Dermatology Research Review™

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In this issue:

Abbreviations used in this issue:

BCC = basal cell carcinoma; **CD** = Crohn's disease; **IBD** = inflammatory bowel disease; **IL** = interleukin; **PASI** = Psoriasis Area and Severity Index; **SC** = subcutaneous; **SCC** = squamous cell carcinoma; **UC** = ulcerative colitis; **UV** = ultraviolet.

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Welcome to issue 33 of Dermatology Research Review.

A Lancet paper reporting a favourable risk-benefit profile for SC methotrexate (although perhaps not as effective as biologicals) for treating patients with moderate-to-severe plaque psoriasis begins this month's issue. Belgian research suggests that a one-time total-body skin examination of adults is the most cost-effective strategy for reducing skin cancer mortality. This is followed by Australian research on skin cancer, with Queensland researchers reporting on the anatomical distributions of SCCs and BCCs seen among their patients. This issue concludes with interesting research suggesting that broccoli sprout extract may provide some benefit for patients with keratin-based disorders, although much more research is needed.

I hope you find this month's selected research of interest. Please keep your comments and suggestions coming.

Kind Regards,

Dr Warren Weightman

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An intensified dosing schedule of subcutaneous methotrexate in patients with moderate to severe plaque-type psoriasis (METOP)

Authors: Warren RB et al.

Summary: Adults with moderate-to-severe plaque psoriasis for ≥6 months were randomised to receive SC methotrexate starting at 17.5 mg/week (n=91) or placebo (n=29), along with folic acid 5 mg/week, for the first 16 weeks, after which all participants received open-label methotrexate for ≤52 weeks, in this phase 3 trial. The methotrexate dose could be increased up to 22.5 mg/week after 8 weeks in participants with <50% reduction in baseline PASI (Psoriasis Area and Severity Index) score at 8 weeks. Compared with placebo, a greater proportion of methotrexate recipients achieved the primary efficacy endpoint of a 75% reduction in PASI score (PASI75) at week 16 (41% vs. 10%; relative risk 3.93 [95% CI 1.31–11.81]). SC methotrexate was well tolerated, with no deaths, serious infections, malignancies or major adverse cardiovascular events, and only three serious adverse events over the entire 52-week study period.

Comment: Prior trials of methotrexate in psoriasis have shown a PASI75 of 45.2%, and in higher quality trials when methotrexate was used as a comparator for biologicals, the PASI75 was 36–42%. The result of SC methotrexate for this group was in line with these other trials but below the benefit achieved with biologicals. The average pretreatment PASI score was 15.4 and mean DLQI (Dermatology Life Quality Index) score was 12, indicating they had moderately severe psoriasis, although the range of values was not given. SC dosing may improve response compared with oral methotrexate, but SC methotrexate has only been assessed in two prior studies. This study shows that methotrexate can be started at a higher dose with no increase in side effects, and SC methotrexate may lead to a more rapid and sustained response compared with oral methotrexate. SC methotrexate is a worthwhile option in patients with moderate psoriasis, but those with more severe psoriasis may benefit more from a biological.

Reference: Lancet 2017;389(10,068):528–37

Abstract

Costs and consequences associated with misdiagnosed lower extremity cellulitis

Authors: Weng QY et al.

Summary: This cross-sectional study sought to characterise the healthcare burden of misdiagnosis in 259 patients admitted to a large urban hospital emergency department in the US for lower-extremity cellulitis. Misdiagnoses of cellulitis were made for 79 of the patients, of whom 52 were admitted primarily for cellulitis treatment. Of these 52 patients, 44 did not require hospitalisation based on their ultimate diagnosis and 48 were prescribed unnecessary antibiotics. The authors estimated that each year 50,000–130,000 hospitalisations in the US are unnecessary as a result of cellulitis misdiagnoses, at a cost of US$195–515 million in healthcare spending. Furthermore, it was projected that >9000 nosocomial infections, 1000–5000 *Clostridium difficile* infections and 2–6 cases of anaphylaxis occur each year due to unnecessary antibiotics and hospitalisation for misdiagnosed cellulitis.

Comment: Misdiagnosis of lower-leg cellulitis is a common problem seen by dermatologists in hospitals. In this study the misdiagnoses included venous stasis dermatitis, lymphoedema, deep venous thrombosis, gout and contact dermatitis. There was no mention of acute lipodermatosclerosis, which in my experience is the most common misdiagnosis. The cost and side effects of misdiagnoses are huge, and significant savings would occur if all suspected cellulitis patients were reviewed by a dermatologist before or shortly after admission. These savings may be enough to fund several consultant dermatologists.

Reference: JAMA Dermatol 2017;153(2):141–6
Abstract

Cost-effectiveness and budget effect analysis of a population-based skin cancer screening

Authors: Pil L et al.

Summary: This research used a Markov model to look at the cost-effectiveness of two population-based skin cancer screening methods used in Belgium and assess their budget effect and the influence on skin cancer epidemiological findings. The model had a latent period of 20 years and a time horizon of 50 years. Six dermatologists performed 1668 total-body skin examinations and 248 lesion-directed screens. The respective incremental cost-effectiveness ratios in men and women were €33,072 and €18,687 per quality-adjusted life-year for total-body skin examination and €34,836 and €19,470 for lesion-directed screening. A 4.0% decrease in the incidence rates of stage III/IV melanoma was predicted at the population level with a one-time screen. A budget effect analysis over 20 years showed that a one-time screen would incur net costs for the healthcare payer of almost €36 million and just over €6 million for total-body skin examinations and lesion-directed screens, respectively, equating to €4.1 and €0.7 per adult, respectively.

Comment: The main message from this trial was that total body skin examinations were more cost effective than lesion-directed screening. In practice a patient will often come in concerned about a particular lesion, but a full-body examination should also be done. Although a one-time screening may pick up some skin cancers and reduce mortality, there may be more effective screening programmes. More frequent screening varying from yearly to every 10 years, depending on risk factors, and targeted from age 40 or 50 years would likely pick up more skin cancers than a once-only examination. The cost effectiveness of this would have to be determined by another study.

Reference: JAMA Dermatol 2017;153(2):147–53
Abstract

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.

Anatomical distributions of basal cell carcinoma and squamous cell carcinoma in a population-based study in Queensland, Australia

Authors: Subramaniam P et al., for the QSkin Sun and Health Study Investigators

Summary: This research from Queensland evaluated the anatomical distribution of BCCs and SCCs in a population-based sample. Among 3398 individuals with diagnoses of keratinocyte cancers, complete data on 5150 cancers were recorded for 2374 people. BCCs accounted for 74.7% of these cancers, with most located on the head and/or neck (40.2%) or the trunk (33.9%). Most of the SCCs were located on the head and/or neck (33.4%) or upper limbs (34.9%). The greatest differences in relative tumour densities were on the hand with a BCC:SCC ratio of 1:14 and the back and/or buttocks with a BCC:SCC ratio of 8:1. Men had a greater relative tumour density of keratinocyte cancers on the scalp and ear than women, whereas women had a greater relative tumour density on the upper arm than men. Compared with individuals aged 40–54 years, those aged 55–69 years had significantly greater relative SCC densities on the scalp (1.07 vs. 0.38) and the back and/or buttocks (0.12 vs. 0.05). There was no difference in patterns of relative BCC densities according to age.

Comment: In my experience, BCCs are seen very uncommonly on the dorsum of the hand, an area that along with the face has the highest amount of sun exposure. This study confirms this observation. One possible explanation for the marked differences in the occurrence of BCCs and SCCs on the dorsum of the hand is that the thicker epidermis on the hand protects the deeply situated basal cells from the UV rays compared with the exposure received by the more superficial squamous cells. This may explain the high incidence of BCCs on the lower eyelids where the epidermis is thinner. BCC was not as strongly associated with sun exposure compared with SCCs, which explains why BCCs are more common on the trunk. The infrequent sun exposure of these sites results in less melanin protection, increasing the risk for sunburn. BCCs on less exposed body sites therefore may arise due to infrequent or intermittent high doses of UV radiation.

Reference: JAMA Dermatol 2017;153(2):175–82
Abstract

Inflammatory bowel disease among patients with psoriasis treated with ixekizumab

Authors: Reich K et al.

Summary: This *post hoc* analysis examined the incidence of adjudicated IBD (inflammatory bowel disease) cases among 4209 patients with psoriasis receiving ixekizumab (6480 patient-exposure years) from seven randomised controlled and uncontrolled trials. Twelve suspected CD (Crohn's disease) and 17 UC (ulcerative colitis) adverse events were reported during the trials and 19 of these were adjudicated as definite/probable IBD (seven CD and 12 UC; respective incidence rates 1.1 and 1.9 per 1000 patient-exposure years). Three occurred during induction (one CD, two UC) and seven during maintenance (four CD, three UC). Among 16 patients with a prior history of IBD, 12 had not experienced an IBD treatment-emergent adverse event or serious adverse event at the time of reporting.

Comment: IBD is increased in psoriasis patients and IL-17 has been implicated in IBD. Previous clinical trials of CD with both brodalumab (IL-17R antagonist) and secukinumab (IL-17A antagonist) failed to show effectiveness, and in some cases CD worsened, which has led to a warning when using IL-17 inhibitors in patients with IBD. In this study of several trials' combined data, the number of IBD cases found was uncommon (<1% and not increased above what is expected) and there was no flaring of the IBD. Dermatologists should be aware of psoriasis patients who have IBD and monitor them closely, but ixekizumab is not a contraindication for starting an IL-17 inhibitor. Registry studies should further clarify this association.

Reference: J Am Acad Dermatol 2017;76(3):441–8
Abstract

Hair pull test: evidence-based update and revision of guidelines

Authors: McDonald KA et al.

Summary: These researchers enrolled 181 participants to complete a questionnaire on demographics, medications and hair health/history, and subjected them to a single hair pull test (scalp vertex), which resulted in a mean of 0.44 hairs removed for each pull. The mean number of hairs removed did not differ significantly when the participants washed or brushed their hair, and nor did it differ between Caucasian-, Asian- and Afro-textured hair, recipients versus nonrecipients of medications affecting hair loss or tight versus other hairstyles.

Comment: This study has clarified the criteria for the hair pull test and simplified the procedure with no restriction on pretest hair washing and permitting brushing of hair. This means that it can be done when the patient presents, rather than leaving it for a later visit. Previous studies had suggested that 5–6 hairs or more was abnormal, but there was no clinical study that had validated this number. This study has validated that a lower number, or two hairs or fewer, is normal. Drugs such as the oral contraceptive pill and different racial hair types had no effect on the result.

Reference: J Am Acad Dermatol 2017;76(3):472–7
Abstract

Erythromelalgia: identification of a corticosteroid-responsive subset

Authors: Pagani-Estévez GL et al.

Summary: Clinical predictors of corticosteroid-responsive erythromelalgia were identified in this retrospective study involving 14 patients who did not respond to corticosteroids, eight who were partial corticosteroid responders and nine who were complete corticosteroid responders. Fifteen patients had a subacute temporal profile to disease zenith (<21 days), among whom 87% were (partial or complete) corticosteroid responders. A precipitant was reported by 67% of the complete corticosteroid responders. Corticosteroids were started sooner among responders compared with nonresponders (3 vs. 24 months [p=0.003]). Seventeen patients received a trial of prednisone ≥200mg cumulatively, of whom 76% were corticosteroid responders.

Comment: Although erythromelalgia is rare, once it becomes chronic it is very difficult to treat. Irreversible damage to peripheral nociceptors with heightened sensitisation may occur if erythromelalgia is not treated early. This study shows that recent-onset erythromelalgia may have an acute precipitant, and early treatment with oral corticosteroids may be effective and give long-term benefit. Corticosteroid responsiveness is not influenced by age, examination findings or the results of ancillary testing, although these are useful for establishing a diagnosis. Paraneoplastic erythromelalgia has been reported in association with solid tumours, chronic myelogenous leukaemia and, in this trial, multiple myeloma, so malignancy should be excluded as a cause.

Reference: J Am Acad Dermatol 2017;76(3):506–11
Abstract

Doxycycline versus prednisolone as an initial treatment strategy for bullous pemphigoid

Authors: Williams HC et al., on behalf of the UK Dermatology Clinical Trials Network BLISTER Study Group

Summary: Adults with bullous pemphigoid who had ≥3 blisters affecting ≥2 sites and linear basement membrane IgG or C3 were stratified by severity and randomised to receive doxycycline 200 mg/day (n=132) or prednisolone 0.5 mg/kg/day (n=121) in this noninferiority trial; localised adjuvant potent topical corticosteroids were permitted during weeks 1–3. The difference between the doxycycline versus prednisolone arm for the primary endpoint of ≤3 blisters at 6 weeks (74% vs. 91%) met the predefined criterion for noninferiority (adjusted between-group difference 90% CI upper limit, <37%). Compared with prednisolone, doxycycline was associated with a lower proportion of participants experiencing severe, life-threatening or fatal adverse events over 52 weeks (18% vs. 36% [p=0.001]) in a modified intent-to-treat analysis.

Comment: I have not had much benefit with tetracyclines and niacinamide used as adjunctive treatment compared with oral steroids in pemphigoid patients. In this trial, there was a difference in efficacy favouring prednisolone, but it was within the 37% margin of noninferiority that appears to have been set arbitrarily. It is not clear why standard statistical measures were not used in this study and whether this would have made a difference to the result and the interpretation. However, 74% of patients on doxycycline had ≤3 blisters at week 6, which is a reasonable improvement although not perfect. Doxycycline may be worthwhile trying as first-line treatment, especially with its good safety profile in patients with mild-to-moderate pemphigoid. Niacinamide is often used in conjunction with doxycycline and further trials need to be done to see if it adds much or any benefit. I would still prefer a short course of oral prednisolone in patients with moderate-to-severe pemphigoid, but doxycycline could be used as a steroid-sparing agent.

Reference: Lancet; Published online March 6, 2017
Abstract

Prevalence and risk of migraine in patients with rosacea

Authors: Egeberg A et al.

Summary: This population-based research explored the relationship between new-onset migraine and rosacea in an overall cohort of 4,361,688 adult Danes, 49,475 of whom had rosacea. Compared with the reference population, patients with rosacea had a higher prevalence of migraine (12.1% vs. 7.3%; adjusted hazard ratio 1.31 [95% CI 1.23–1.39]). Moreover, the risk of migraine was increased with patients with ocular rosacea (n=6977; adjusted hazard ratio 1.69 [95% CI 1.43–1.99]), but not in those with phymatous rosacea (n=594; 0.45 [0.11–1.80]). Also, the association between rosacea and migraine was greater in patients aged ≥50 years than in younger patients, and was only significant among women.

Comment: This national population-based study has confirmed earlier smaller studies that migraine is associated with rosacea, particularly in women and with ocular rosacea. The cause has not been determined, but a vascular abnormality is central to the pathogenesis of both disorders. This study did not distinguish between the erythematotelangiectatic and papulopustular subtypes of rosacea, and it would be worthwhile knowing if one subtype has a higher association than the other. Several triggers for migraine share an overlap with rosacea triggers, including stress and alcohol. Migraine is a symptom that should be enquired about in women who present with rosacea. It's possible that some of the treatments for migraine may also help the vascular abnormalities in rosacea.

Reference: J Am Acad Dermatol 2017;76(3):454–8
Abstract

Randomized, split-body, single-blinded clinical trial of topical broccoli sprout extract: assessing the feasibility of its use in keratin-based disorders

Authors: Kerns ML et al.

Summary: Four evaluable adults had broccoli sprout extract (500 nmol of sulforaphane/mL) and vehicle alone applied to the inner aspect of their arms each day in this 1-week, randomised, split-body trial. Compared with vehicle alone, topical broccoli sprout extract application was associated with activation of nuclear factor (erythroid-derived 2)-like 2 and upregulation of K (keratin) 17 in the epidermis of all participants, had variable effects on K16 and K6 expression, and no effect on K14 or K5 expression.

Comment: Topical broccoli sprout extract is a novel treatment, which in these normal subjects increased K17 and had variable effects on K16 and K6 without affecting K14 or K5. There need to be trials in epidermolysis bullosa simplex patients to see if these patients have a therapeutic response. This should not be an expensive treatment and may work both topically and orally, but further trials will be needed. Until further trials are done, it may be worthwhile recommending increasing broccoli in the diet.

Reference: J Am Acad Dermatol 2017;76(3):449–53
Abstract

