Dermatology RESEARCH REVIEW™

Making Education Easy

Issue 1– 2020

In this issue:

Abbreviations used in this issue

BCC = basal cell carcinoma
DLQI = Dermatology Life Quality Index
PASI = Psoriasis Area Severity Index

Welcome to the latest issue of Dermatology Research Review.

Patient and clinician awareness and early suspicion of skin cancer leading to early diagnosis and management are important for better outcomes. In this issue, we see an 11-fold higher incidence of subcutaneous panniculitis-like T-cell lymphoma in Māori and Pasifika patients. MoleMap NZ dermoscopist-recommended biopsy/excision finds a higher proportion of melanoma-in-situ than invasive melanoma at a benign:malignant ratio of 5:1, but combining face-to-face dermatologist clinical and imaging techniques significantly improves sensitivity and specificity accuracy. Increasing the levels of histopathology analysis improves BCC subtype diagnosis. Although most BCCs are cured with appropriate surgery, for patients with advanced disease unsuitable for surgery, sonidegib brings hope for alternative treatment. Mycophenolate is worth considering in patients with more extensive severe morphoea. Apremilast, effective in chronic plaque psoriasis, now shows promise for severe scalp psoriasis too. Dose tapering can be achieved whilst maintaining psoriasis disease control in patients taking adalimumab, etanercept or ustekinumab. Other advances in clinical responses to biologics show that: rituximab for pemphigus reduces corticosteroid use and achieves earlier disease remission; dupilumab significantly reduces itch and then eczema clinical signs in atopic dermatitis; and continuing adalimumab for 3 years results in a significant reduction in duration and number of hidradenitis suppurativa disease flares.

We hope that you find these articles of academic or relevant clinical interest and welcome any feedback you may have.

Kind regards,

Dr Louise Reiche
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The epidemiology of subcutaneous panniculitis-like alpha-beta T-cell lymphoma in New Zealand

Authors: Kim Y et al.

Summary: This retrospective study examined the epidemiology of subcutaneous panniculitis-like alpha-beta T-cell lymphoma in NZ. 10 cases were identified in Auckland in 2005–2017 (5 male and 5 female; median age at diagnosis, 38.5 years). Nine patients were Māori/Pacific, and 1 was European. The relative risk of subcutaneous panniculitis-like alpha-beta T-cell lymphoma in individuals of Māori/Pacific versus European ethnicity was found to be 11.1 (95% CI 1.83–246.1; p=0.005).

Comment: Subcutaneous panniculitis-like T-cell lymphoma clinically mimics lipoma but histologically resembles panniculitis. Lipomas are common non-tender fatty tumours, whereas panniculitis (subcutaneous fat inflammation) is rare and manifests as tender lumps or indentations. Cutaneous lupus has a higher incidence in Māori and Pasifika people and subcutaneous panniculitis is one manifestation, so the incidence is higher in this population group. This study also shows a much higher incidence of the rare subcutaneous panniculitis-like T-cell lymphoma. So we should have a lower threshold for biopsying (requesting immunofluorescence and T-cell studies too and divide specimens among formalin, and normal saline or Michel's solution and T-cell study medium) a Māori or Pasifika patient presenting with new fatty lumps before diagnosing benign lipoma.

Reference: Australas J Dermatol 2020;61(2):196-9

Abstract

Real-world outcomes of melanoma surveillance using the MoleMap NZ telemedicine platform

Authors: Greenwald E et al.

Summary: This study assessed the effectiveness of MoleMap NZ as a melanoma early detection programme. A review of 2108 melanocytic lesions recommended for biopsy or excision by MoleMap NZ dermoscopists in 2015–2016 was undertaken. Pathological diagnoses were available for 1571 lesions. Of these, 83% were benign and 17% were diagnosed as melanoma (melanoma-specific benign:malignant ratio of 5:1). The number needed to biopsy to find 1 melanoma was 6.

Comment: Australasia has among the highest incidence of melanoma in the world. Early detection is key to driving early management and good patient outcomes. Skin cancer surgery is an increasing health cost so accurate pre-surgical diagnosis is critical for optimising good patient health outcomes, workforce and health dollar efficiency. This study of the MoleMap NZ dermoscopist recommendation for biopsy excision of suspicious lesions generated a benign:malignant ratio of 5:1. 74% of the melanomas were in situ so were detected at a curative stage.

Reference: J Am Acad Dermatol 2020; published online Feb 27
Abstract

The use of non-invasive imaging techniques in the diagnosis of melanoma

Authors: MacLellan A et al.

Summary: This study compared a dermatologist's clinical examination, teledermatology, and non-invasive imaging techniques (FotoFinder®, MelaFind®, and Verisante Aura®) for the detection of melanoma. 184 patients at an outpatient dermatology clinic were included. 59 lesions from 56 patients had a histopathological diagnosis of melanoma, while 150 lesions from 128 patients were benign. Sensitivities and specificities for detecting melanoma were 88.1% and 78.8%, respectively, for FotoFinder® Moleanalyzer Pro, 82.5% and 52.4%, respectively, for MelaFind®, and 21.4% and 86.2%, respectively, for Verisante Aura®. Sensitivities and specificities of teledermatology were 84.5% and 82.6%, respectively, and for a local dermatologist were 96.6% and 32.2%, respectively.

Comment: This study comparing histopathological diagnoses of melanoma among those detected clinically by dermatologists, teledermatology and 3 different non-invasive imaging techniques showed highest sensitivity clinically and higher specificity with imaging techniques. Thus imaging techniques cannot replace clinical decision making, but utilising both improves diagnostic accuracy.

Reference: J Am Acad Dermatol 2020; published online Apr 11
Abstract

Independent commentary by Dr Louise Reiche MBChB (Otago) FRACP MD FNZDSI

Dr Louise Reiche is a New Zealand physician trained vocational specialist dermatologist. Louise runs general dermatology clinics within integrated family health care: Kauri HealthCare, Palmerston North. She has additional special interests in eczema, patch testing, skin cancer surveillance and preventative dermatology health. Louise is an active executive member of the NZ Dermatological Society, Founder and Chairperson for the NZ Dermatology Research Trust, Clinical advisor for Melanoma NZ, and member of Melnet NZ, and works alongside these groups and on behalf of the NZ Dermatological Society with Cancer Society NZ and other relevant bodies in the interest of New Zealander skin health.

Single versus multiple level sectioning for the subtyping of basal-cell carcinoma

Authors: van Delft LCJ et al.

Summary: This retrospective study investigated whether evaluating 4 levels of a punch biopsy instead of 1 or 2 levels leads to more accurate subtyping of BCC. 87 punch biopsies of histologically confirmed BCCs were reviewed; 85 cases were available for analysis. In 16.5% of cases, subtyping based on 1 level resulted in discrepancies with 4-level diagnosis. 14 of 58 nonsuperficial BCCs (24.1%) were underdiagnosed. Seven of 38 nodular BCCs (18.4%) were diagnosed as superficial in 1 level, and 7 of 20 infiltrative BCCs (35%) were diagnosed as superficial or nodular in 1 level.

Comment: More comprehensive clinical skin examinations are less likely to miss skin cancer detection than limited or cursory examination. It is not surprising that the same approach to histological examination of a skin biopsy specimen yields similar findings: more slices/levels of histopathological analysis and the more accurate is the BCC subtype. And why does this matter for BCC, considered far less aggressive than melanoma? Because a true superficial BCC may be managed by topical therapies or simple excision whereas an aggressive infiltrative morphoeic BCC will require wider margins of surgical clearance with consequential differences in morbidity, expense and risk of recurrence.

Reference: Dermatology 2020;236(3):237-40
Abstract

Long-term efficacy and safety of sonidegib in patients with advanced basal cell carcinoma

Authors: Dummer R et al.

Summary: This 42-month analysis of the phase 2 BOLT study evaluated the efficacy and safety of sonidegib in patients with advanced BCC. 230 adults with no prior hedgehog pathway inhibitor therapy were randomised 1:2 to receive sonidegib 200mg or 800mg once daily for up to 42 months. The objective response rate at study end was 56% for locally advanced BCC and 8% for metastatic BCC in the 200mg group, and 46.1% and 17%, respectively, in the 800mg group. There were no new safety concerns.

Comment: BCC is the most common skin cancer in Australasia but typically has the least aggressive course of the 3 commonest skin cancers (melanoma, squamous cell carcinoma and BCC). However, a small number do indeed have aggressive pathology. Recurrent tumours and those in high-risk anatomical sites (e.g. "H" zone of the face), and neglected giant tumours have a higher risk of aggressive disease course and poor outcomes. Adequately wide (4–6mm) clinical surgical clearance margins of early primary tumours reduce this risk. Although the vast majority of BCCs are amenable to surgical clearance, more aggressive tumour subtypes require wider surgical margins of clearance and more complex, higher skilled surgical techniques (e.g. Mohs surgery) to achieve this. Comorbidities, being older and being immunosuppressed increase the risk of adverse outcomes from BCCs and complications of complex long surgical procedures. Options for alternative therapies are thus attractive and sonidegib is available in Australia and although approved for use in NZ is not yet funded. Watch this space.

Reference: Br J Dermatol 2020;182(6):1369-78
Abstract

Evaluation of the effectiveness and tolerability of mycophenolate mofetil and mycophenolic acid for the treatment of morphea

Authors: Arthur M et al.

Summary: This retrospective cohort study evaluated the effectiveness and tolerability of mycophenolate (mycophenolate mofetil or mycophenolic acid) for the treatment of morphoea. Outcomes among 77 patients (61 females; median age at disease onset, 36 years) with morphoea who were treated with mycophenolate in 1999–2018 were reviewed. The most common types of morphoea were generalised morphoea (48%), pansclerotic morphoea (16%), and linear morphoea of the trunk and/or extremities (12%). 64% of patients had severe disease. 12 patients received initial treatment with mycophenolate as monotherapy or combination therapy and the remainder received it after prior treatment was ineffective or poorly tolerated (methotrexate, systemic corticosteroids, hydroxychloroquine, and/or phototherapy). 66 of 73 patients had stable or improved disease after 3–6 months' treatment and 47 of 54 patients had stable or improved disease after 9–12 months' treatment. 35% of patients achieved disease remission. Gastrointestinal adverse effects occurred in 31% of mycophenolate recipients; cytopenia (4%) and infection (3%) occurred less frequently.

Comment: Early localised morphoea may be successfully treated with combined topical corticosteroid and calcipotriol but more extensive disease is harder to manage with topical therapies from pragmatic and disease-response perspectives. Second-line systemic treatment with methotrexate helps the majority of patients with more extensive disease. However, there is always a small group of patients with less responsive recalcitrant disease requiring other (e.g. systemic corticosteroids, hydroxychloroquine) and more prolonged therapies and for whom long-term therapeutic safety is important. In this study, mycophenolate stabilised or improved severe morphoea in 90% after 3–6 months, and achieved disease remission in 35% by 1 year of therapy. However, about one-third of patients suffered gastrointestinal adverse effects. The take-home message is that mycophenolate therapy is worth considering in patients with more extensive severe morphoea.

Reference: JAMA Dermatol 2020;156(5):521-8
Abstract

Efficacy and safety of apremilast in patients with moderate to severe plaque psoriasis of the scalp

Authors: van Voorhees AS et al.

Summary: This phase 3b study evaluated the efficacy and safety of oral apremilast for moderate to severe scalp psoriasis. 303 adults who had an inadequate response or intolerance to topical scalp psoriasis therapy were randomised to receive oral apremilast 30mg or placebo twice daily. The primary end-point was the proportion of patients who achieved Scalp Physician Global Assessment response at week 16. Secondary end-points included at least a 4-point improvement from baseline in Whole Body Itch and Scalp Itch Numeric Rating Scales (NRSs) and improvement in DLQI at week 16. Significantly more apremilast than placebo recipients achieved Scalp Physician Global Assessment (43.3% vs 13.7%), Scalp Itch NRS (47.1% vs 21.1%), and Whole Body Itch NRS (45.5% vs 22.5%) response at week 16 (all $p<0.0001$). Mean improvement in DLQI was also greater in the apremilast group (–6.7 vs –3.8; $p<0.0001$). Adverse events reported with apremilast included diarrhoea (30.5%), nausea (21.5%), headache (12.0%), and vomiting (5.5%).

Comment: Apremilast oral therapy inhibits phosphodiesterase 4, important in chronic inflammation cascades in psoriasis. It has previously been reported to be most effective in palmoplantar psoriasis. This phase 3 study shows promise for those with moderately severe scalp psoriasis. Common gastrointestinal adverse effects, headache, increased risk of depression, potential drug interactions with drugs that increase activity of hepatic cytochrome p450 enzymes, dose reduction in renal impairment, and unknown effects in pregnancy, will restrict use of apremilast to those resistant to topical scalp therapies and significant morbidity. Apremilast is available in NZ for moderately severe plaque psoriasis.

Reference: J Am Acad Dermatol 2020;83(1):96-103
Abstract

Comparison of tightly controlled dose reduction of biologics with usual care for patients with psoriasis

Authors: Atalay S et al.

Summary: This study in the Netherlands investigated whether dose reduction of biologics is noninferior to usual care in patients with stable psoriasis. 120 patients with plaque psoriasis and stable low disease activity who were receiving treatment with adalimumab, etanercept, or ustekinumab were randomised 1:1 to dose reduction or usual care. In the dose reduction group, injection intervals were gradually prolonged, leading eventually to 50% of the original dose. Median PASI scores at 12 months were 3.4 in the dose reduction group and 2.1 in the usual care group (noninferiority not demonstrated), and median DLQI scores were 1.0 and 0.0 in the respective groups (noninferiority demonstrated). 28 patients in the dose reduction group had tapered their dose successfully by 12 months. Dose reduction did not result in an increase in flares.

Comment: Psoriasis patients with more severe disease have greater morbidity and lower DLQI scores, are more recalcitrant to treatments, have higher levels of relapse and thus often require systemic therapies for a significant portion of their lives. Use of biologics in psoriasis management is considerably more expensive than preceding systemic disease-modifying agents such as methotrexate, but as time passes initial safety concerns regarding biologics are waning for the majority of patients. Simultaneously, expectations of complete skin clearance are increasing. Reducing drug doses or increasing intervals between doses is attractive for fiscal reasons (and possibly to reduce adverse effects) provided disease control continues. Interpreting double negative language is complex. This Dutch study shows dose tapering can be successfully achieved in patients with plaque psoriasis and stable low disease activity receiving treatment with adalimumab, etanercept, or ustekinumab (biologics used in NZ).

Reference: JAMA Dermatol 2020;156(4):393-400
Abstract

Rituximab is an effective treatment in patients with pemphigus vulgaris and demonstrates a steroid-sparing effect

Authors: Chen DM et al., for the French Study Group on Autoimmune Bullous Diseases

Summary: This post hoc analysis of the Ritux 3 study investigated the efficacy and safety of rituximab in patients with moderate to severe pemphigus vulgaris. 74 patients were randomised to rituximab plus 0.5 or 1.0 mg/kg/day prednisone tapered over 3 or 6 months, or 1.0 or 1.5 mg/kg/day prednisone alone tapered over 12 or 18 months. At 24 months, 90% of patients randomised to rituximab plus short-term prednisone had achieved complete remission compared with 28% of patients randomised to prednisone alone. Median total cumulative prednisone dose was 5800mg and 20,520mg in the respective groups. 34% of patients taking rituximab plus prednisone and 67% of patients taking prednisone alone had a grade 3/4 corticosteroid-related adverse event.

Comment: Prior to the advent of glucocorticosteroids, most pemphigus patients died. Mortality and morbidity are higher in those with more extensive disease, particularly involving the mucosa and in older patients. Glucocorticosteroid-treated pemphigus has a 5–15% mortality rate, 3 times higher than the background population, and is related to infection and other corticosteroid chronic adverse effects. Effective treatment to reduce or cure the disease and reduce or avoid corticosteroid use is much needed and rituximab ticks this box. Earlier treatment not only reduces morbidity but is associated with quicker disease remission, so in several international countries, rituximab is used first line. The NZ Dermatological Society is working with PHARMAC to create criteria for use of rituximab as first- and second-line treatment of pemphigus for patients in NZ who do not yet have access to funded rituximab.

Reference: Br J Dermatol 2020;182(5):1111-9
Abstract

Dupilumab treatment results in early and sustained improvements in itch in adolescents and adults with moderate to severe atopic dermatitis

Authors: Silverberg JI et al.

Summary: This analysis of four phase 3 randomised studies (SOLO 1, SOLO 2, AD ADOL, and CHRONOS) evaluated the effect of dupilumab on itch in patients with moderate to severe atopic dermatitis. Data from 1505 patients treated for up to 52 weeks in the studies were included. Adults received dupilumab 300mg every 2 weeks or placebo monotherapy (SOLO 1 and SOLO 2), with concomitant topical corticosteroids (CHRONOS). Adolescents received dupilumab 200mg or 300mg (according to bodyweight) every 2 weeks or placebo (AD ADOL). Analysis of the data showed that dupilumab caused rapid and significant improvements in daily Peak Pruritus Numerical Rating Scale scores compared with placebo (by day 2 in adults and day 5 in adolescents). At study end, dupilumab recipients had significantly greater mean percent changes in the weekly average of Peak Pruritus Numerical Rating Scale scores compared with placebo: –47.5% vs –20.5% in SOLO; –47.9% vs –19.0% in AD ADOL; and –57.3% vs –30.9% in CHRONOS.

Comment: Scratching skin can both generate and perpetuate eczema. Effective antipruritic therapy helps break this cycle as is shown in this review of 4 different studies of adolescents and adults. Effects were seen within a few days of commencing dupilumab, and had sustained benefit i.e. no tachyphylaxis out to 1 year. Crossover, longer-duration studies are now required to guide clinicians on optimal durations of therapy, expected duration and percentage of itch and disease relapse. If dupilumab could indeed positively alter the natural history of atopic dermatitis, it may be more attractive for PHARMAC to fund its use in NZ.

Reference: J Am Acad Dermatol 2020;82(6):1328-36
Abstract

Weekly adalimumab treatment decreased disease flare in hidradenitis suppurativa over 36 weeks

Authors: van der Zee HH et al.

Summary: This analysis of two phase 3 PIONEER trials examined the impact of weekly adalimumab administration on disease flares in patients with moderate to severe hidradenitis suppurativa. In the first 12 weeks of treatment, the proportion of patients who experienced a flare was significantly lower with adalimumab versus placebo (12.3% vs 35.3%; p<0.001). Adalimumab recipients also had longer time to first flare (101 vs 57 days; p<0.001) and shorter flare duration (18.9 vs 32.0 days; p=0.001). 20.2% of adalimumab recipients had a flare through 36 weeks of treatment (only 5.7% of those who achieved at least a partial clinical response to adalimumab at 12 weeks experienced a flare).

Comment: Weight loss and smoking cessation have profound beneficial effects in patients with hidradenitis suppurativa, but are extremely difficult to achieve from a physician and patient perspective. Being both uncomfortable and self-conscious with poor self-esteem hinders attempts to overcome undesirable habitual behaviours. A treatment which reliably reduces disease flares brings improved quality of life and this longer study of weekly adalimumab (out to 3 years) showed statistically significant reductions in frequency and duration of disease flares compared to placebo. Addressing lifestyle changes in this setting might provide more sustainable disease-free and drug-free intervals.

Reference: J Eur Acad Dermatol Venereol 2020;34(5):1050-6
Abstract