# Dermatology RESEARCH REVIEW™

Making Education Easy

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## In this issue:



**Abbreviations used in this issue**
**BCC** = basal cell carcinoma
**COVID-19** = coronavirus disease 2019
**IL** = interleukin
**OR** = odds ratio
**PASI** = Psoriasis Area and Severity Index
**PCR** = polymerase chain reaction
**SARS-Cov-2** = severe acute respiratory syndrome coronavirus 2
**TNFi** = tumour necrosis factor inhibitor



# Welcome to the latest issue of Dermatology Research Review.

Over a year on from the outbreak of the COVID-19 pandemic we now have research evidence to show that patients taking a TNFi or methotrexate are at no greater risk of hospitalisation or death, and very few patients presenting with otherwise unexplained acral chilblains have positive PCR or serology evidence of COVID-19. Laboratory switching of RNA expression from that seen with lesional towards non-lesional psoriasis from therapies (in advance of what could be seen clinically) may be a future tool guiding appropriate patient-individualised management. A large multinational real world setting shows that complete clinical clearance is seen in only 20–25% of psoriasis patients, with poorer results seen in those who have increased comorbidities and higher prior biologic use. Should patients develop TNFi-induced psoriasis, we should change therapeutic class rather than switch to another TNFi. Worryingly, there have been reports of early severe cardiovascular events soon after initiating ustekinumab in those with higher cardiovascular risk parameters so they require closer monitoring. Avoiding or stopping therapy provides better outcomes for drug-induced lupus, post finasteride syndrome patients, and children with pigmented purpuric dermatosis, but incomplete skin cancer primary surgical excision has worse patient outcomes. Finally, because the risk is higher with morpheaform BCC of the nose and ear, this may be a category for which upfront Mohs surgery would be justified.

We hope that you find these articles of academic or relevant clinical interest and welcome any feedback you may have.

Kind regards,


**Dr Louise Reiche**
louisereiche@researchreview.co.nz


## Clinical outcomes of COVID-19 in patients taking tumor necrosis factor inhibitors or methotrexate

**Authors:** Yousaf A et al.


**Summary:** This multicentre research network study evaluated the impact of biologics and immunomodulators on COVID-19-related hospitalisation and mortality. 53,511,836 patient records from the global federated health research network TriNetX (Cambridge, MA) were analysed. Of these, 32,076 (0.06%) had a documented COVID-19 diagnosis. 214 patients with COVID-19 and recent TNFi or methotrexate exposure were compared with 31,862 COVID patients without TNFi or methotrexate exposure. After propensity matching, the likelihood of hospitalisation (risk ratio 0.91, 95% CI 0.68–1.22; p=0.5260) and mortality (risk ratio 0.87, 95% CI 0.42–1.78; p=0.6958) did not differ significantly between groups.


**Comment:** Immunosuppression is associated with a higher susceptibility to infections and worse outcomes from infections. Intuitively, early in the COVID-19 pandemic when there was little evidence-based research to direct clinical decision-making, it seemed clinically prudent to avoid or reduce immunosuppressive treatment when possible for patients at higher risk of contracting COVID-19. Subsequently, immunosuppressants (particularly steroids) were used to reverse cascading COVID-19–induced immune reactivity. This very large study revealed that recent exposure to methotrexate or a TNFi was not associated with worse outcomes (increased hospitalisation or mortality), and is reassuring for patients and clinicians desiring to use these therapies in severe dermatological conditions.


***Reference: J Am Acad Dermatol 2021;84(1):70-5***
Abstract


### Independent commentary by Dr Louise Reiche MBChB (Otago) FRACP MD FNZDSI

Dr Louise Reiche is a New Zealand physician trained vocational specialist dermatologist. Louise runs general dermatology clinics within integrated family health care: Kauri HealthCare, Palmerston North. She has additional special interests in eczema, patch testing, skin cancer surveillance and preventative dermatology health. **For full bio CLICK HERE**

## Most chilblains observed during the COVID-19 outbreak occur in patients who are negative for COVID-19 on polymerase chain reaction and serology testing

**Authors:** Le Cleach L et al.

**Summary:** This French study evaluated the prevalence of acral manifestations (mainly chilblains) in patients with COVID-19. A national survey was launched on 30 March 2020 by the French Society of Dermatology that asked physicians to report cases of skin manifestations in patients with suspected or confirmed COVID-19 during the national lockdown period. 311 patients with acral manifestations (58.5% women, median age 25.7 years) were reported; chilblains (65%) were the most frequent clinical presentation. 93 (30%) of the patients with acral manifestations had clinical signs of COVID-19, 67 (22%) had less specific infectious symptoms, and 151 (49%) had no clinical symptoms of COVID-19 preceding or during the course of acral lesions. Histological analysis of skin biopsies was consistent with chilblains. 150 (48%) patients were tested for COVID-19. Overall, 70 of 75 patients were seronegative for SARS-Cov-2 serology and 114 of 121 patients were negative for SARS-CoV-2 reverse transcription PCR.

**Comment:** Early into the COVID-19 pandemic a rise in acral lesions, particularly chilblain vasculitis, was observed and was found to be associated with a milder clinical course and a higher incidence in younger patients. It became an important clinical manifestation of COVID-19. This study reveals that only a minority of patients presenting with acral lesions, mainly chilblains, are due to laboratory confirmed COVID-19 infection (reverse transcription PCR or SARS-Cov-2 serology). The take-home message is to exclude possible COVID-19 infection should you observe acral chilblains, particularly during the pandemic despite COVID-19 being an unlikely cause.

***Reference: Br J Dermatol 2020;183(5):866-74***
Abstract

## Association of the psoriatic microenvironment with treatment response

**Authors:** Wang G et al.

**Summary:** This study reported the development of a bioinformatic gene signature score derived from skin mRNA to predict psoriasis treatment response. 1145 skin samples from patients in 12 retrospective psoriasis studies were analysed using the CIBERSORT algorithm to define the immune landscape of psoriasis lesions and controls. Random forest classification and principal component analysis algorithms were used to estimate psoriatic microenvironment (PME) signature genes and construct a PME score. In psoriasis lesions, the expression of 33 PME signature genes defined 2 immune phenotypes that could be simplified to a numerical PME score. A high PME score was characterised by keratinocyte differentiation, and a low PME score exhibited an immune activation signature. A high PME score correlated with a better treatment response (75.8% PASI reduction; p=0.03), whereas a low PME score was associated with a worse response (53.5% PASI reduction; p=0.03). The PME score after 4 weeks' treatment correlated with future responder versus nonresponder status for etanercept, methotrexate plus adalimumab, and tofacitinib, 8–12 weeks earlier than PASI correlations.

**Comment:** Lesional and non-lesional psoriasis skin demonstrates different immune profiles when analysed by whole genome RNA expression. Effective therapy effects conversion of lesional whole genome RNA expression to that seen in non-lesional skin. The PME score is a biometric measure of this conversion and is seen in advance of clinical change. Were this to become a readily available clinical tool in future, it would reap benefits for patients and clinicians knowing in advance which therapy is likely to be most effective (as culture sensitivities direct appropriate antibiotic prescribing), be fiscally wise for the health sector, and avoid drug waste with carbon footprint implications.

***Reference: JAMA Dermatol 2020;156(10):1057-65***
Abstract

## A multinational, prospective, observational study to estimate complete skin clearance in patients with moderate-to-severe plaque PSOriasis treated with BIOlogics in a REAL world setting (PSO-BIO-REAL)

**Authors:** Seneschal J et al.

**Summary:** The observational PSO-BIO-REAL study estimated complete skin clearance in patients with moderate-to-severe plaque psoriasis treated with biologics in a real world setting. 846 patients from the US, France, Italy, the UK and Germany who were taking a biologic (TNFi or anti-IL-12/23) were followed-up for 1 year. Prior to study entry, 60% of patients were biologic-naïve. 23% and 26% of patients achieved complete skin clearance at 6 and 12 months, respectively. The proportion of patients achieving complete skin clearance was better in biologic-naïve patients (25% at month 6 and 30% at month 12) than in biologic-experienced patients (20% at both time-points). The rate of complete skin clearance decreased with increasing number of prior biologics and baseline comorbidities.

**Comment:** The more severe cases of psoriasis with respect to degree, extent, and duration of disease have long been observed to be associated with greater comorbidities and reduced therapeutic response. Most trials of new biologics are undertaken in biologic-naïve patients and those with moderate disease, in whom better responses would be predictable. Furthermore, although 75% improvement in skin disease measured by PASI, Dermatology Life Quality Index or similar scores is indicative of excellent disease improvement, real-life patients desire complete clearance of skin disease. Fiscal restraint reduces drug accessibility to more severe and therapeutic-resistant disease. This multinational study provides practical real-life data, showing around 25% complete skin clearance at 6 and 12 months in adults with moderate-to-severe plaque psoriasis treated with biologics. As the number of baseline comorbidities and the number of prior biologics increased, the rate of complete skin clearance decreased. 75% of our most severe psoriasis patients thus remain in need of further novel therapies.

***Reference: J Eur Acad Dermatol Venereol 2020;34(11):2566-73***
Abstract



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## TNF-α inhibitor–induced psoriasis: A decade of experience at the Cleveland Clinic

**Authors:** Mazloom SE et al.

**Summary:** This retrospective study characterised a cohort of patients with TNFi-induced psoriasis who were treated at the Cleveland Clinic over a 10-year period from 2003 to 2013. Overall, 102 patients (mean age of onset 40 years, 73.5% female) were evaluated. Crohn's disease (48%) and rheumatoid arthritis (24.5%) were the most frequent primary conditions, and infliximab (52% of cases) was the most common inciting agent. Subtypes of TNFi-induced psoriasis included plaque-type psoriasis (49.5%), scalp psoriasis (47.5%), and palmoplantar pustulosis (41%). TNFi-induced psoriasis improved or resolved after treatment with topical medications alone in 63.5% of patients. Ciclosporin and methotrexate (>10mg weekly) were often effective if topical treatments failed. TNFi-induced psoriasis improved or resolved in 67% of refractory cases after TNFi discontinuation, but persisted or recurred in 64% of patients after switching to another TNFi.

**Comment:** Psoriasis is associated with several autoimmune diseases and many of these are considered psoriasis comorbidities, such as rheumatoid arthritis and Crohn's disease. So it may not be surprising that patients with these conditions later develop psoriasis. However, TNF inhibitors are used to treat both psoriasis and other autoimmune diseases such as Crohn's and rheumatoid arthritis and hence development of new psoriasis whilst undergoing TNFi therapy seems paradoxical. Should it arise in your patient, this study is therapeutically helpful, advising cessation of the TNFi, rather than switching to another TNFi.

***Reference: J Am Acad Dermatol 2020;83(6):1590-8***
Abstract

## Association between early severe cardiovascular events and the initiation of treatment with the anti-interleukin 12/23p40 antibody ustekinumab

**Authors:** Poizeau F et al.

**Summary:** The monoclonal antibody ustekinumab (targeting IL-12/23p40) is effective in the treatment of moderate-to-severe psoriasis, psoriatic arthritis, and Crohn's disease. This case-time-control study used data from the French national health insurance database to evaluate whether treatment with ustekinumab is associated with increased risk of severe cardiovascular events (SCEs). Of 9290 patients exposed to ustekinumab (52% male; mean age 43 years), 179 experienced SCEs (acute coronary syndrome, unstable angina, or stroke) within 6 months of exposure. There was a significant association between initiation of ustekinumab and SCE occurrence in patients with high baseline cardiovascular risk (OR 4.17, 95% CI 1.19–14.59) but not in patients with low cardiovascular risk.

**Comment:** More severe and extensive psoriasis is associated with higher comorbidities including cardiovascular disease. Reducing global patient inflammation is considered important for reducing psoriasis and comorbidity risk. Whilst weight reduction, exercise and anti-inflammatory diets (e.g. Mediterranean diet) promote holistic anti-inflammation, most patients with severe disease benefit from therapeutic assistance to stimulate a positive spiral of lifestyle change. The results of this study are concerning because the very group of psoriasis patients we would consider prescribing ustekinumab for in NZ are those with severe and extensive psoriasis, and these patients are also more likely to be at higher cardiovascular risk. Until further studies provide appropriate mitigating therapeutic advice, patients commencing ustekinumab warrant closer cardiovascular surveillance and consideration of cardiology review.

***Reference: JAMA Dermatol 2020;156(11):1208-15***
Abstract

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## Association between drug use and subsequent diagnosis of lupus erythematosus

**Authors:** Halskou Haugaard J et al.

**Summary:** This Danish case-control study evaluated the association between drug use and subsequent diagnosis of lupus erythematosus. 3148 patients with cutaneous lupus erythematosus (CLE) or systemic lupus erythematosus (SLE) who were on the Danish National Patient Register in 2000–2017 were compared with 31,480 matched controls. Many significant associations were found between drug use and a subsequent diagnosis of CLE and SLE, but most were likely due to protopathic bias. New plausible causal associations with CLE/SLE were observed for fexofenadine (OR 2.61 for SLE and 5.05 for CLE), levothyroxine (2.46 and 1.30, respectively), metoclopramide (3.38 and 1.47), and metronidazole (1.57 and 1.93).

**Comment:** Nearly one-third of subacute CLE and 15% of SLE cases are estimated to be triggered by medications. Hydralazine, isoniazid, procainamide (no longer available in NZ), minocycline and quinidine are well recognised. Newer associations include TNF inhibitors, fexofenadine, levothyroxine, metoclopramide and metronidazole. Not all cases of lupus will resolve on removal of the aetiological culprit agent, but those patients where it does will benefit enormously when clinicians are cognisant of drug triggers and able to identify and remove the causative agent.

***Reference: JAMA Dermatol 2020;156(11):1199-1207***
Abstract

## Finasteride and suicide

**Authors:** Irwig MS

**Summary:** This postmarketing case series examined the clinical histories and symptoms reported by 6 suicide victims who were taking finasteride for treatment of androgenic alopecia. Medical records and autopsy reports were provided by family members, and relevant information was extracted according to guidelines for submitting adverse event reports. An important pattern of symptoms (insomnia and persistent sexual dysfunction after medication discontinuation) was common among all cases. There was no documentation of concomitant medication or any baseline medical or psychiatric diagnoses prior to starting finasteride, except for 1 patient with hyperlipidaemia.

**Comment:** Androgenetic alopecia affects nearly half of Caucasian men by the age of 50 years and causes greater morbidity when it arises at an earlier age, driving sufferers to seek reversal therapy. Finasteride halts hair loss or regrows hair in 90% of men taking it long term, revealing high efficacy. Persistent erectile dysfunction may affect around 1% of users. Post finasteride syndrome (PFS) causing persistent or irreversible sexual, physical, mental and neurological symptoms is a rare side effect currently with no evidence-based effective treatments, and associated with a higher incidence of depression and suicide. We await further research results elucidating genetic and other factors that may predispose to PFS. Chronic sleep deprivation also predisposes to depression and suicide. Compared to double-blind studies, case series interpretations are inferior. Nonetheless, this series reveals cautionary concerns for those patients who suffer from PFS, and all patients seeking finasteride for androgenetic alopecia need to be informed of this rare but severe potential adverse effect.

***Reference: Dermatology 2020;236:540-5***
Abstract



## Pigmented purpuric dermatosis in children

**Authors:** Ollech A et al.

**Summary:** This retrospective study assessed the clinical course and utility of vitamin C and rutoside treatment in 101 paediatric patients with pigmented purpuric dermatosis (PPD) who were treated at a Chicago Hospital between 2008 and 2018. The female:male ratio was 1.3:1, and the median age at diagnosis was 8.8 years. The most common PPD subtypes were lichen aureus (43%) and Schamberg (34%). 53 patients had evaluable follow-up documentation via medical records or a phone questionnaire (median follow-up, 7.13 months). 28 patients were treated with vitamin C or rutoside (or combination therapy) and 25 patients received no treatment. 24 (45.3%) patients had clearance of the rash, including 10 (42%) in the treated group and 14 (58%) in the untreated group. Seven patients (13.2%) had recurrence of the rash. Treatment with vitamin C and/or rutoside was well tolerated.

**Comment:** PPD is typically a chronic condition featuring reddish-brown skin lesions caused by leaky capillaries, most commonly located on the lower legs but may arise at any site. The lesions are sometimes itchy. In contrast to stasis dermatitis where haemosiderin deposition occurs around deeper blood vessels, in PPD haemosiderin tends to occur in the superficial papillary dermis. There are many subvariants and whilst many medications have been recognised to trigger PPD, the majority of cases are idiopathic. Although benign, the condition may flare and persist chronically in adults and so therapeutic relief is desired, particularly for cosmesis. This study shows that while vitamin C and rutoside were well tolerated in the paediatric group, watchful waiting ("no therapy") was associated with a higher clearance rate.

***Reference: J Eur Acad Dermatol Venereol 2020;34(10):2402-8***
Abstract

## Surgical treatment of basal cell carcinoma: A case series on factors influencing the risk of an incomplete primary excision

**Authors:** Kappelin J et al.

**Summary:** This study evaluated the rate of positive surgical margins after primary excision of BCC at a tertiary dermatology clinic in Sweden, and determined factors associated with incomplete primary excision. Patients scheduled for standard excision of BCC (without perioperative margin control) in 2008–2015 were included. Overall, 4.6% of 3911 BCC tumours were incompletely excised. The rate of incomplete excisions was higher for facial tumours and tumours with an aggressive histological subtype. The highest rate of incompleted excisions was found for morpheaform BCC on the nose (61.5%) and ear (50%).

**Comment:** Complete skin cancer excision is vital to minimise risk of skin cancer recurrence. Recurrent skin cancers are typically more aggressive and frequently require more extensive procedures resulting in greater expense and morbidity. It has been well documented that skin cancer experts, and dermatologists in particular, have the highest rates of accurate clinical skin cancer diagnosis and complete primary surgical excisions. Perioperative examination of pathology margins is integral to Mohs surgery and this technique has the highest skin cancer cure rate. Mohs surgery is more labour intensive and more expensive. Morpheaform BCC on the nose or ear is more aggressive, has indistinct clinical margins and higher incomplete excision rates even in the hands of experts, so these are clinical subtypes that could arguably be managed upfront by Mohs surgery to minimise morbidity and be most cost effective.

***Reference: J Eur Acad Dermatol Venereol 2020;34(11):2518-25***
Abstract