Dermatology Research Review™

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Issue 121 - 2025

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Abbreviations used in this issue:

AD = atopic dermatitis; **BCC/SCC** = basal/squamous cell carcinoma; **B-VEC** = beremagene geperpavec-svdt; **CV** = cardiovascular; **DALY** = disability-adjusted life-year; **EASI** = Eczema Area and Severity Index; **IGA** = Investigator Global Assessment; **JAK** = Janus kinase; **OR** = odds ratio; **RCT** = randomised controlled trial.

Welcome to issue 121 of Dermatology Research Review.

This issue begins with a phase 3 trial of ivarmacitinib, a selective oral JAK1 inhibitor, for the treatment of moderate-to-severe AD. There is also research reporting on the burden of skin cancers in elderly individuals over the three decades up to 2021, with predictions out to 2050. Also on the topic of skin cancers, the impact of lymphovascular invasion in cutaneous SCC for predicting major poor outcomes has been investigated. The final two papers in this issue report on the long-term safety of baricitinib for severe alopecia areata and B-VEC (beremagene geperpavec-svdt) for dystrophic epidermolysis bullosa.

We hope you find the selected research interesting. We are always happy to receive feedback and comments from our readers.

Kind Regards,

Associate Professor John Frew
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Ivarmacitinib for moderate to severe atopic dermatitis in adults and adolescents

Authors: Zhao Y et al.

Summary: Patients aged 12–75 years with moderate-to-severe AD were randomised to receive ivarmacitinib 4mg (n=113), ivarmacitinib 8mg (n=112) or placebo (n=111) once daily for 16 weeks in this phase 3 trial. Compared with placebo recipients, significantly greater proportions of ivarmacitinib 4mg and ivarmacitinib 8mg recipients had achieved an IGA score of 0 or 1 with a ≥2-grade improvement by week 16 (36.3% and 42.0%, respectively, vs. 9.0% [both p<0.001]) and EASI-75 responses by week 16 (54.0% and 66.1% vs. 21.6% [both p<0.001]). The incidences of treatment-emergent adverse events in the ivarmacitinib 4mg, ivarmacitinib 8mg and placebo arms were 69.0%, 66.1% and 64.9%, respectively, and the respective incidences of serious treatment-emergent adverse events were 2.7%, 1.8% and 2.7%.

Comment: JAK inhibitors have transformed the landscape of therapies in moderate-to-severe AD. Upadacitinib, baricitinib and abrocitinib are approved in many countries worldwide for AD, with topical JAK inhibitors including delgocitinib and ruxolitinib also approved for topical therapy. This phase 3 RCT provides new evidence regarding ivarmacitinib (another JAK1 inhibitor) for AD treatment. In comparison with other phase 3 studies, the cohort of patients in this RCT was relatively severe (baseline EASI score of 27–29) and included a significant proportion of patients from China, as opposed to the largely Caucasian populations in other RCTs. Safety outcomes were favourable, with no cases of thromboembolic events or major CV events. Three serious infections were identified – one in the placebo arm and two in the 4mg arm, with no serious infections in the 8mg arm. Otherwise, upper respiratory tract infection was reported as the most common adverse event, with creatine kinase level elevation in a dose-response relationship as expected. Efficacy demonstrated around 60% of individuals achieving EASI-75 with over 40% of individuals achieving clear or almost clear skin at week 16 (IGA 0/1). This provides additional data regarding the overall safety and efficacy of JAK1 inhibition in AD. This medication requires further long-term safety and efficacy data beyond the 16-week timepoint.

Reference: JAMA Dermatol 2025;161:688–97
Abstract

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Australian College of Rural and Remote Medicine (ACRRM) Professional Development Program (PDP) participants can claim Educational Activity hours in the self-directed learning category for reading Research Reviews. More info.

The Royal Australian College of General Practitioners (RACGP) members can **Quick Log** (self-record) a CPD activity such as reading a Research Review publication or watching a video under the CPD activity type 'Educational Activites'. More information is avaliable at RACGP - Your myCPDhome member resources

Neighborhood socioeconomic status and new hidradenitis suppurativa diagnoses in a single health system

Authors: Chang AY et al.

Summary: These researchers examined the relationship between neighbourhood-level socioeconomic status and new hidradenitis suppurativa diagnoses in 65,766 patients attending dermatology clinics at the University of California San Francisco, 485 of whom were newly diagnosed with hidradenitis suppurativa during the evaluation period. Compared with patients from the highest socioeconomic status quintile, those from quintiles 1–4 were at increased risk of a new hidradenitis suppurativa diagnosis (respective adjusted ORs 3.32 [95% CI 2.46–4.49], 2.25 [1.62–3.12], 1.97 [1.46–2.66] and 1.44 [1.06–1.96]; p<0.01 for linear trend). Race-stratified analyses revealed that new hidradenitis suppurativa diagnosis were increased for patients from lower socioeconomic status neighbourhoods, but statistical significance was not attained for all racial and ethnic groups.

Comment: Whilst multiple factors (genetic, behavioural, hormonal) have been identified as contributory to the pathogenesis of the disease, the socio-environmental impacts are still quite opaque. This novel and interesting study examined neighbourhood socioeconomic status as a covariate in the odds of a hidradenitis suppurativa diagnosis. The factors that may potentially underly neighbourhood factors contributing to hidradenitis suppurativa diagnosis could include healthcare accessibility, dietary options such as healthy food options, second-hand neighbourhood environmental impacts such as smoking and industrial neighbourhood locations and other poorly understood associated factors. This study was robust in that it examined the multiplicative impact of socioeconomic factors for each racial background, demonstrating consistent trends of increased risk with lower socioeconomic status. When looking at the confounding effect of other known factors, obesity had the greatest impact on socioeconomic status. Roughly 30% of the impact of socioeconomic status was mediated by obesity, and 4–8% was mediated by smoking status. This implies a complex and bidirectional interplay between socioeconomic status and obesity in the population examined in this study. The results indicate a three times increased odds in the risk of a hidradenitis suppurativa diagnosis in the lowest socioeconomic category compared with the highest reference quintile. This was after adjustment for age, sex and ethnicity. In terms of opportunities for interventions, this suggests for our lowest socioeconomic individuals, management of obesity may be a unique opportunity to reduce the risk of hidradenitis suppurativa diagnoses. Further replicated data in international cohorts would also be positive to promote such a preventative strategy.

Reference: JAMA Dermatol 2025;161:707–14
Abstract

Burden of skin cancer in older adults from 1990 to 2021 and modelled projection to 2050

Authors: Wang R et al.

Summary: This retrospective observational study used population-based registry data from the Global Burden of Diseases study (1990–2021) to assess the global burden of skin cancer among individuals aged ≥65 years. Worldwide, there were an estimated 153,993 melanoma, 1,463,424 SCC and 2,802,354 BCC cases for 2021. SCC had the highest age-standardised prevalence (236.91 per 100,000), rate of death (6.16 per 100,000) and DALYs (95.50 per 100,000). BCC had the highest incidence rate (371.97 per 100,000). Disease burden was higher in males than females. The global burden of skin cancer among older people had a generally upward trend, primarily determined by population growth. There was a disproportionately higher burden in countries with higher sociodemographic indices. It was predicted that by 2050, the incidence and prevalence rates of keratinocyte cancer will have increased, as will the BCC-related DALYs rate.

Comment: With an ageing population, the burden of skin cancer is growing in the global community. In Australia, we are well aware of the burden of cutaneous malignancy and the increasing demand on dermatologists and general practitioners regarding the increasing incidence of skin cancers. The Global Burden of Diseases study was conducted in 2021 and consists of comprehensive data from multiple global sources to analyse the global trends in disease incidence, mortality and morbidity. Overall, the data showed from a global perspective an increase in the incidence of cutaneous malignancies, most commonly BCC, followed by SCC and melanoma. The rates were highest in older populations, increasing with older age groups. The greatest burden as measured by DALYs was found to be from SCC. The Australasian region had the highest incidence of melanoma, but with a decreasing trend in the mortality from melanoma. Regarding keratinocyte cancers, north America had the greatest burden of disease, but with BCCs, east Asian countries demonstrated a dramatic increase in the incidence of BCCs in older age groups. Future projections from the data suggested that while a dramatic increase in the incidence of BCCs would occur, particularly in south east Asian populations, the overall burden of melanoma and SCC should decrease. Whilst these projections should be interpreted with caution, this study does provide some interesting insights into populations who may see an increase in age-related cutaneous malignancies over the next 25 years, and hopefully inform policy regarding future population medical needs.

Reference: JAMA Dermatol 2025;161:715–22
Abstract

The association between hidradenitis suppurativa and psychiatric disease

Authors: Folkmann CL et al.

Summary: These researchers undertook a narrative analysis of 83 studies, with quantitative analysis conducted on 76, reporting on psychiatric diseases in patients with hidradenitis suppurativa; half the studies were assessed to be of high quality. It was found that compared with the general population, patients with hidradenitis suppurativa were at increased risk of depression (OR 2.06 [95% CI 1.75–2.41]), anxiety (1.91 [1.64–2.22]), bipolar disorder (3.68 [1.11–12.20]), schizophrenia (2.00 [1.21–3.30]), substance use disorder (3.58 [2.01–6.37]), alcohol abuse (1.88 [0.98–3.58]) and completed suicide (1.56 [1.14–2.14]); the risks were greater in females, and also in participants from studies from North America compared with European studies. The risk of depression was greater for adults with hidradenitis suppurativa than children.

Comment: Hidradenitis suppurativa is a debilitating chronic disease with a clear psychosocial impact. Rates of anxiety and depression are significantly elevated compared with healthy controls. The reasons underlying these significantly elevated rates of psychiatric disease are complex, but can be partially attributable to the severity and long-term nature of the disease, the lack of highly effective therapies, and issues surrounding timely diagnosis and access to appropriate care. This systematic review and meta-analysis highlights the significantly elevated risk of various psychiatric disorders associated with hidradenitis suppurativa, including anxiety, depression, bipolar disorder, schizophrenia, substance use disorder and completed suicide. Interestingly, North American studies had higher rates of psychiatric comorbidities than European studies, suggesting a role of the healthcare system, affordability and accessibility of care as important factors in psychiatric comorbidities in the disease. These data are a call to action for the identification and development of more effective therapies for hidradenitis suppurativa, as well as the need for more timely and effective therapies in moderate disease prior to the progression to severe disease. Additionally, dermatologists being aware of the psychiatric risks to patients allows for early referral to appropriate psychological services as part of the overall management of hidradenitis suppurativa patients.

Reference: Br J Dermatol 2025;193:212–20
Abstract

Understanding eyebrow and eyelash involvement in patients with alopecia areata and responsiveness to treatment with baricitinib

Authors: Mostaghimi A et al.

Summary: Results were reported for the BRAVE-AA1 and BRAVE-AA2 trials, in which patients with alopecia areata were randomised to baricitinib 2mg, baricitinib 4mg or placebo. Compared with placebo recipients, baricitinib 2mg recipients and baricitinib 4mg recipients had greater eyebrow response rates (28.2% and 44.3%, respectively, vs. 12.6%) and greater eyelash response rates (25.1% and 46.4% vs. 12.4%) at week 36, with ~80% of baricitinib 4mg recipients who achieved hair regrowth at one site also achieving regrowth at the other. Among baricitinib 4mg recipients with a scalp response at week 52, 78.5% and 82.6% achieved eyebrow and eyelash responses, respectively, and 71.1% achieved both eyebrow and eyelash responses; the corresponding values for scalp nonresponders were 46.7%, 48.7% and 35.4%, and baricitinib 2mg recipients showed similar trends but with lower response rates.

Comment: The emergence of JAK inhibitors has been a gamechanger in the therapeutic landscape of alopecia areata, but as in other inflammatory disorders, often specific high-impact areas can have a disproportionate psychosocial impact upon individuals, despite the relatively low surface area of involved disease. For alopecia, patients often report the significant impact of loss of eyelashes and eyebrows, which are much more difficult to conceal cosmetically, and often result in significant social impact to the patient. This study performed a subanalysis of the phase 3 clinical trials of baricitinib in alopecia areata examining the correlation of eyebrow and eyelash loss with scalp alopecia and the response to therapy. Overall, compete loss of scalp and eyelashes was associated with a larger degree of scalp loss, and eyebrow and eyelash regrowth was often seen at earlier timepoints than overall scalp regrowth. Although there was good concordance of eyebrow and eyelash growth with scalp regrowth, a small proportion of patients achieved eyebrow and eyelash growth without similar degrees of scalp regrowth. The response of eyebrows and eyelashes tended to cluster together; no evidence of isolated eyebrow (without eyelash or *vice versa*) regrowth was seen in this re-analysis. Overall, this suggests that the status of eyebrow and eyelashes in individuals with alopecia areata can be seen as a surrogate read out of disease severity, and to response to systemic treatment with JAK inhibitors.

Reference: Br J Dermatol 2025;193:240–9
Abstract

Lymphovascular invasion is an independent predictor of metastasis and disease-specific death in cutaneous squamous cell carcinoma

Authors: Hirotsu KE et al.

Summary: This retrospective study examined if lymphovascular invasion could predict major poor outcomes in 23,166 cutaneous SCCs, 0.8% of which had lymphovascular invasion. Compared with SCCs without lymphovascular invasion, those with lymphovascular invasion were associated with a higher 3-year cumulative incidence of major poor outcomes (33.5% vs. 3.2%; adjusted subdistribution hazard ratio 1.82 [p=0.002]), particularly low-stage Brigham and Women's Hospital tumours (20.7% vs. 1.61% [p<0.001]).

Comment: It is well established that perineural invasion in SCC is a strong predictor of metastases and disease recurrence. However, only recently has lymphovascular invasion been included in the AJCC8. It has been long noted as a high-risk feature, and known to be associated with metastasis risk in solid-organ malignancies, but specific evidence in cutaneous SCC is limited. This multicentre retrospective study identified over 21,000 cutaneous SCCs with 179 demonstrating lymphovascular invasion. Analysis via time-to-event analysis demonstrated significant less time to occurrence of nodal metastases, distant metastases and disease specific mortality compared with those without lymphovascular invasion. Interestingly, there was not necessarily a high degree of correlation with perineural invasion, and lymphovascular invasion was observed in a significant proportion of moderately differentiated SCC as well as poorly differentiated lesions. Overall, this suggests that consideration of lymphovascular invasion may be important to consider in synoptic reports of high-risk SCC, in order to direct monitoring and other investigations to prevent recurrence and metastases.

Reference: J Am Acad Dermatol 2025;93:368–77
Abstract

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The efficacy and safety of minocycline, metronidazole, ivermectin, and azelaic acid in moderate-to-severe papulopustular rosacea

Authors: Shaheen EA et al.

Summary: This was a systematic review with network meta-analysis of data from 19 RCTs assessing topical agents for moderate-to-severe papulopustular rosacea in a total of 8208 participants. For improvement in IGA score, the greatest effect size was seen with 20% azelaic acid (OR 8.54 [95% CI 2.48–29.45]), whereas effect sizes were comparable for 15% azelaic acid, 0.75% metronidazole and 1% ivermectin. The risk of adverse events was increased for 15% azelaic acid (OR 1.95 [95% CI 1.30–2.93]), with the risks not increased significantly for the other topical agents.

Comment: The evidence base for effective treatment of rosacea remains inconclusive. The relative heterogeneity of the condition means that often multiple agents or various combinations are often tried to achieve the best clinical results in various patients with rosacea. This network meta-analysis examined a number of RCTs examining the impact on IGAs. Overall, azelaic acid 20% was identified as the most effective intervention, but also had the greatest rates of cutaneous adverse events with regards to irritation. The difficulty with conducting an accurate network meta-analysis in rosacea is that the populations are quite heterogeneous, and an underlying assumption of network meta-analysis is the equivalency of the populations examined. Additionally, IGA can be prone to unidentified bias, but newer outcome measures are not backwards compatible with previously conducted studies. Certainly the limitation of this study to papulopustular rosacea means that other complications such as rhinophyma are not considered in this analysis. Overall, the safety and efficacy of azelaic acid was supported in this analysis; however, the development and integration of more novel outcome measures would support a more robust analysis of clinical outcomes in rosacea.

Reference: JAAD Int 2025;20:23–30
Abstract

Independent commentary by Associate Professor John Frew

Associate Professor John Frew is a fellow of the Australasian College of Dermatologists and researcher in the field of inflammatory skin diseases with a focus on hidradenitis suppurativa. He holds a staff specialist position at Liverpool Hospital and is a conjoint lecturer at the University of New South Wales supervising dermatology trainees and postgraduate research students. He completed his post-doctoral fellowship at the Rockefeller University in New York City identifying immunological pathways and novel therapies for the treatment of hidradenitis suppurativa. He has over 100 peer-reviewed publications and contributions to international dermatology and immunology textbooks in the field of inflammatory skin disease.

Rapid itch improvement and skin clearance with upadacitinib versus placebo (Measure Up 1 and Measure Up 2) and versus dupilumab (Heads Up)

Authors: Simpson EL et al.

Summary: Patients with moderate-to-severe AD received oral upadacitinib 15mg, upadacitinib 30mg or placebo once daily for 16 weeks in the phase 3 Measure Up 1 and Measure Up 2 trials, or oral upadacitinib 30mg once daily or subcutaneous dupilumab 300mg every 2 weeks after a 600mg loading dose for 24 weeks in the phase 3 Heads Up trial; this analysis focussed on rapid improvements in itch assessed by WP-NRS (Worst Pruritus Numerical Rating Scale) scores. Upadacitinib was associated with significantly greater proportions of participants achieving WP-NRS scores of 0 or ≤1 compared with both placebo at week 16 and dupilumab at week 24 ($p<0.001$), with significant differences emerging by days 8 and 2 for achieving scores of 0 and ≤1, respectively. Similar patterns were seen for improvements in EASI-90 and EASI-100 scores, combined EASI-90 plus WP-NRS scores of ≤1, and combined EASI-100 plus WP-NRS scores of 0 with upadacitinib versus placebo and dupilumab.

Comment: With the variety and availability of highly effective advanced therapies for AD, focus has now shifted to specific burdensome patient outcomes and the comparative efficacy of different agents in achieving reduction in symptoms such as severe itch. Both dupilumab and upadacitinib are highly effective at reducing itch; however, the proportion of deep levels of response can differ between agents. This *post hoc* analysis of the Measure Up 1 and 2 studies, comparing upadacitinib with dupilumab and placebo, were queried to assess the degree of complete itch clearance and the relationship between complete clearance of itch and other standard metrics, including EASI-75 and EASI-90 outcomes. The overall finding was that a very rapid reduction in itch occurred as early as the second day of therapy. A greater proportion of patients treated with upadacitinib reported complete resolution of itch compared with those on dupilumab or placebo. The main limitation was the lack of longer term data beyond the 52-week timepoint, which is needed to assess the ongoing maintenance of itch reduction in the real-world setting.

Reference: Dermatol Ther 2025;15:2061–76
Abstract

Safety of baricitinib in adults with severe alopecia areata from two phase III trials over a median of 2.3 years and up to 4 years of treatment

Authors: King B et al.

Summary: Pooled safety data, including from long-term and bridging extension periods, were reported for 1303 participants with severe alopecia areata who received baricitinib for a median 825 days in the phase 2–3 BRAVE-AA1 and phase 3 BRAVE-AA2 trials. Most of the treatment-emergent adverse events reported in these trials were of mild or moderate severity. The incidence rates of serious adverse events and associated treatment discontinuations were 2.6 and 1.7 per 100 patient-years, respectively; these were considered to be generally low and similar to data from ≥104 weeks of follow-up. There were no new serious infections, opportunistic infections, major adverse CV events, deep vein thromboses or pulmonary emboli seen during an additional year of follow-up. The respective incidence rates of nonmelanoma skin cancer and other malignancies were 0.1 and 0.2 per 100 patient-years, and they remained stable over time. The incidence rate of herpes zoster was 1.9 per 100 patient-years, an incidence comparable with that of previous reports. Consistency was seen over time for laboratory changes, and there were no deaths reported.

Comment: Many dermatologists have concerns regarding the long-term use of JAK inhibitors, particularly in younger populations for AD and alopecia areata. Whilst some safety signals regarding infection and malignancy risk exist in the rheumatology literature, the side effects cannot be directly translated to a completely different disease state due to the fact that some side effects are a product of the disease rather than the therapy. These 4-year safety data from the phase 3 clinical studies of baricitinib in alopecia areata demonstrated no reports of mortality, and no reports of malignancy between the previously reported 2-year data and the presented 4-year data. No reports of deep vein thrombosis or tuberculosis have been reported, with only one major CV event in an individual aged over 50 years across the 4 years of safety data. Whilst hyperlipidaemia and creatine kinase level elevation were seen, there were no new safety concerns suggesting novel safety signals out to 4 years with the use of baricitinib in alopecia areata, highlighting reassuring data of ongoing efficacy and reasonable safety profiles for longer term use.

Reference: Am J Clin Dermatol 2025;26:611–22
Abstract

Long-term safety and tolerability of beremagene geperpavec-svdt (B-VEC) in an open-label extension study of patients with dystrophic epidermolysis bullosa

Authors: Marinkovich MP et al.

Summary: Results were reported for an open-label extension of a phase 3 study of B-VEC for dystrophic epidermolysis bullosa, in which significant improvements in wound healing at 3 and 6 months relative to placebo had been previously reported; there were 24 participants who had rolled over from phase 3 and 23 who were treatment-naïve who received B-VEC weekly for a median of 81 weeks. Adverse events were reported in 74.5% of participants, with most being mild or moderate in severity. None of the 17 serious adverse events or 14 severe adverse events were considered to be treatment-related, and no adverse events led to discontinuation of treatment or the study. The participants reported high levels of treatment satisfaction, although results concerning quality of life were inconclusive. Among the participants who rolled over into the extension phase, high closure rates were maintained during the extension phase for wounds that had responded during phase 3.

Comment: B-VEC is an exciting development as a topical gene therapy for dystrophic epidermolysis bullosa. Using an HSV1 viral vector, corrected *COL7A1* genes are delivered topically to target wounds, with significant improvements in wound healing compared with placebo. Concerns with topical gene therapy in epidermolysis bullosa include the possibility of decreased efficacy, or the development of antibodies against the new collagen VII, leading to epidermolysis bullosa acquisita-like symptoms on top of the existing genodermatosis. Overall, this long-term extension study shows that the safety and efficacy of B-VEC is highly reassuring, with consistent maintenance of 100% closed wounds, and significant improvements in the surface area of wounds that did not achieve 100% closure. Although dystrophic epidermolysis bullosa is relatively rare, the patient impact is extremely high, with novel therapies such as B-VEC lowering the burden on patients, caregivers and the health system overall. The promise of topical gene therapy may eventually translate to other monogenic cutaneous disorders, placing this treatment as an area to watch in future dermatology research.

Reference: Am J Clin Dermatol 2025;26:623–35
Abstract