Dermatology Research Review™

Making Education Easy

Issue 31 - 2017

In this issue:

Abbreviations used in this issue:

AD = atopic dermatitis; **HPV** = human papilloma virus; **IGA** = Investigator's Global Assessment; **SC** = subcutaneous; **SCC** = squamous cell carcinoma; **UVA/B** = ultraviolet A/B

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Welcome to issue 31 of Dermatology Research Review.

Highlights for this issue include the encouraging findings from two phase 3 trials (published as a single paper in New Engl J Med) of dupilumab, a monoclonal antibody, in the treatment of moderate-to-severe AD (atopic dermatitis), and also for the Janus kinase inhibitor tofacitinib for treating severe alopecia areata. Authors from Denmark have reported increased 10-year mortality in patients who had been hospitalised for AD (but not as much as those hospitalised for psoriasis), likely because of more cardiovascular comorbidities often present in patients with severe AD. This issue concludes with a paper reporting some success with 308nm excimer light therapy in a small series of patients with treatment-resistant alopecia universalis.

Please keep your feedback and suggestions coming as we begin another year of bringing you the latest in dermatology research.

Kind Regards,

Dr Warren Weightman

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Two phase 3 trials of dupilumab versus placebo in atopic dermatitis

Authors: Simpson EL et al., for the SOLO 1 and SOLO 2 Investigators

Summary: This report of two identical randomised clinical trials (SOLO 1 and SOLO 2) investigated the efficacy of dupilumab in adults with moderate-to-severe AD whose disease was inadequately controlled by topical treatment. The studies' participants were randomised 1:1:1 to receive SC dupilumab 300mg or placebo weekly or the same dose of dupilumab every 2 weeks alternating with placebo. The primary outcome was the proportion of participants who had both a score of 0 or 1 (clear or almost clear) on the IGA (Investigator's Global Assessment) and a reduction of ≥2 points in IGA score from baseline at week 16. In SOLO 1 (n=671), the primary outcome occurred in 38% of patients who received dupilumab every other week and 37% of those who received dupilumab weekly, compared with 10% of those who received placebo (p<0.001 for both). The results were similar among the 708 participants enrolled in SOLO 2 (36% and 36%, respectively, vs. 8% [p<0.001]). Dupilumab also improved pruritus, symptoms of anxiety or depression and quality of life.

Comment: These are further phase 3 trials showing the effectiveness of dupilumab in AD. Approximately one-third of patients in both trials were clear or almost clear or had a reduction of 2 points from baseline at week 16, which is significant and encouraging, but not as good as the current biological treatments for severe psoriasis. Although the AD in the trial patients was moderate-to-severe, the criterion for inclusion was being uncontrolled on topical treatment, so they may not reflect the most severe patients who require oral treatment and are the ones who are most difficult to control. The effectiveness of dupilumab in these patients remains to be seen, but when available it will still be a welcome addition to the current treatments.

Reference: N Engl J Med 2016;375(24):2335–48

Abstract

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Reexamining the threshold for reexcision of histologically transected dysplastic nevi

Authors: Fleming NH et al.

Summary: The long-term risk of associated melanoma was retrospectively investigated in biopsied mild or moderate dysplastic nevi with clinically observed positive versus negative histological margins from 498 patients. There were 170 evaluable re-excised positive-margin dysplastic nevi and 304 that were clinically observed without further surgery. Mean follow-up was 5.5 years. Compared with re-excised nevi, those that were observed were more likely to recur (3.3% vs. 0% [p=0.02]) and develop to melanoma (2.0% vs. 0.06%). There was only one case of thin invasive melanoma (≤1mm), and there were no melanoma-related deaths from biopsy-proven dysplastic nevi during follow-up. New primary melanomas developed at other sites in 9.9% and 9.4% of excised and resected dysplastic nevi, respectively.

Comment: When an excisional biopsy is done with the intent to remove the whole lesion and there is no residual clinically apparent lesion, it is reasonable to observe these patients if the pathology shows mild or moderate dysplasia. If however a partial biopsy is done, a complete re-excision should always be done as there were six melanomas in this group, although five of these were melanoma *in situ*. There is always a risk of sampling error if a partial biopsy is done. If a re-excision cannot be done, then regular follow-up is essential. A multicentre study of up to 3000 retrospectively collected histological dysplastic nevi is currently being done to identify the risk of malignant transformation in excisional biopsied lesions with positive histological margins to give further advice on this topic.

Reference: JAMA Dermatol 2016;152(12):1327–34
Abstract

Nonmelanoma skin cancer in nonwhite organ transplant recipients

Authors: Pritchett EN et al.

Summary: This retrospective medical record review of 259 nonwhite organ transplant recipients identified 19 skin cancers affecting six black patients, five Asian patients and four Hispanic patients. All SCCs among black patients were diagnosed in the *in situ* stage, were located on sun-protected sites and occurred in individuals with HPV-positive lesions and/or who had a history of condyloma acuminata or verruca vulgaris. Among the Asian patients, most skin cancers were located on sun-exposed areas and occurred in individuals who had emigrated from equatorial regions.

Comment: This study confirms that all transplant patients are at increased risk of skin cancer no matter the skin type. Of particular relevance is that in black patients, all nine skin cancers were in sun-protected sites, with six in the genital and groin area and one on the fingertip. This shows that a full skin examination, including the groin, genital and perianal area, is essential in all transplant patients but especially those with a dark skin colour. A history of warts, both common and genital, was common and also needs to be looked for in all transplant patients, as HPV is a risk factor for malignant transformation.

Reference: JAMA Dermatol 2016;152(12):1348–53
Abstract

Association between β-genus human papillomavirus and cutaneous squamous cell carcinoma in immunocompetent individuals

Authors: Chahoud J et al.

Summary: This was a meta-analysis of 14 case-control and cohort studies that included 3112 immunocompetent adults with cutaneous SCC and 6020 controls and reported data on the relationship between β-genus HPV and cutaneous SCC. The overall association between β-HPV and cutaneous SCC development was significant (adjusted odds ratio 1.42 [95% CI 1.18–1.72]), as were the associations with HPV types 5, 8, 15, 17, 20, 24, 36 and 38 (1.4 [1.18–1.66], 1.39 [1.16–1.66], 1.25 [1.04–1.50], 1.34 [1.19–1.52], 1.38 [1.21–1.59], 1.26 [1.09–1.44], 1.23 [1.01–1.50] and 1.37 [1.13–1.67], respectively); the associations with β-HPV and HPV subtypes 5, 8, 17, 20, 24 and 38 remained significant in a subgroup analysis of studies using only serology for HPV detection.

Comment: HPV is a significant risk factor for skin cancer in both immunocompromised and healthy individuals. This raises the need for the development of a vaccine to prevent SCC, which is currently being investigated by Professor Ian Fraser who developed an HPV vaccine for cervical cancer. This would be a great advance in Australia where SCCs are the second most common form of skin cancer. Gardasil vaccine protects against HPV types 6, 11, 16 and 18, which are different from the HPV types shown in this study, so a new vaccine will need to be developed.

Reference: JAMA Dermatol 2016;152(12):1354–64
Abstract

Tofacitinib for the treatment of severe alopecia areata and variants

Authors: Liu LY et al.

Summary: This study evaluated the safety and efficacy of the Janus kinase 1/3 inhibitor, tofacitinib, in a series of 90 patients with alopecia areata and ≥40% scalp hair loss. The primary endpoint was the percent change in SALT (Severity of Alopecia Tool) score during treatment. The clinical response rate was 77%, with 58% of patients achieving >50% change in SALT score over 4–18 months of treatment. Patients with alopecia areata had a higher percent change in SALT score (81.9%) than patients with alopecia totalis or alopecia universalis (59.0%).

Comment: The effectiveness of tofacitinib for severe alopecia areata was good in this study, especially for severe alopecia areata compared with totalis and universalis. In another article in the same journal issue, tofacitinib was also effective in adolescents in which alopecia areata is not uncommon. Some patients who were not showing significant regrowth with tofacitinib monotherapy had pulsed prednisolone, which led to sustained hair growth in these patients. Relapses occurred in 12.3% of patients with a tapering dose of prednisolone, but retreatment with tofacitinib and adjuvant prednisolone in two patients achieved regrowth. After 10 years of complete hair loss, there was less response to tofacitinib, and with each year leading up to 10 years, there was a trend for decreased complete hair growth, indicating that the earlier the treatment starts the better. Further trials with placebo controls are needed to fully assess the effectiveness.

Reference: J Am Acad Dermatol 2017;76(1):22–8
Abstract

Olumacostat glasaretil, a novel topical sebum inhibitor, in the treatment of acne vulgaris

Authors: Bissonnette R et al.

Summary: Patients with moderate-to-severe facial acne vulgaris were randomised to receive twice-daily application of olumacostat glasaretil (n=53) or vehicle (n=55) applied twice daily for 12 weeks in this phase 2a research. Compared with vehicle, olumacostat glasaretil was associated with greater reductions at week 12 in both inflammatory (–63.9% vs. –45.9% [p=0.0006]) and noninflammatory (–48.1% vs. –28.8% [p=0.0025]) lesions, and a greater proportion of participants with in improvement of ≥2 points on IGA score (24.5% vs. 7.3% [p=0.007]). Olumacostat glasaretil was associated with more application-site events, but they were typically mild or moderate.

Comment: Topical olumacostat glasaretil is a novel treatment with good results for both inflammatory and noninflammatory lesions, with clinical improvements similar to combination products for acne. The long-term benefit was not assessed. Combination therapy for acne has become the standard of treatment for acne, and olumacostat glasaretil could be combined with other topical treatments and oral antibiotics. A comparative trial against oral antibiotic therapy should be done, and if the results are similar, then it may be an alternative to oral antibiotics in a significant number of patients.

Reference: J Am Acad Dermatol 2017;76(1):33–9
Abstract

Ten-year mortality is increased after hospitalization for atopic dermatitis compared with the general population, but reduced compared with psoriasis

Authors: Egeberg A et al.

Summary: These authors reported 10-year mortality for adults from the Danish population with a first-time hospitalisation due to AD (n=576) or psoriasis (n=951) and AD-matched controls (n=5760). Death occurred during the study period in 65 and 286 of those hospitalised for AD and psoriasis, respectively. The mortality risk was lower among the patients with AD than those with psoriasis (hazard ratio 0.75 [95% CI 0.57–1.00]), but was higher than for the control group (1.71 [1.20–2.44]), with death occurring at an average age that was 8.3 years younger than in the control group.

Comment: There have been no previous studies on mortality in AD patients, although mortality is increased in patients with psoriasis. The 10-year mortality rate was 71% higher than the general population in patients whose AD was severe enough for them to be hospitalised. This result may not be able to be extrapolated to patients with milder AD. AD was found to be associated with higher rates of obesity, high blood pressure, adult-onset diabetes, rheumatoid arthritis, inflammatory bowel disease, haematological malignancy and cardiovascular disease. The main cause of the increased mortality is cardiovascular disease.

Reference: J Am Acad Dermatol 2017;76(1):98–105
Abstract

Low-dose oral isotretinoin for moderate to severe seborrhea and seborrheic dermatitis

Authors: de Souza Leão Kamamoto C et al.

Summary: Forty-five patients with moderate-to-severe seborrhoea or seborrhoeic dermatitis received isotretinoin 10mg every other day or topical antiseborrhoeic treatment in this 6-month randomised trial. The isotretinoin recipients had a significant decrease in the rate of sebum production, while improvements were seen in both groups for patient opinion, investigator assessment and quality of life.

Comment: Low-dose isotretinoin is helpful in patients with severe seborrhoea, but was not more beneficial in seborrhoeic dermatitis compared with standard treatment. The standard treatment consisted of antiseborrhoeic shampoo to the scalp and hair three times a week and a salicylic acid soap on the face twice a day. The dose of isotretinoin was very low at 10mg on alternate days regardless of weight. The seborrhoeic dermatitis treatment described above would not be expected to be very effective for moderate-to-severe seborrhoeic dermatitis, so the benefit of isotretinoin in seborrhoeic dermatitis is uncertain. If refractory, isotretinoin remains an option for severe seborrhoeic dermatitis, but a higher dose may be worthwhile. Further studies are needed.

Reference: Int J Dermatol 2017;56(1):80–5
Abstract

Ustekinumab treatment in severe atopic dermatitis: down-regulation of T-helper 2/22 expression

Authors: Weiss D et al.

Summary: These authors reported on three patients with severe AD who were treated with SC ustekinumab 45mg for 16 weeks. A gradual improvement was recorded for all patients, with a 50% decrease in EASI (Eczema Area and Severity Index) score seen by week 16. The degree of epidermal hyperplasia/proliferation and the numbers of infiltrating dermal T-cells, dendritic cells and mast cells had significantly decreased on post-treatment biopsies. Quantitative real-time PCR of lesional skin revealed a reduction of T-helper 2-/22-associated molecules post-treatment.

Comment: This study on three patients shows an improvement in EASI, SCORAD and pruritus after ustekinumab for AD, although the numbers are too small to draw a conclusion. The clinical findings were supported by the changes in immunohistology suggesting a role of the interleukin-12/23 pathway in the pathogenesis of AD. Ustekinumab was given 45mg SC, 8 weekly after the initial and 4-week doses, which is more frequent than the dose for psoriasis. The immune pathways in AD are more heterogeneous than in psoriasis and there may be a subset of patients with eczema who respond to ustekinumab. The new biologicals being used for AD may benefit certain subtypes of AD, and the future will be in identifying which AD patients will benefit from which one.

Reference: J Am Acad Dermatol 2017;76(1):91–7
Abstract

Three hundred and eight nanometer excimer light therapy for alopecia universalis that is resistant to other treatments

Authors: Arakawa Y et al.

Summary: Outcomes from 11 patients with treatment-resistant alopecia universalis who were treated with a 308nm excimer light at 2-week intervals for >16 sessions were reported; the radiation dose was increased until marked erythema developed. Good responses were seen in four patients, including all three with Japanese skin type 1, who also exhibited strong pigmentation at the irradiated sites. Two patients had poor responses.

Comment: The results are not better than narrow-band UVB or PUVA (psoralen and UVA) tested in other studies for alopecia areata, but the advantages are it is a localised treatment and fewer sessions are needed. The treatments were done fortnightly and continued for an average of 31 sessions. The results may have been different with once or twice weekly treatment, which is the regimen for excimer laser in vitiligo, and a higher dose may have been able to be given more quickly. Although the success rate is low, 4 of the 11 patients had a good response, so it would be worthwhile trying on patients who are not responding to other treatments.

Reference: J Dermatol 2016;43(12):1412–6
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.

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