Dermatology Research Review™

Making Education Easy

Issue 20 – 2016

In this issue:

Welcome to the latest issue of Dermatology Research Review.

Highlights include a report of the genetic alterations that occur during melanoma progression, and promising results for nicotinamide for the prevention of skin cancer (albeit at a dosage of 1g per day). We also report the use of mass drug administration for scabies control in Fiji, and excellent responses to brimonidine gel (a Section 29 medicine) in patients with rosacea. Other studies include a comparison of topical and oral treatments for toenail onychomycosis, a new checklist for diagnosing acral melanoma, and the benefits of a virtual lesion clinic for patients with suspected melanoma.

We hope you find these and the other selected studies interesting, and look forward to receiving any feedback you may have.

Kind regards,

Associate Professor Amanda Oakley
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The genetic evolution of melanoma from precursor lesions

Authors: Shain H et al.

Summary: This study determined the succession of genetic alterations during melanoma progression. 293 cancer-relevant genes in 150 areas of 37 primary melanomas and their adjacent precursor lesions were sequenced. The results showed distinct evolutionary trajectories for different melanoma subtypes. Ultraviolet radiation was implicated as a major factor in both the initiation and progression of melanoma.

Comment: Clinicians with an interest in the identification and management of melanoma have to keep abreast of advances in molecular biology. Gene sequencing doesn't get any easier to understand, but it's a lot cheaper and more comprehensive than it used to be. Some mutations associated with melanoma (such as $BRAF_{V600E}$) are also present in many benign melanocytic naevi. When found in melanoma, $BRAF_{V600E}$ mutations are often associated with younger patients from sites that have been intermittently sun damaged. Melanomas with NRAS mutations and $BRAF_{V600K}$ or $BRAF_{K601E}$ mutations occur predominantly on chronically sun-damaged skin of older patients (read the article to learn more). These researchers looked at 37 invasive melanomas. They microdissected formalin-fixed, paraffin-embedded melanomas to identify benign, intermediate probably benign, intermediate probably malignant areas, and areas of definite melanoma in the tumour. For each sample, they sequenced 293 known cancer genes and attempted to validate their findings by fluorescence in situ hybridisation (FISH). Benign areas in their cohort (13) all had $BRAF_{V600E}$ mutations. The pathologists had difficulty classifying intermediate areas of the melanoma, but 19/21 of these had multiple pathogenic mutations, e.g. telomerase reverse transcriptase (TERT; a promoter). Mutations in malignant areas were numerous and highly variable. They concluded that ultraviolet "signatures" (dominant mutations) are present in the majority of melanomas.

Reference: N Engl J Med 2015;373:1926-36
Abstract

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A phase 3 randomized trial of nicotinamide for skin-cancer chemoprevention

Authors: Chen A et al.

Summary: This study investigated the use of nicotinamide (vitamin B_3) for prevention of skin cancer. 386 patients with a history of nonmelanoma skin cancers were randomised to receive nicotinamide 500mg twice daily or placebo for 12 months in a double-blind design and were assessed by dermatologists every 3 months. At 12 months, nicotinamide reduced the number of new nonmelanoma skin cancers by 23% (p=0.02), new basal-cell carcinomas by 20% (p=NS), new squamous-cell carcinomas by 30% (p=0.05), and new actinic keratoses by 13% (p=0.001) compared with placebo.

Comment: Sun protection is the most important advice we can give our skin cancer patients: when outdoors (if you must) wear broad-brimmed hat, long sleeves, long trousers, and apply sunscreen on uncovered areas. Year round. Reapply sunscreen every 2 hours during summer months or after bathing. Do not smoke. Should we also recommend supplemental nicotinamide 1g daily? Perhaps. It is difficult to obtain nicotinamide 500mg capsules (try online pharmacies). The dose in usual once daily multivitamins (7.5–20mg) is not sufficient.

Reference: N Engl J Med 2015;373:1618-26
Abstract

Mass drug administration for scabies control in a population with endemic disease

Authors: Romani L et al.

Summary: This study investigated the use of mass drug administration for scabies control in Fiji. Three island communities (n=2051) were randomly assigned to 1 of 3 interventions for scabies control: standard care involving the administration of permethrin to affected persons and their contacts (standard-care group), mass administration of permethrin (permethrin group), or mass administration of ivermectin (ivermectin group). From baseline to 12 months, the prevalence of scabies declined significantly in all groups, with relative reductions of 49%, 62% and 94%, respectively. The prevalence of impetigo also declined in all groups, with relative reductions of 32%, 54% and 67%, respectively, at 12 months. Adverse events were mild and were reported more frequently with ivermectin than with permethrin (15.6% vs 6.8%).

Comment: When you are facing yet another case of scabies, spare a thought for rural Pacific Islanders. Some of them may bring their infestation to NZ; remain vigilant. We have a very high incidence of serious cutaneous infections in children and adults in this country and this is not infrequently due to underlying infestation. The diagnosis of scabies depends on finding burrows – locating a grey "jet plane" or "hang-glider" at the end of a burrow using dermoscopy confirms the presence of active mite infestation. Note that ivermectin is convenient to use but it is only subsidised by PHARMAC under certain circumstances on Special Authority application. Two doses at 8–10 day intervals are not always effective; in fact properly applied topical therapy with permethrin on 2 occasions probably has a higher cure rate.

Reference: N Engl J Med 2015;373:2305-13
Abstract

Cutaneous toxic effects of BRAF inhibitors alone and in combination with MEK inhibitors for metastatic melanoma

Authors: Carlos G et al.

Summary: This retrospective study compared the cutaneous toxic effects of BRAF inhibitor monotherapy (dabrafenib or vemurafenib) and CombiDT therapy (dabrafenib plus the MEK inhibitor trametinib) in a large cohort of patients. The medical records of 185 Australian patients with unresectable stages IIIC and IV melanoma were reviewed. 119 patients had received dabrafenib, 36 had received vemurafenib and 30 had received CombiDT therapy. The most common cutaneous adverse effects seen in patients taking dabrafenib or vemurafenib were Grover disease (42.9% and 38.9% of patients, respectively), plantar hyperkeratosis (39.5% and 38.9%), verrucal keratosis (66.4% and 72.2%), and cutaneous squamous cell carcinoma (26.1% and 36.1%). Photosensitivity was more common with vemurafenib (38.9%) than with dabrafenib (0.8%; p<0.001). Compared with dabrafenib, CombiDT therapy was associated with more folliculitis (40.0% vs 6.7%; p<0.001) but less cutaneous squamous cell carcinoma (0% vs 26.1%; p<0.001), verrucal keratosis (0% vs 66.4%; p<0.001), and Grover disease (0% vs 42.9%; p<0.001).

Comment: MEK inhibitors appear to reduce the adverse effects of BRAF inhibitors, with the exception of folliculitis, which is more frequent. Dabrafenib (Tafinlar®) and trametinib (Mekinist®) are approved in NZ as monotherapy and in combination for the treatment of BRAF+ advanced melanoma. They are not subsidised and are prohibitively expensive (Mims Gateway: Tafinlar® 50mg tablets Patient Charge $10,903.48 for about 3 weeks' supply and Mekinist® 2mg tablets Patient Charge $16,355.23 for 1 month's supply).

Reference: JAMA Dermatol 2015;151(10):1103-09
Abstract

Genetic vs environmental factors that correlate with rosacea

Authors: Aldrich N et al.

Summary: This cohort-based survey of twins examined the genetic and environmental factors associated with rosacea. 275 pairs of identical or fraternal twins were asked about risk factors implicated in rosacea and were given a rosacea score according to the National Rosacea Society (NRS) grading system. Using the ACE model (proportion of variance in a trait heritable secondary to additive genetics [A] vs the proportions due to a common environment [C] and unique environment [E]), the genetic contribution was calculated to be 46%. Environmental factors associated with rosacea were age, lifetime ultraviolet radiation exposure, body mass index, smoking, alcohol consumption, cardiovascular comorbidity, and skin cancer history.

Comment: Rosacea is common, and commonly distressing. The development of new treatments is leading to epidemiological research in an attempt to understand it. The findings of strong genetic susceptibility and the importance of lifetime ultraviolet exposure for rosacea are unsurprising.

Reference: JAMA Dermatol 2015;151(11):1213-1219
Abstract

Time spent reading this publication has been approved for CME for Royal New Zealand College of General Practitioners (RNZCGP) General Practice Educational Programme Stage 2 (GPEP2) and the Maintenance of Professional Standards (MOPS) purposes, provided that a Learning Reflection Form is completed. Please **CLICK HERE** to download your CPD MOPS Learning Reflection Form. One form per review read would be required.

Time spent reading this publication has been approved for CNE by The College of Nurses Aotearoa (NZ) for RNs and NPs. For more information on how to claim CNE hours please **CLICK HERE**.

Brimonidine gel 0.33% rapidly improves patient-reported outcomes by controlling facial erythema of rosacea

Authors: Layton A et al.

Summary: This study evaluated the use of brimonidine gel in patients with rosacea. 92 patients with self-perceived severe erythema were randomised to use brimonidine 0.33% gel or vehicle gel once daily. After 8 days, more patients in the brimonidine group than in the vehicle group were satisfied with their facial appearance (36.9% vs 21.5%; p<0.05), as well as with the overall treatment effect (69.6% vs 40.4%; p<0.01), and with the improvement in facial redness (67.4% vs 33.3%; p<0.001). More patients in the brimonidine group had at least a 1-grade improvement from baseline in the Clinician Erythema Assessment score (71.7% vs 35.7%; p=0.0011) and Patient Self-Assessment score (76.1% vs 47.6%; p=0.004) at day 8.

Comment: This open access article reports that rosacea patients are very satisfied with the rapid reduction in erythema they can achieve with once-daily brimonidine gel. As it is not yet registered or funded in NZ, brimonidine gel for topical use in rosacea must be obtained from the distributor under Section 29. The gel should be applied evenly to all areas of redness; 1g should cover the entire face. A moisturiser can be used to minimise treatment-related irritation. It starts to reduce facial erythema within 30 minutes and its action persists for about 12 hours. The drug is registered in NZ in prescription eye drops to treat glaucoma. There are some contraindications and cautions.

Reference: J Eur Acad Dermatol and Venereol 2015;29(12):2405-10
Abstract

Efficacy of topical resin lacquer, amorolfine and oral terbinafine for treating toenail onychomycosis

Authors: Auvinen T et al.

Summary: This study compared the efficacies of a topical spruce resin lacquer, a topical amorolfine lacquer and systemic terbinafine in patients with toenail onychomycosis. 73 patients with onychomycosis were randomised to use a 30% resin lacquer once daily for 9 months, a 5% amorolfine lacquer once weekly for 9 months, or oral terbinafine 250mg once daily for 3 months. At 10 months, complete mycological cure rates with the resin, amorolfine and terbinafine treatments were 13%, 8% and 56%, respectively (p≤0.002).

Comment: Topical therapies for onychomycosis are very disappointing. To get good response in clinical practice, choose young motivated patients with minimal and superficial, distal disease. Subsidised generic amorolfine nail lacquer costs $20 for 5ml. These authors note that oral treatment with terbinafine is much more effective than topicals. It is also less expensive; a 3-month course of generic oral terbinafine now costs very little. Mims Gateway states the price to be $1.50 for 14 tablets. A recent editorial in JAMA Dermatology (http://archderm.jamanetwork.com/article.aspx?articleid=2475008) discusses a paper that shows empirical treatment with oral terbinafine is more cost-effective than treatment after confirmatory testing. I caution readers to be quite certain that a dystrophic nail is infected with a responsive fungus (they don't all clear with terbinafine) in a responsive patient (young, fit), and that risks and side effects have been considered (these include very rare severe adverse drug reactions).

Reference: Brit J Dermatol 2015;173(4):940-48
Abstract

Independent commentary by Associate Professor Amanda Oakley

Associate Professor Oakley is a specialist dermatologist at Waikato Hospital and is an Honorary Associate Professor at Waikato Clinical Campus (Auckland University School of Medicine). She is the website manager and chief editor of the successful web site, DermNetNZ.org. She is an Honorary Member of the American Academy of Dermatology, the American Dermatological Society, the Indian Society of Teledermatology, and MelNet New Zealand. She is on the Board of the Australasian Dermatological Research Association. She has numerous publications in the medical literature and is frequently invited to lecture in New Zealand and overseas. Research interests include all aspects of virtual health and early diagnosis of melanoma.

The BRAAFF checklist: a new dermoscopic algorithm for diagnosing acral melanoma

Authors: Lallas A et al.

Summary: This study investigated the diagnostic accuracy of dermoscopic criteria for acral melanoma (AM). Dermoscopic images of histopathologically diagnosed AMs and acral naevi were evaluated by 3 independent investigators for the presence of predefined criteria. A total of 603 lesions (472 naevi and 131 AMs) were included. The BRAAFF scoring system was found to have the highest diagnostic accuracy for AM. It uses four positive (irregular blotches, ridge pattern, asymmetry of structures and asymmetry of colours) and two negative predictors (furrow pattern and fibrillar pattern).

Comment: Some people love acronyms. This is another one to add to many in the existing dermatoscopic literature. The most important letter in the diagnosis of cutaneous malignancy at any site is, "A for Asymmetry of structure and colour".

Reference: Brit J Dermatol 2015;173(4):1041-49
Abstract

Making sense of the effects of the cumulative dose of isotretinoin in acne vulgaris

Author: Rademaker M

Summary: This study compared the influence of daily and cumulative isotretinoin dosage on acne relapse. Medical charts of 1453 patients who received isotretinoin for acne were reviewed. 326 patients (22.4%) had received a second course of treatment after relapse (study population); the remainder served as controls (n=1127). Isotretinoin dosage varied from 10 mg/week to 1.1 mg/kg/day, cumulative dosage from 1 to >300 mg/kg, and duration of treatment from 8 weeks to 5 years. Compared with controls, patients who received a second course were more likely to be women, and received higher daily and cumulative doses. Patients treated with very low doses and/or low cumulative doses did not relapse more often than controls.

Comment: The paper reports a single author's experience with isotretinoin. It's very effective for acne, whatever dose is used, and relapse rates are independent of daily or cumulative dose during a course of treatment. These mirror my own experience, but I am biased by my close professional association with the author, A/Prof Marius Rademaker. The message is to start low, adjust dose as necessary, keep going until clear and then a further 2–3 months, and stop. Tell the patient you can restart treatment if it recurs.

Reference: Int J Dermatol 2015; published online Oct 15
Abstract

Daylight photodynamic therapy with methyl aminolevulinate cream is effective and nearly painless in treating actinic keratoses

Authors: Lacour J-P et al.

Summary: This study compared the efficacy and safety of daylight photodynamic therapy (DL-PDT) and conventional PDT (c-PDT) in patients with facial/scalp actinic keratoses. Adults with multiple mild-moderate actinic keratoses were treated once with methyl aminolevulinate (MAL) DL-PDT on one side of the face and MAL c-PDT contralaterally. At week 12, the total lesion complete response rate with DL-PDT was similar to c-PDT (70% vs 74%). The efficacy of DL-PDT was demonstrated regardless of weather conditions (sunny or cloudy). DL-PDT was nearly painless compared to c-PDT ($p<0.001$) and had higher patient satisfaction.

Comment: Pain significantly inhibits patients from requesting a second treatment with conventional PDT. This is eliminated by using daylight to activate the drug, instead of a red, light-emitting diode (LED) lamp. This paper examined efficacy at different latitudes in Europe and found very similar results to an earlier Australian study. The current NZ Data Sheet (June 2015) includes the use of daylight PDT for thin or non-hyperkeratotic and non-pigmented actinic keratoses of the face and scalp. It is an excellent treatment option for people that can afford the cost of the cream (Mims Gateway: Patient Charge $776.25 for 2g Metvix® cream).

Reference: J Eur Acad Dermatol Venereol 2015;29(12):2342-48
Abstract

Successful melanoma triage by a virtual lesion clinic (teledermatoscopy)

Authors: Congalton A et al.

Summary: This study assessed the diagnostic accuracy of a virtual lesion clinic (VLC) for melanoma. Patients with suspected melanoma were referred from primary care to a local skin imaging centre, where a teledermatologist assessed each lesion and recommended a course of action. 613 skin lesions in 310 patients were evaluated over a 12-month period. Median time between receipt of referral and attendance at the VLC was much faster than for standard outpatient assessment (9 vs 26.5 days). 66% of lesions were considered benign, and 12% were suspicious for melanoma. Of 129 lesions excised, 98 were skin cancers including 48 histologically confirmed melanomas, 1 spitzoid tumour of unknown malignant potential (STUMP) and 49 non-melanoma skin cancers. Teledermatoscopic diagnosis of melanomas had a positive predictive value of 63%. The cost of running the VLC for 1 year was $NZ1174/patient less than that of a conventional outpatient clinic.

Comment: As one of the authors of this paper, I am happy to draw it to your attention. We reported that teledermatoscopic diagnoses led to savings in money and time for a public hospital melanoma service. Skin cancers were promptly removed by appropriately trained surgeons, while unnecessary outpatient visits and surgeries for benign lesions were reduced.

Reference: J Eur Acad Dermatol Venereol 2015;29(12):2423-28
Abstract

Real-life effectiveness of once-daily calcipotriol and betamethasone dipropionate gel vs. ointment formulations in psoriasis vulgaris

Authors: Lambert J et al.

Summary: This final analysis of the 52-week PRO-long study reported the real-life effectiveness of calcipotriol and betamethasone dipropionate (CAL-BD) gel compared with ointment formulations in patients with psoriasis vulgaris. 328 patients were prescribed the gel or ointment formulation in clinical practice. At week 52, treatment satisfaction was higher in patients using the gel. A higher proportion of patients found the gel 'easy' to use compared with the ointment (66.7% vs 45.2%). Daily application of treatment took ≤5 min for 86.1% of patients using gel and 71.0% of patients using ointment.

Comment: This paper describes an industry-sponsored study that supports my patients' preference for gel over ointment when prescribed CAL-BD once daily for chronic plaque psoriasis. They included 328 patients with psoriasis of variable severity in all ages. CAL-BD gel has similar efficacy to ointment, but is easier and nicer to use. CAL-BD is a first-line treatment for mild-moderate psoriasis. The authors do not tell us how much product was used, nor do they comment on its continuous use over 52 weeks or its use in children. The Daivobet® Data Sheet (July 2013) published on the Medsafe website instructs: maximum daily dose ≤15g; maximum weekly dose ≤100g; treated area should not be ≥30% of body surface; recommended treatment period is 4 weeks; not recommended for use in patients aged ≤18 years.

Reference: J Eur Acad Dermatol Venereol 2015;29(12):2349-55
Abstract