis factor (TNF) inhibition in psoriasis patients included in the PsoProtect registry. Among the patient-reported reasons for declining COVID-19 vaccination were concerns about psoriasis worsening.

The Psoriasis Patient Registry for Outcomes, Therapy and Epidemiology of COVID-19 Infection (PsoProtect) was created early-on during the pandemic in March 2020 to learn about the effect of SARS-Cov-2 infection on patients with psoriasis [1,2]. PsoProtect collects data from clinicians, who provide detailed data on their psoriasis patients with confirmed or suspected COVID-19 on a global online platform. Prof. Catherine Smith (King's College London, UK) reported the latest findings from a data-cut in July 2021 that included 1,272 cases [1].

The cohort consisted of 40% women, had a mean age of 49 years, and 86% were White. Systemic treatment was given to 87% of the patients, with 70% receiving biologics. "We found that, as in our earlier analysis, risk factors associated with hospitalisation in people with psoriasis are the same as in the general population: male sex, age, non-White ethnicity, and comorbidities," Prof. Smith stated. Concerning comorbidities, significantly increased likelihoods of hospitalisation were seen for hypertension (odds ratio [OR] 1.81; 95% CI 1.18–2.78), chronic liver disease (OR 2.48; 95% CI 1.37–4.48), and chronic lung disease (OR 2.5; 95% CI 1.41–4.43). Also, patients on non-biologic immunosuppression, mostly with methotrexate, acitretin, or apremilast, were more prone to hospitalisation than those on biologics (OR 2.37; 95% CI 1.5–3.76).

To achieve the necessary amount of statistical power to differentiate between treatment regimens, PsoProtect sought collaboration with registries of other immune-mediated inflammatory diseases. This led to pooled data of over 6,000 patients with psoriasis, rheumatologic diagnoses, and inflammatory bowel disease. The analysis that assessed the risk of hospitalisation for COVID-19 or death suggested that anti-TNF monotherapy was protective compared with standard systemic immunotherapy. Prof. Smith stressed that it was reassuring that findings seemed to be consistent across all 3 registries. The pooled analysis of risk for hospitalisation or death in patients with suspected and confirmed COVID-19 led to an OR of 2.0 (95% CI 1.57–2.56) for methotrexate monotherapy versus TNF-inhibitor monotherapy (see Figure). The sensitivity analysis, comprising only confirmed cases, resulted in an OR of 2.1 (95% CI 1.62–2.72) for the same comparison (see Figure). "But these findings need to be interpreted with caution: first, this is an association and not causation, but also the reporting of patients through these registries is subject to bias and findings really do need to be validated in population-based data sets," Prof. Smith pointed out.

Figure: Comparison of the likelihood for COVID-19 hospitalisation or death in psoriasis patients treated with immunomodulatory therapy versus TNF monotherapy (adjusted odds ratios) [1,4]



The related PsoProtectMe registry consists of data from self-reports of over 4,000 patients from more than 80 countries all over the world and has different patient characteristics than PsoProtect [1,3]. The mean age of participants is 47.2 years and 62% are women. Of the 38.1% of these patients who were on systemic medication during the pandemic, 18.4% were non-adherent to their regimen. This was linked to a significantly higher risk of psoriasis worsening (OR 2.9; 95% CI 2.31–3.6). Reasons for stopping the systemic treatment included fear of COVID-19 complications.

Over 80% of PsoProtectMe participants reported receiving at least 1 dose of a COVID-19 vaccine. The 8.3% who refused to be vaccinated had overall the same reasons for this decision as the general population. Furthermore, worries about a potential worsening of their psoriasis also played an important role.

Prof. Smith concluded that "both PsoProtect and PsoProtectMe have proved extremely powerful mechanisms for very rapid accrual of data and we hope that we will be able to deploy them in the future for research."

1. Smith C. The impact of the COVID-19 pandemic on people with psoriasis: an update from the PsoProtect and PsoProtectMe global registries. FC16, Psoriasis from Gene to Clinic 2021, 9–11 December.
2. PsoProtect. https://psoprotect.org [Last accessed 06 January 2022].
3. PsoProtectMe. https://psoprotectme.org [Last accessed 06 January 2022].
4. Izadi Z, et al. JAMA Netw Open. 2021;4(10):e2129639.

Patients on immunomodulators need 2 COVID-19 vaccinations before seroconversion

Encouraging results of 2 recent studies found that almost all patients on immunomodulating treatment for immune-mediated inflammatory diseases (IMID) show antibody positivity after full vaccination. However, in contrast to healthy persons, up to 17% of them do not seroconvert after their first shot of a COVID-19 vaccine. In addition, cellular immune responses are lower in these patients, questioning the durability of antibody response in this patient population.

The results of vaccine trials led to a robust knowledge of immune-response in healthy subjects, but less is established about patients on immunomodulatory treatment [1]. "We know that healthy subjects have close to a 100% seroconversion 15–35 days after the first vaccine dose, and if we consider seroconversion as a potential surrogate of vaccine efficacy, we could investigate whether this is the case in patients on immunomodulatory drugs," Dr Ali Al-Janabi (University of Manchester, UK) pointed out.

The current study included 357 patients on immunomodulators for IMID, among them a great majority with psoriasis (n=290), followed by psoriatic arthritis (n=79), and rheumatoid arthritis (n=48). Some patients had more than 1 diagnosis. Samples were collected ≥10 days after vaccine administration and analysed with immunoassays for antibodies against spike protein S1 to assess the vaccine-induced antibody formation. Further, a second immunoassay was performed to exclude participants with antibodies against nucleocapsid antigen, originating from a preceding infection.

After the first dose of any of the available vaccines, 17% did not demonstrate a positive antibody response. "If we look at some of the baseline variables, we see that as age increases, the percentage of participants with a positive antibody response decreases and this is statistically significant," Dr Al-Janabi noted. Regarding different drug classes, the group of patients on biologics had the greatest rate of positive responses (73%), while 69% of the group treated with oral immunomodulators were positive for antibodies, and 61% of participants receiving a combination of both. A logistic regression analysis that took biologic therapy as a reference and adjusted for age, sex, and disease found significantly reduced odds for mounting a positive antibody response, with an adjusted odds ratio (OR) of 0.21 (95% CI 0.05–0.87) only for the cohort of participant with combination treatment of biologic plus immunotherapy. In further exploring the sub-categories of IMID treating drugs, methotrexate was associated with a significant reduction in the likelihood of seroconversion (adjusted OR 0.09; 95% CI 0.02–0.56) compared with tumour necrosis factor (TNF) inhibition.

After the second vaccination, 192 out of 194 patients were positive for anti-spike antibodies. So, reassuringly, 99% of IMID patients on immunomodulation had a positive antibody response after their second vaccination.

"By now, there is an argument to minimise the interval between vaccine doses, since almost everybody seroconverts after the second vaccine dose. There is also an argument for methotrexate in particular that we should pause treatment either before or after the vaccine," Dr Al-Janabi commented on the results.

Reduced T-cell responses in a third of patients taking therapeutic immunosuppression

A second study presented in the COVID session also dealt with COVID-19 vaccine immunogenicity in people receiving therapeutic immunosuppression [2]. "There is emerging

research but this has largely focused on seroconversion alone, which may not be representative of the complex and multifaceted immune response to vaccinations," said Dr Satveer Mahil (Guy's and St Thomas' NHS Foundation Trust and King´s College London, UK). In his study, he assessed the impact of monotherapy with methotrexate or biologics targeting TNF, IL-17, and IL-23 on both humoral and cellular immunogenecity to the COVID-19 vaccine BNT162b2 [2]. They took blood samples at day 0 and day 28 post-dose 1, and day 14 post- dose 2. The researchers performed 2 immunogenicity assays, a humoral assessing seroconversion and neutralisation, and a cellular, assessing T helper 1 (Th1; i.e. IFNy, IL-2) and T follicular helper cell (Tfh; i.e. IL-21) responses.

In total, blood samples were analysed of 82 patients with a median age of 44 years (67 receiving immunosuppressants and 15 controls). Similar to the study by Dr Al-Janabi, seroconversion rates following the first vaccine dose were lower in patients receiving immunosuppressants than in controls (78% vs 100%), and lowest in those taking methotrexate. Reassuringly, all patients seroconverted on the second dose. Moreover, the functional capacity of plasma to neutralise wild-type, alpha and delta SARS-CoV-2 variants was similar after the second dose in patients receiving immunosuppression and controls. However, the neutralisation activity against wild-type SARS-CoV-2 and the alpha variant was lower in methotrexate-treated patients but still above the response threshold after the second dose.

Moving on to cellular responses, researchers assessed Th1 responses and were also interested in T follicular helper cell responses, which is important to maintain long-term antibody-mediated immunity. T-cell response rates following the first vaccine dose were similar in patients receiving methotrexate, biologics, and controls. However, T cell response rates following the second dose were lower in patients receiving immunosuppression compared with controls. "29% of individuals taking therapeutic immunosuppression had no evidence of T-cell response following the second vaccine dose," Dr Mahil said. The durability of antibody response in the context of absent cellular responses is uncertain and merits further study. Thus, she concluded that larger and longer-term cohort studies analysing immunogenicity of further vaccine doses including vaccines against novel variants of concern are vital. Immune correlates of vaccine effectiveness remain to be determined.

1. Al-Janabi A. Antibody responses to SARS-CoV-2 vaccination in patients receiving immunomodulators for immune-mediated inflammatory disease. FC17, Psoriasis from Gene to Clinic 2021, 9–11 December.
2. Mahil S. The impact of methotrexate and targeted immunosuppression on humoral and cellular immunogenicity of the COVID-19 vaccine BNT162b2 in people with psoriasis: a prospective longitudinal cohort study. FC18, Psoriasis from Gene to Clinic 2021, 9–11 December.

Paradoxical Reactions to Biologics

The Yin and Yang of opposing vectors: an explanation for side effects of biologics

Although classical and paradoxical psoriasis have a similar phenotype, their pathogenesis is completely different. A Yin-Yang effect between 2 opposing vectors seems to be a general principle in immunology. Thus, selective targeting of inflammatory pathways may displace inflammatory balance and cause dermatological side effects.

Psoriasis is a Th1 and/or Th17 cell-mediated autoimmune disease affecting the skin of genetically predisposed individuals. It has been 15 years since a key innate immune pathway was uncovered for triggering psoriasis [1]. In the early (acute) phase, plasmacytoid dendritic cells (pDCs) accumulate in the skin of psoriasis patients and become activated, for example by mechanical stimulation of the skin to produce interferon (IFN)α. Through the production of IFNα, pDCs drive the activation and expansion of autoimmune T cells in pre-psoriatic skin, leading to the development of psoriasis. In contrast, IFNα does not play a role in the chronic phase of the disease. Accordingly, therapy with MEDI-545, a fully human anti-IFNα monoclonal antibody, failed to show a therapeutic effect in established plaque psoriasis [2].

"Tumour necrosis factor (TNF) blockers have been the gold standard for 10 years in the therapy of plaque psoriasis," Prof. Curdin Conrad (Lausanne University Hospital, Switzerland)

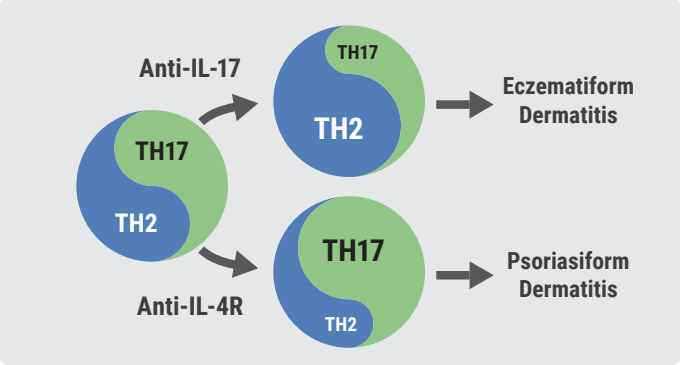
said [3]. A well-known side effect of anti-TNF therapy is psoriasiform eruptions, which resemble classical psoriasis but are immunologically distinct. Numerous cases have been published in the literature. "About 2–5% of patients receiving anti-TNF treatment develop paradoxical psoriasis independent of underlying disease," Prof. Conrad said. The pathogenesis of this phenomenon is unknown. Paradoxical psoriasis is a class effect of all anti-TNFs. Prof. Conrad pointed out that this phenomenon is selective for anti-TNF and a side effect of TNF-blocker, not *de novo* psoriasis. "If you switch patients to another class of drugs, psoriasis disappears," Prof. Conrad explained. In contrast to classic plaque psoriasis, only skin lesions of patients with paradoxical psoriasis show overexpression of both IFNα2 and IFN-ß1 [4]. Other characteristics only seen in paradoxical psoriasis are a dermal accumulation of pDCs and reduced T-cell numbers. Anti-TNF treatment prolongs type I interferon production by pDCs through inhibition of their maturation. The resulting type I interferon overexpression is responsible for the skin phenotype of paradoxical psoriasis, which, unlike classical psoriasis, is independent of T cells [4].

Paradoxical psoriasis: a type I interferon-driven innate inflammation

Thus, paradoxical psoriasis represents an ongoing, overactive innate inflammatory process, driven by pDC-derived type I interferon that does not lead to T-cell autoimmunity [4]. "Based on this, we proposed the so-called Yin and Yang of TNF and IFNα, where those 2 cytokines represent opposing vectors (TNF/IFNα)," Prof. Conrad said. TNF-inhibitors can dysregulate this balance and thus induce an IFN-driven inflammation. "Although the clinical picture is very similar, the pathogenesis of classical psoriasis and paradoxical psoriasis is completely opposing. One is driven by TNF, is a T-cell mediated disease and therefore shows relapses, while the other is induced by the blockade of TNF, is T-cell independent, and therefore does not show any relapses and represents an ongoing IFNα-driven innate inflammation," Prof. Conrad explained.

"Depending on the genetic background, you could get other side effects than paradoxical psoriasis. Something that gets activated through interferon is B cells, so one could get an induction of autoimmune antibodies or lupus or even an induction of anti-drug antibodies – all linked to the same pathway," Prof. Conrad explained. So, is this Ying-Yang concept true for TNF/IFNα only, or is it a general concept in immunology that 2 opposing vectors or 2 pathways control each other? Indeed, there is another example: Biologics targeting IL-17A can induce eczema and pruritus in patients with plaque psoriasis. Eczematous skin lesions develop despite initial response to anti-IL-17A therapy. Eczematous manifestations are noticed in 5–6% of anti-IL17A-treated patients and show no association with atopy. "Typically, these lesions are seen after a good resolution of the underlying psoriasis," according to Prof. Conrad. In patients with eczema following anti-IL-17A treatment, he found a complete switch from Th17 to Th2 signature typical for atopic dermatitis. "Based on this, we also propose to see the Th17 and Th2 pathways as a Yin and Yang" (see Figure). Blockade of Th17 can lead to a switch to Th2 disease like atopic dermatitis. Vice versa, psoriasiform skin lesions developed despite a response of eczematous lesion to anti-IL-4R, 3 months after the start of dupilumab [5]. "These experiences suggest that Th2/Th17 pathways control each other, and the Yin-Yang between 2 opposing vectors seems to be a general concept in immunology. At least 2 could be described, between TNF and type I interferon and between Th17 and Th2. "Therefore, selective targeting of an inflammatory pathway may displace the inflammatory balance," Prof. Conrad concluded.

Figure: The Yin-Yang of Th2/Th17. Modified from [1]



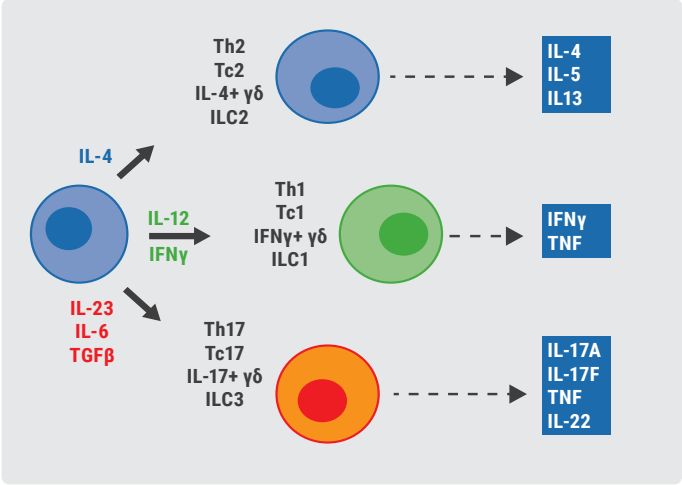
1. Nestle FO, et al. J Exp Med 2005;202:135–143.
2. Bissonnette R, et al. J Am Acad Dermatol 2010;62:427–436.
3. Conrad C. Paradoxical reactions to biologics: mechanisms, features and management. Psoriasis from Gene to Clinic 2021, 9–11 December.
4. Conrad C, et al. Nat Commun 2018;9:25.
5. Ferrucci S, et al. Clin Exp Dermatol 2020;45:625–626.

Explaining arthropathy development through IL-4 and IL-13 blockade

Evidence has been found of a previously unknown protective role of IL-4/IL-13 in entheseal induction of the IL-23/IL-17 axis. This might explain clinical observations of emerging musculoskeletal entheseal pathology following dupilumab therapy.

IL-4 and IL-13 are key cytokines that are involved in typical Th2 diseases such as atopic dermatitis, asthma, and allergy. Thus, according to Dr Charlie Bridgewood (University of Leeds, UK), blocking IL-4 and IL-13 can be an interesting option for treating Th2 disease. "Something very interesting is that dupilumab therapy has been associated early on with paradoxical disease," Dr Bridgewood said. Numerous patients show not only new onset of psoriasis but also psoriatic arthritis (PsA) and enthesitis. A possible explanation of this phenomenon is the polarisation of one T-cell pathway that might come at the expense of another. If one pathway is blocked T cells might enter opportunistic pathways (see Figure). "Maybe that is why we get Th17 disease. However, there are 2 sides to this coin: if we give patients ustekinumab, they sometimes develop eczema – a type 2 phenotype," Dr Bridgewood explained.

Figure: T-cell effector functions [1]



IFNγ, interferon gamma; IL, interleukin; ILC, innate lymphoid cell; TGFβ, transforming growth factor beta; Tc2, cytotoxic T cell type 2; Th2, T helper 2; TNF, tumour necrosis factor.

IL-4/IL-13 blockade: a more than 12-fold risk for enthesitis

To better understand paradox reactions following dupilumab therapy, Dr Bridgewood and his team analysed 37,849 patients on dupilumab for incidence of psoriatic and other inflammatory diseases in VigiBase, a World Health Organization's global Individual Case Safety Report (ICSR). The researchers formed disease groups according to autoimmune or autoinflammatory nature. Following dupilumab therapy, the rates of seronegative arthritis (OR 9.61), enthesitis (OR 12.6), psoriasis (OR 1.48), and nail psoriasis (OR 4.71) were all elevated. In addition, the frequency of certain Th1 diseases, such as acne and vitiligo, also increased after dupilumab intake. "Interestingly, Crohn´s disease was less frequent with dupilumab therapy, so the take-home message is that classical autoimmunity with autoantibody involvement is less common, whereas Th1-driven and Th17-driven disease are more common," Dr Bridgewood concluded.

In vitro studies revealed that myeloid cells in the human enthesis are the main source of local IL-23 production [2]. Both IL-4 and IL-13 block IL-23 from these cells. "If you remove IL-4 and IL-13, you can increase IL-23," Dr Bridgewood said. These novel findings point towards a previously unknown role for IL-4 and IL-13 as having a protective function in entheseal induction of IL-23/IL-17 axis cytokines and their associated disease such as psoriasis and PsA. This is the molecular explanation for why anti-IL-4/IL-13 therapy may induce musculoskeletal entheseal pathology as has been demonstrated in this analysis of a large database.

1. Bridgewood C, et al. Interleukin (IL)-4/IL-13 blockade is associated with psoriatic disease: evidence from the clinic and in vitro. FC25, Psoriasis from Gene to Clinic 2021, 9–11 December.
2. Bridgewood C, et al. Rheumatol (Oxford) 2021;60:2461–2466.w

Best of the Posters

Potential biomarker discovered for treatment response to ustekinumab

Investigation of blood immune cells found that IL-23 induced signal transducer and activator of transcription (STAT)3 nuclear translocation in mucosal-associated invariant T (MAIT) cells could serve as a biomarker of treatment response to ustekinumab. If further validated, this may offer future guidance for ustekinumab therapy.

Finding blood biomarkers able of predicting clinical response to systemic treatment of psoriasis is an emerging field of research. To evaluate whether or not STAT3 activation in IL-23 responsive cells could be a candidate for prediction, participants were enrolled from the Psoriasis Stratification to Optimise Relevant Therapy (PSORT) consortium [1]. IL-23-induced STAT3 translocation was determined by imaging flow cytometry of peripheral blood mononuclear cells (PBMCs) and quantified.

PBMCs were collected from the participants at baseline and during treatment with ustekinumab at weeks 1, 4, and 12.

The study cohort consisted of 10 adult Psoriasis Area and Severity Index (PASI) 75 responders and 10 PASI 75 non-responders at week 12, as well as 10 healthy volunteers, all matched by age, ethnicity, and sex. Mucosal-associated invariant T (MAIT) cells, IL-17 producing CD8 T cells, and IL-17 producing CD4 T cells were recognised as relevant immune cell populations. The baseline results for MAIT cells with IL-23-induced STAT3 translocation demonstrated no difference between healthy controls and participants with psoriasis. "We observed that in mucosal-associated invariant T cells or MAIT cells, STAT3 activation is significantly higher in ustekinumab PASI 75 responders compared with PASI 75 non-responders at baseline before therapy. Furthermore, we observed that STAT 3 translocation in MAIT cells at baseline significantly correlates with a clinical response at week 12 of ustekinumab therapy," Mr Shane Solanky (King's College London, UK) elaborated. For example, MAIT cells of psoriasis patients not experiencing PASI 75 on ustekinumab had significantly less IL-23-induced STAT3 translocation than PASI 75 responders. Overall, STAT3 translocation in MAIT cells, as well as IL-17 producing CD8 T cells were decreased by the ustekinumab treatment.

Exploring validity and reliability of baseline values of IL-23-induced STAT3 translocation in MAIT cells as a potential biomarker for response to ustekinumab, the receiver operator characteristic analysis resulted in an area under the curve of 99.1%, sensitivity of 100% and specificity of 87.5%. "Our research has identified IL-23-induced STAT3 translocation in MAIT cells as a potential biomarker predictive of response to ustekinumab, which warrants replication and further validation," Mr Solanky concluded.

1. Solanky S, et al. IL-23-induced STAT3 translocation in circulating MAIT cells is a potential biomarker of clinical response to ustekinumab in psoriasis. P60, Psoriasis from Gene to Clinic 2021, 9–11 December.

TNF inhibitor for immune-mediated inflammatory disease doubles the risk of paradoxical psoriasis

According to a Danish cohort study, patients with immune-mediated inflammatory disease treated with a tumour necrosis factor-alpha (TNFα) inhibitor had a 2-fold increased risk of new-onset psoriasis compared with those receiving conventional therapy. The risk to develop pustular psoriasis was 3 times higher compared with patients treated with a non-TNF biologic.

Some patients with immune-mediated inflammatory disease develop paradoxical induction or worsening of psoriasis during treatment with TNFα inhibitors. As this side effect is poorly understood, a Danish cohort study explored the risk of new-onset psoriasis during treatment with a TNF inhibitor compared with the risk during treatment with non-biologic conventional treatment [1]. Dr Nikolai Loft (Copenhagen University Hospital, Denmark) and colleagues evaluated the risk of developing any type of psoriasis, non-pustular and pustular psoriasis. Data was derived from the Danish national registries, which includes all patients with inflammatory bowel disease (IBD) and/or rheumatoid arthritis (RA) who received either conventional therapy or TNF inhibitor treatment between 1995 and 2018.

The analysis included 20,910 patients treated with TNF inhibitors, of whom 108,024 patients were treated conventionally, and 4,909 patients were treated with non-TNF inhibitor biologics. During the follow-up period, 1,471 (1.4%) patients developed psoriasis. Most patients (n=1,332) suffered from non-pustular psoriasis, another 127 from psoriasis pustulosis palmoplantaris, and 12 from generalised pustular psoriasis.

The relative risk of developing non-pustular psoriasis during treatment with a TNF inhibitor was 2.12 times higher than with conventional treatment. An even higher risk of TNF inhibitor intake was associated with developing pustular psoriasis (HR 6.5). When the risk of TNF inhibitor use was compared with the risk of non-TNF biologics, TNF inhibitor use was associated with an HR of 1.85 for non-pustular and 3.11 for pustular psoriasis. Based on this data, the researchers calculated that exposure to TNF inhibitors for 241 patient-years is needed for 1 additional patient with any type of TNF inhibitor-induced psoriasis. Although non-pustular types for psoriasis constituted the most events, pustular types of psoriasis had the highest relative risk. The researchers emphasised that practitioners who treat patients with immune-mediated inflammatory disease should be aware of the risk of TNF inhibitor-induced psoriasis.

1. Thein D, et al. Risk of anti-TNF-induced psoriasis in patients with immune-mediated inflammatory diseases – a Danish nationwide cohort study. P27, Psoriasis from Gene to Clinic 2021, 9–11 December.

Secukinumab also tolerable in paediatric psoriasis patients

The safety of a biologic is a key concern in children with psoriasis. A pooled safety analysis of 2 phase 3 trials including 198 paediatric patients with moderate-to-

severe plaque psoriasis revealed similar tolerability of secukinumab in children and adolescents compared to adult patients [1].

Approximately 1% of all children and adolescents suffer from psoriasis. Although children are less likely to develop the disease than adults, their suffering is particularly severe as the condition negatively impacts their quality of life. In addition, it affects their long-term psychological well-being. The IL-17 blocker secukinumab has been proven to be efficacious in children 6 to <18 years of age in 2 phase 3 trials [2,3]. In these studies, children (aged 6 to <12 years) and adolescents (aged 12 to <18 years) received either 75 mg or 150 mg of secukinumab, depending on their body weight (<50 kg or ≥50 kg). The biologic improved skin symptoms and quality of life at all doses studied. This led to its approval for children aged between 6 and <18 years with moderate-to-severe psoriasis.

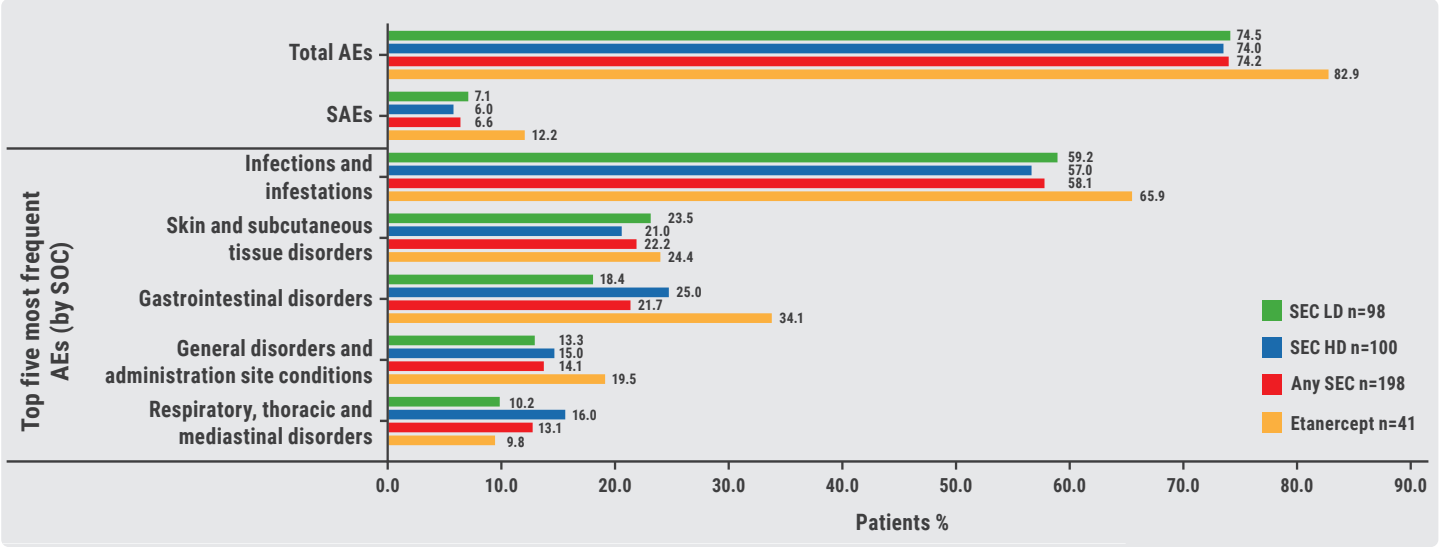
The issue of safety is of particular interest when it comes to children and adolescents. To explore this further, pooled safety analyses of the 2 phase 3 studies (NCT02471144 and NCT03668613) evaluated all patients who received at least 1 dose of secukinumab. Prof. Michael Sticherling (University Erlangen–Nürnberg, Germany) presented 2 analyses: one on the safety data up to week 12, and the second with data up to week 52 [1].

The safety profile of secukinumab was comparable in both studies and was consistent with that seen in adults with plaque psoriasis. In the 12-week analysis, infections (particularly nasopharyngitis) were most common. Infections occurred in 31.7% of children treated with the low dose of secukinumab and 35.4% with the high dose of secukinumab compared with 39% with placebo. In addition, gastrointestinal disturbances occurred in 8.5% of patients treated with the low secukinumab dose and 14.6% treated with the high secukinumab dose.

By week 52, 74.2% of children in both secukinumab groups reported adverse events (compared with 82.9% of children treated with etanercept). The incidence of serious adverse events was 6.6% in any secukinumab-treated children compared with 12.12% of those treated with etanercept (see Figure). Infections were also most common at 1 year (in 58.1% of all patients treated with secukinumab compared with 65.9% on etanercept therapy), followed by skin and subcutaneous tissue disorder, gastrointestinal disorders, general disorders and administration site conditions, and respiratory, thoracic and mediastinal disorders. More paediatric patients in the etanercept group (34.1%) had gastrointestinal problems compared with children treated with secukinumab (18.4% in the low-dose group compared with 25% in the high-dose group), and 2% of children treated with secukinumab had *Candida* infections.

In general, the safety profile of secukinumab-treated paediatric patients was comparable to that of the placebo group. There was also no significant difference between the 2 doses. In addition, no new or unexpected safety signals

Figure: Adverse events in paediatric patients treated with secukinumab or etanercept by week 52. Modified from [1]



AEs, adverse events; HC, high dose; LD, low dose; SAEs, serious adverse events; SEC, secukinumab; SOC, system organ class.

were identified in children and adolescents. The frequency of adverse events was comparable to those seen in an adult population. The proportion of patients with infections was also similar between the 2 paediatric age subgroups.

1. Sticherling M, et al. Pooled safety analysis from two phase 3 studies of secukinumab in paediatric patients for up to week 52 with moderate to severe plaque psoriasis. P49, Psoriasis from Gene to Clinic 2021, 9–11 December.
2. Bodemer C, et al. J Eur Acad Dermatol Venereol 2021;35:938–947.
3. Magnolo N, et al. J Am Acad Dermatol Venereol 2022;86:122–130.

High treatment success with ixekizumab in patients with psoriasis and diabetes

A marked proportion of participants from 3 phase 3 psoriasis trials with comorbid diabetes experienced a benefit in the Psoriasis Area and Severity Index (PASI) with ixekizumab. The post-hoc analysis of these trials also detected no deterioration of blood pressure, body mass index (BMI), and lipid profile.

The anti-IL-17A antibody ixekizumab has been assessed for treatment of moderate-to-severe psoriasis within the UNCOVER trials (NCT01474512, NCT01597245, NCT01646177) [1,2]. The results revealed long-term maintained efficacy and consistent safety up to 5 years of treatment. A new post-hoc analysis by Dr Alexander Egeberg (Copenhagen University Hospital Gentofte, Denmark) and colleagues investigated ixekizumab in patients suffering from type 1 or 2 diabetes mellitus at baseline [3]. The analysis included 184 patients from the 3 randomised, placebo-controlled, phase 3 UNCOVER-1, -2, and -3 studies. The participants all had a Body Surface Area (BSA) of ≥10, a static Physician Global Assessment of ≥3, and a PASI of ≥12. From the evaluated participants with diabetes, 103 had been randomised to an ixekizumab group and 81 to a placebo arm in the original trials. The treatment with ixekizumab was administered at a loading dose of 160 mg, followed by 80 mg every 2 weeks until week 12, and the same dose every 4 weeks through week 60. The rates of participants reaching PASI 75, 90, and 100 were primarily evaluated for efficacy. Of further interest were values such as blood pressure and lipids. Mixed models repeated measures and logistic regression were used for data analyses.

As for the baseline characteristics, some variation existed between the ixekizumab and placebo groups in mean age (54.2 vs 53.7 years) and male sex (65.1% vs 71.6%), while groups were comparable for PASI (19.5 vs 20.9). In both arms, the mean BMI was 34.8 kg/m^2, and over 90% of patients had a diagnosis of type-2 diabetes.

The results demonstrated significance for higher rates attaining psoriasis improvements on ixekizumab. At week 12, PASI 75 was found in 94.2% on the study drug and 2.5% on placebo. The matching outcome percentages for PASI 90 were 61.2% versus 0% and for PASI 100 23.3% versus 0%, respectively (P<0.001 for all comparisons). The levels of fasting serum glucose were not substantially altered by ixekizumab treatment through week 60, with a mean baseline measure of 8.7 mmol/L and 8.8 mmol/L at study completion. Further, ixekizumab did not impact cholesterol, triglycerides, BMI, or blood pressure levels.

The authors concluded that despite high BMI and PASI scores at baseline, ixekizumab was efficacious in patients with psoriasis and comorbid diabetes mellitus.

1. Leonardi C, et al. Dermatol Ther (Heidelb). 2020;10(3):431–447.
2. Blauvelt A, et al. J Am Acad Dermatol. 2021;85(2):360–368.
3. Egeberg A, et al. efficacy of ixekizumab in patients with moderate-to-severe plaque psoriasis and comorbid diabetes mellitus. P30, Psoriasis from Gene to Clinic 2021, 9–11 December.