Dermatology Research Review™

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Abbreviations used in this issue:

B/SCC = basal/squamous cell carcinoma; **CV** = cardiovascular; **IL** = interleukin; **PASI** = Psoriasis Area and Severity Index; **RCT** = randomised controlled trial.

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Welcome to issue 35 of Dermatology Research Review.

This month we begin with a phase 2 trial from a recent issue of N Engl J Med reporting that selective IL-23 blockade with risankizumab provides better clinical responses than ustekinumab for the treatment of moderate-to-severe plaque psoriasis. This is only one of four papers focusing on psoriasis included this month. The others include a meta-analysis of the risk of major adverse CV events associated with the use of biological agents, the increased risk of avascular necrosis, and an analysis of data from the UNCOVER-1 and UNCOVER-2 trials comparing outcomes for patients treated with ixekizumab who continued treatment with those who withdrew then restarted treatment.

I hope you enjoy these and the other dermatology research papers included in this issue. I look forward to receiving your feedback and comments.

Kind Regards,

Dr Warren Weightman

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Risankizumab versus ustekinumab for moderate-to-severe plaque psoriasis

Authors: Papp KA et al.

Summary: Patients with moderate-to-severe plaque psoriasis were randomised to receive SC risankizumab 18mg at week 0 (n=43) or 90mg (n=41) or 180mg (n=42) at weeks 0, 4 and 16, or to receive ustekinumab 45mg or 90mg according to bodyweight (n=40) at weeks 0, 4 and 16. Compared with ustekinumab, risankizumab at 90mg or 180mg (pooled) was associated with a greater proportion of participants with a ≥90% reduction in PASI score at week 12 (primary endpoint; 77% vs. 40% [p<0.001]) and a greater proportion with a 100% reduction in PASI score (45% vs. 18%), with efficacy maintained out to 20 weeks after the final risankizumab dose. The respective serious adverse event rates in the risankizumab 18mg, 90mg and 180mg and ustekinumab arms were 12%, 15%, 0% and 8%; these included two BCCs and one major CV adverse event.

Comment: Risankizumab is the third IL-23 inhibitor in development, with the other two, guselkumab and tildrakizumab, at phase 3 trial stage. All of these biologicals target the p19 subunit, which is only found in IL-23, whereas ustekinumab targets the p40 subunit, which is found in both IL-12 and IL-23. Previous studies have shown that inhibition of IL-23 is the primary reason for the effectiveness of ustekinumab. Studies with the p19 IL-23 inhibitors have all shown superior results to ustekinumab, but there has not been a direct head-to-head comparison before this study. This study shows a significant benefit of risankizumab over ustekinumab, but was only a phase 2, dose-finding study with small numbers and treatment for 16 weeks, so larger numbers and longer trials to 52 or 60 weeks will be needed. All of the p19 IL-23 inhibitors are highly effective treatments for psoriasis, and comparison with the IL-17 inhibitors will be useful as their efficacy is similar. If a 3-monthly dosing regimen is decided on as suggested by this early trial, then flaring before the next dose, as occurs with ustekinumab, could be a problem.

Reference: N Engl J Med 2017;376(16):1551–60

Abstract

Association between programmed death ligand 1 expression in patients with basal cell carcinomas and the number of treatment modalities

Authors: Chang J et al.

Summary: This cross-sectional study investigated PD-L1 (programmed death ligand-1) expression in 62 patients with 60 treatment-naive and 78 treated BCCs. PD-L1 expression in tumour cells was detected in 89.9% of BCCs, and PD-L1 expression in tumour-infiltrating lymphocytes was detected in 94.9% (>5% positive immunohistochemical staining in the respective cell populations). Compared with treatment-naive BCCs, treated BCCs had significantly greater PD-L1 immunohistochemical staining intensity in tumour cells (32% vs. 7% [p=0.003]) and tumour-infiltrating lymphocytes (47% vs. 18% [p=0.008]) after adjustment for age at diagnosis. There was a significant positive relationship between PD-L1 staining intensity in tumour cells and number of distinct prior treatment modalities after adjustments for age, sex and BCC location.

Comment: PD-L1 expression in tumour cells is an indicator that they may be responsive to immunotherapy such as pembrolizumab. In cancers such as lung cancer that respond to the programmed death inhibitors, the threshold for treatment is 5% positives, but in BCC the level of PD-L1 expression was significantly higher at 50%. This indicates that BCCs may respond very well to this type of treatment. Currently, a phase 2 trial is recruiting patients with metastatic or unresectable BCCs for randomisation into two groups of pembrolizumab with or without vismodegib. The intensity of PD-L1 expression is increased with the number of prior treatments, which is a form of immune priming that increases the host antitumour immune response by uncovering tumour antigens. This could increase further the responsiveness of these tumours to immunotherapy. The other benefit of immunotherapy is the potential of a long-lasting response. Further trials will need to be done.

Reference: JAMA Dermatol 2017;153(4):285–90
Abstract

Association of oncogenic mutations in patients with advanced cutaneous squamous cell carcinomas treated with cetuximab

Authors: Picard A et al.

Summary: These researchers identified somatic *HRAS*, *KRAS*, *NRAS*, *BRAF* and *EGFR* mutations in 31 patients with advanced cutaneous SCC treated with cetuximab, and reported efficacy and tolerance of cetuximab according to such mutations. *RAS* mutations were identified in only two of the participants' samples, namely an *NRAS* and an *HRAS* point mutation; no *KRAS*, *BRAF* or *EGFR* mutations were detected. One of the patients with an *RAS* mutation had a partial response to cetuximab and the other had a complete response. During mean follow-up of 19 months, the disease control rate at 6 weeks was 67.8%, the median overall survival duration was 13 months and the median progression-free survival duration was 9 months. Cetuximab was continued without dose reduction in all patients.

Comment: There have been several case reports of EGFR (epidermal growth factor receptor) inhibitors used to treat cutaneous SCCs, and there are now ongoing trials of cetuximab, erlotinib and panitumumab for treating advanced cutaneous SCCs. A recent meta-analysis showed significantly higher response rates and disease-free survival using cetuximab compared with cisplatin, which is the current standard of care treatment for advanced cutaneous SCC. Somatic mutations of the *HRAS*, *KRAS*, *NRAS*, *BRAF* and *EGFR* genes in advanced cutaneous SCC may indicate responsiveness to EGFR inhibitors, but this trial showed that even though these mutations were low in cutaneous SCCs, there was still a good response to cetuximab. Although the response to cetuximab was not related to the mutations tested, the future of chemotherapy will be to identify mutations to individualise treatments.

Reference: JAMA Dermatol 2017;153(4):291–8
Abstract

Impact of biologic therapies on risk of major adverse cardiovascular events in patients with psoriasis

Authors: Rungapiromnan W et al.

Summary: This was a systematic review and meta-analysis of 38 RCTs (n=18,024) reporting adverse events in adults with plaque psoriasis who had received ≥1 dose of a biological agent, conventional systematic therapy or placebo. Nine of the RCTs reported major adverse CV events affecting ten participants, with the remaining RCTs reporting none. The risk of major adverse CV events was not significantly increased with use of biological therapies overall (odds ratio 1.45 [95% CI 0.34–6.24]), tumour necrosis factor-α inhibitors (0.67 [0.10–4.63]), anti-IL-17A agents (1.00 [0.09–11.09]) or ustekinumab (4.48 [0.24–84.77]); there was no heterogeneity evident in these comparisons.

Comment: The findings that there is no increased risk of major adverse CV events with the current biological treatments is welcome, but the evidence is still limited and more data are needed. The trials were mostly over a 12-month period and this may be too short a timeframe to detect a significant increase in major adverse CV events. The majority of the included studies were phase 3 trials, which tend to enrol patients with fewer comorbidities than those seen in routine clinical practice, and also exclude elderly patients, who are at increased risk of major adverse CV events. Thus, the background risk for trial patients is likely to be lower, which may limit the generalisability of the findings. Long-term data from registries will be important to assess whether there is an increased risk of major adverse CV events.

Reference: Br J Dermatol 2017;176(4):890–901
Abstract

A clinical, histologic, and follow-up study of genital melanosis in men and women

Authors: Haugh AM et al.

Summary: Retrospective clinical and histological data from 41 patients with genital melanosis were analysed to describe these lesions and the risk they confer for genital and nongenital melanoma. The authors found that genital melanosis can clinically mimic melanoma, but it usually develops at a younger age than typically seen for genital melanoma. Most of the lesions stabilised or regressed over time. Melanoma history was present for five of the patients, but with only one having had genital melanoma. Compared with patients without a history of melanoma, those with such a history were significantly more likely to exhibit melanocytes with suprabasal movement and have a higher melanocyte count.

Comment: Genital melanosis is a rare condition but can have a worrying appearance. Histological diagnosis is needed and multiple biopsies may be needed to exclude melanoma. If there is no evidence for melanoma, then observation can be done, but there is an increased risk of melanoma elsewhere and whole-body examinations should be done regularly. Extensive surgery is not recommended on patients with genital melanosis who have benign histology.

Reference: J Am Acad Dermatol 2017;76(5):836–40
Abstract

Increased risk of avascular necrosis in patients with psoriatic disease

Authors: Chiu H-Y et al.

Summary: The relationship between psoriasis and avascular necrosis was explored using Taiwanese health insurance data for a cohort of 28,268 patients with psoriasis and 113,072 matched controls without psoriasis. Compared with controls, patients with psoriasis were at significantly greater risk of developing avascular necrosis (adjusted hazard ratio 1.96 [95% CI 1.62–2.38]). The risk of avascular necrosis increased as psoriasis severity increased and was greater when arthritis was also present. Males were also at higher risk of developing avascular necrosis than females, as were patients aged <30 versus ≥30 years.

Comment: Several studies have shown that proinflammatory cytokines might be involved in the pathogenic mechanisms of avascular necrosis, and avascular necrosis is increased in a number of autoimmune diseases. The risk of avascular necrosis was higher in patients with more severe psoriasis, which suggest that inflammation has a role in the development of avascular necrosis. In other studies, arthritis is an independent risk factor for avascular necrosis (i.e. when associated with systemic lupus erythematosus), and in this trial the risk of avascular necrosis was higher in those who also had psoriatic arthritis. This is likely to be due to the additional increase in inflammation. Males less than 30 years of age were most at risk. The role of topical steroids as a risk factor could not be determined, although oral steroids were a risk factor. It would be prudent to limit topical steroids in psoriatic patients, especially for widespread disease and patients at higher risk.

Reference: J Am Acad Dermatol 2017;76(5):903–10
Abstract

Silk textile with antimicrobial AEM5772/5 (Dermasilk): a pilot study with positive influence on acne vulgaris on the back

Authors: Schaunig C & Kopera D

Summary: This research enrolled 14 patients with acne vulgaris papulopustulosa on their back to wear t-shirts made with 'Dermasilk' (a polymerisate of fibroin and an antimicrobial) every night for 6 weeks; no concomitant treatments or changes in lifestyle or living conditions were permitted. At 6 weeks, clinically significant reductions in acne lesions on the participants' backs were evident on photographs.

Comment: This is an interesting study as the only intervention was wearing the Dermasilk t-shirts overnight for 6 weeks. Seventy percent of patients showed a statistically significant improvement, but four patients were lost to follow-up, so only seven of the original 14 or 50% would have improved if an intent-to-treat analysis had been done. The presumed mechanism may be due to the antimicrobial in the Dermasilk. It is worthwhile knowing if the antibacterial is removed with regular washing and if so, does it lose its benefit. With small numbers, high dropout and no controls in this trial, Dermasilk cannot be recommended at this time for the treatment of acne.

Reference: Int J Dermatol 2017;56(5):589–91
Abstract

Bacterial biofilm in chronic lesions of hidradenitis suppurativa

Authors: Ring HC et al.

Summary: These researchers set out to determine and quantify the potential presence of bacterial aggregates in the biopsied lesional and perilesional skin of 42 consecutive patients with chronic hidradenitis suppurativa. Two-thirds of chronic lesion samples and three-quarters of perilesional samples were found to contain biofilms. Compared with perilesional skin, lesional skin exhibited a greater mean diameter of aggregates, with aggregates >50µm in diameter found in a greater proportion of lesional samples versus perilesional samples (42% vs. 5% [p=0.009]). Most of these large biofilms (63%) were located in sinus tracts, of which 75% contained active bacterial cells, which were associated with inflammation; 37% of large biofilms were situated in the infundibulum.

Comment: The pathogenesis of hidradenitis suppurativa is still not clear, with evidence for both inflammatory and infective causes. This study showed a high incidence of biofilms, especially in sinus tracts and the infundibulum. Previous studies have shown a lower incidence of around 20%, but this may reflect different definitions and increased sensitivity of techniques. Biofilms in many diseases show little response to antibiotic treatment, and this may explain the poor response in hidradenitis suppurativa. Surgical treatments such as excision or deroofing may be the best way to clear the biofilms. Deroofing is a relatively simple procedure that can be performed by dermatologists with an acceptable cosmetic result.

Reference: Br J Dermatol 2017;176(4):993–1000
Abstract

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Selection of papers and comments are provided by Dr Warren Weightman, who has practiced Dermatology for over 25 years and is currently Head of the Department of Dermatology at the Queen Elizabeth Hospital, Adelaide and a Senior Lecturer with Adelaide University. He has been Chief Censor and President of the Australasian College of Dermatologists. Dr. Weightman has been involved in clinical research and has a particular interest in treatment of actinic keratoses and superficial basal cell cancers with topical therapies including methyl aminolevulinate and photodynamic therapy, imiquimod, and ingenol mebutate. His other interests include the management of non-melanoma skin cancer in transplant patients, the use of biologics in psoriasis and other skin disorders, and the role of oral retinoids.

Continuous dosing versus interrupted therapy with ixekizumab

Authors: Blauvelt A et al.

Summary: This was an integrated analysis of the phase 3 UNCOVER-1 and UNCOVER-2 trials conducted in patients with psoriasis. The participants had been randomised to receive 12 weeks of treatment with ixekizumab every 2 or 4 weeks or placebo. This analysis focussed on outcomes for participants with a static PGA (Physician's Global Assessment) score of 0 or 1 at week 12 who were rerandomised to maintenance ixekizumab every 4 weeks (n=416) or every 12 weeks (not included) or placebo (n=402); 333 participants withdrawn from active treatment were retreated with ixekizumab every 4 weeks for 24 weeks in the event of disease relapse, which occurred in a median of ~20 weeks. Week 60 results showed that 90% of participants continuously treated with ixekizumab every 2 or 4 weeks had achieved PASI-75 and 81.9% had a static PGA score of 0 or 1. Among participants retreated every 4 weeks for disease relapse, PASI-75 was achieved by 87.0% and 95.1% of those from the every 2-week and every 4-week initial arms, respectively, and static PGA scores of 0 or 1 were achieved by 70.7% and 82.3%, respectively. Adverse events were comparable between continuously treated and retreated participants.

Comment: This study confirms that in most patients ixekizumab needs to be continued to maintain a benefit, and this applies to the other biologicals too. The median time to relapse was about 5 months, so if ixekizumab needs to be stopped for surgery or a severe infection and can be restarted after 2–3 months, there may not be much worsening. If a relapse occurs the median time to recapture PASI-75 was 4 weeks, which occurred in 69%, but after a second treatment interruption with subsequent retreatment, only 42.4% achieved PASI-75, indicating that the less treatment cessations the better. In the secukinumab trials when treatment was ceased and restarted after relapse, 95% of patients achieved PASI-75, but in these trials a loading dose was given, and this may be worthwhile doing for ixekizumab with any prolonged treatment cessation.

Reference: J Eur Acad Dermatol Venereol; Published online March 31, 2017
Abstract

Clinical markers of vitiligo activity

Authors: Benzekri L & Gauthier Y

Summary: These authors developed a rapid, accurate, noninvasive assessment of vitiligo state. Using daylight and Wood's light examinations, they identified two common clinical types of vitiligo: i) amelanotic with sharply demarcated borders; and ii) hypomelanotic with poorly defined borders. They obtained photographs and performed skin biopsies at the edge of vitiligo lesions at the time of initial examination, and 1 year later they classified vitiligo as stable (no new lesions) or active (increased lesion number and/or size). Skin biopsies from 71 patients were stained and immunostained for melanocytes, $CD8^+$ T-cells and E-cadherin. Active lesions were significantly associated with a hypomelanotic appearance with poorly defined borders, and histologically with $CD8^+$ T-cell infiltration in the epidermis and dermis, with strong E-cadherin expression.

Comment: Vitiligo activity is difficult to determine clinically, and this study helps dermatologists to assess clinically whether vitiligo is active or stable. Histology is the gold standard for assessment of activity, but is not usually performed, and confocal microscopy is also an effective method, but is not routinely available. History is useful and there are scoring systems such as the VIDA (Vitiligo Disease Activity) score, but these rely on patient recall and may be variable and misleading. Although not mentioned in the article, amelanotic vitiligo with sharp borders represents end-stage disease, with histology showing that the T-cells are not adjacent to the melanocytes. It would be useful to design studies to see which type of vitiligo responds better to treatment. It is likely that the active hypomelanotic type would have the better response.

Reference: J Am Acad Dermatol 2017;76(5):856–62
Abstract

