Dermatology Research Review™

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In this issue:

Abbreviations used in this issue:

AK = actinic keratosis;
DRESS = drug reaction with eosinophilia and systemic symptoms;
GI = gastrointestinal; **IVIG** = intravenous immunoglobulin;
NB-UVB = narrow-band **UV**B; **PUVA** = psoralen plus **UV**A;
RCM = reflectance confocal microscopy; **RCT** = randomised controlled trial;
UV = ultraviolet.

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Welcome to issue 32 of Dermatology Research Review.

A phase 2 dose-escalation RCT comparing three strengths of sirolimus gel and placebo for facial angiofibromas in the tuberous sclerosis complex begins this issue. This is followed by a randomised trial demonstrating the beneficial effects of NB-UVB (narrow-band UVB) and PUVA (psoralen plus UVA) in managing steroid-dependent, antihistamine-refractory chronic urticaria. In other RCTs included, IVIG (intravenous immunoglobulin) was found to be beneficial in the treatment of steroid-resistant bullous pemphigoid, as was gabapentin for haemodialysis patients with uraemic pruritus.

I trust you are finding these regular updates in dermatology research helpful in your everyday practice. Please don't hesitate to send your comments and suggestions.

Kind Regards,

Dr Warren Weightman

warren.weightman@researchreview.com.au

Efficacy and safety of topical sirolimus therapy for facial angiofibromas in the tuberous sclerosis complex

Authors: Wataya-Kaneda M et al.

Summary: Eighteen children and 18 adults with tuberous sclerosis complex and facial angiofibromas were randomised to receive 0.05%, 0.1% or 0.2% sirolimus gel or placebo applied twice daily to the lesions for 12 weeks in this phase 2 trial. Changes in a predefined improvement factor representing tumour size reduction and a lessening of the redness of the three target tumours at 12 weeks were significant in all active treatment groups receiving 0.2% sirolimus gel ($p<0.001$), but not in adult subgroups receiving 0.1% and 0.05% sirolimus gel. There were no significant adverse effects reported, although 36% of participants experienced mild skin dryness and 31% experienced mild skin irritation. Blood sirolimus concentrations <0.25 ng/mL were detected in 25% and 50% of the 0.1% and 0.2% sirolimus gel adult recipients, respectively, and in 25%, 50% and 100% of the 0.05%, 0.1% and 0.2% sirolimus gel paediatric recipients, respectively.

Comment: This was a well-designed trial that showed that topical 0.2% sirolimus was the most effective concentration to treat facial angiofibromas, and when all patients were compared there was a significant improvement. Topical sirolimus was more effective in reducing redness than tumour size. The lower concentrations were not effective in the adult population but were effective in the paediatric population, indicating that children are more responsive and may benefit with lower concentrations. Blood sirolimus levels were increased in the 0.1% and 0.2% groups and in the childhood groups. This is due to thinner skin in children but would also explain the increased response to all concentrations in children. However, blood sirolimus concentrations for topical treatment (<0.25 ng/mL) compare with trough concentrations of 5–15 ng/mL with oral treatment, so are not likely to cause significant problems. Dry and irritated skin occurred in all groups including placebo but was increased in the 0.2% concentration group indicating that sirolimus may in part be the culprit. The earlier the patient is treated, the better the response. There was no long-term follow-up, so it is not known whether retreatment is needed.

Reference: JAMA Dermatol 2017;153(1):39–48

Abstract

Phototherapy using narrowband ultraviolet B and psoralen plus ultraviolet A is beneficial in steroid-dependent antihistamine-refractory chronic urticaria

Authors: Bishnoi A et al.

Summary: Fifty patients with steroid-dependent, antihistamine-refractory chronic urticaria were randomised to receive PUVA or NB-UVB for 90 days, and followed for a further 90 days. Both the PUVA and NB-UVB treatments led to progressive reductions in urticaria activity mean scores from 4.9 to 1.9 and from 5.0 to 1.4, respectively, by day 90, and to 1.5 and 1.4 by day 180; similarly, outcome scoring scale scores progressively increased from 1.6 to 3.9 and from 1.3 to 4.0, respectively, by day 90 and they remained at these values at day 180. NB-UVB was associated with significantly superior improvements compared with PUVA at different timepoints. Adverse events were minimal with no treatment discontinuations.

Comment: NB-UVB three times weekly for 90 days is an attractive option for patients with chronic urticaria. The urticaria was severe as it was steroid-dependent and refractory to antihistamines. PUVA was also effective, although NB-UVB more so and PUVA had more side effects. The benefit was maintained 90 days after ceasing, which is an added bonus, although the natural history of urticaria cannot be predicted, and some of these patients may have improved without treatment, although the average duration of disease was more than 3 years. The main failing of the study was there was no placebo group. Both NB-UVB and PUVA significantly converted positive autologous serum skin tests and autologous plasma skin tests to negative post-treatment, and PUVA also significantly reduced serum IgE levels. The degree of response was comparable with pivotal trials with omalizumab. There was only one relapse in the NB-UVB group. NB-UVB, if practicable, should be the next treatment choice after failure of antihistamines or short courses of oral steroids.

Reference: Br J Dermatol 2017;176(1):62–70

Abstract

Statin use and the risk of herpes zoster

Authors: Matthews A et al.

Summary: These researchers sought to quantify the effect of statin exposure on herpes zoster risk using data from 144,959 adults with an incident diagnosis of herpes zoster from the UK Clinical Research Practice Datalink each matched to ≤4 control subjects. Compared with statin nonexposure, statin exposure was associated with a significantly greater likelihood of herpes zoster (adjusted odds ratio 1.13 [95% CI 1.11–1.15]), with evidence of a dose-dependent effect among patients who were currently or had recently been receiving statin treatment ($p<0.001$ for trend), and attenuation of the increased risk among prior statin users as the time since last exposure increased ($p<0.001$ for trend).

Comment: The results from this large population-based study suggest that there is an association between statins and herpes zoster, especially as the risk increased with increased dose and lessened after the statin was ceased. Other studies have also supported these findings. The mechanisms by which statins increase the risk of herpes zoster are not established, but they have immunomodulating properties that can cause impairment of T-cell activation and proliferation. There should be increased effort to recommend herpes zoster vaccine in patients who start or have been on a statin, especially in those at increased risk for herpes zoster.

Reference: Br J Dermatol 2016;175(6):1183–94
Abstract

Overlap between maculopapular exanthema and drug reaction with eosinophilia and systemic symptoms among cutaneous adverse drug reactions in a dermatology ward

Authors: Pinto Gouveia M et al.

Summary: Clinical and laboratory data were reported for 132 inpatients with cutaneous adverse drug reactions, including 37 patients with DRESS (drug reaction with eosinophilia and systemic symptoms), 28 with maculopapular exanthema, 34 with maculopapular exanthema overlapping with DRESS and 33 with other patterns. Allopurinol was associated with DRESS and overlapping maculopapular exanthema/DRESS in 40.5% and 29.4% of cases, respectively, and antimicrobials were associated with maculopapular exanthema in 35.7%. The latency period in overlapping maculopapular exanthema/DRESS was longer than in maculopapular exanthema but shorter than in DRESS cases. Overlapping maculopapular exanthema/DRESS cases had similar hospitalisation times to DRESS cases, but shorter durations of therapy and follow-up. Exanthema/erythroderma was associated with facial oedema in 73.5% of overlapping maculopapular exanthema/DRESS cases and 89.2% of DRESS cases, but only 42.0% of maculopapular exanthema cases. Compared with DRESS cases, overlapping maculopapular exanthema/DRESS cases had similar but milder keratinocyte vacuolisation and perivascular and interstitial infiltration of lymphocytes, eosinophils and neutrophils, with less interface dermatitis, exocytosis and spongiosis, on histopathology. Liver involvement and eosinophilia were each seen in 78.4% of DRESS cases, but in only 64.7% and 11.8%, respectively, of overlapping maculopapular exanthema/DRESS cases.

Comment: This study highlights the similarities between maculopapular exanthemata and DRESS syndrome. Drug causes were similar and included allopurinol and antibiotics but with a reduced latency period and shorter duration of the reaction. When present, organ involvement found in the overlapping group had severity similar to that seen in DRESS. Maculopapular exanthemata may also be the initial presentation of a more serious reaction, including Stevens-Johnson syndrome/toxic epidermal necrolysis, DRESS or acute generalised exanthematous pustulosis. Progression of maculopapular exanthemata can occur and increasing severity may warrant treatment with oral steroids. Prednisolone was given to all cases of maculopapular exanthemata overlap in this study, but the treatment courses were shorter in this group compared with DRESS. Patients who do not fulfil the criteria of DRESS but have some of the features should be considered as a milder form that should be investigated and treated along similar lines to DRESS.

Reference: Br J Dermatol 2016;175(6):1274–83
Abstract

A randomized double-blind trial of intravenous immunoglobulin for bullous pemphigoid

Authors: Amagai M et al., for the Bullous Pemphigoid Study Group

Summary: Patients with steroid-resistant bullous pemphigoid (n=56) were randomised to receive IVIG 400 mg/kg/day or placebo for 5 days in this research. Compared with placebo, IVIG was associated with a nonsignificant 12.5-point lower disease activity score on day 15 (primary endpoint; $p=0.089$), with significantly lower scores during the observation period ($p=0.041$). The disease activity score on day 15 was also significantly lower in the IVIG group among participants with baseline disease activity score ≥40 ($p=0.046$). There was no significant between-group difference for anti-BP180 antibody titres.

Comment: The primary endpoint was disease activity score on day 15, which did not significantly differ between the IVIG and placebo groups, although it was lower in the IVIG group. There was a significant difference when a *post hoc* analysis was done of covariance and also a significant difference when only the severe cases were assessed. The anti-BP180 titre was lower in the IVIG group but not significantly different to placebo. The benefit of IVIG remains unproven on these results and further trials are needed. The endpoint at day 15 may have been too soon to get a significant benefit and it may be preferable to have monthly courses of IVIG for 3–6 months rather than a single course to improve response. IVIG, though, with a good safety profile remains an option in patients with difficult and poorly responsive bullous pemphigoid.

Reference: J Dermatol Sci 2017;85(2):77–84
Abstract

Rosacea and gastrointestinal disorders

Authors: Egeberg A et al.

Summary: This population-based cohort study explored associations between rosacea and coeliac disease, Crohn's disease, ulcerative colitis, *Helicobacter pylori* infection, small intestinal bacterial overgrowth and irritable bowel syndrome using data from 49,475 patients with rosacea and 4,312,213 controls from the general population. Compared with controls, patients with rosacea were more likely to have coeliac disease (adjusted hazard ratio 1.46 [CI 1.11–1.93]), Crohn's disease (1.45 [1.19–1.77]), ulcerative colitis (1.19 [1.02–1.39]) and irritable bowel syndrome (1.34 [1.19–1.50]), but not *H. pylori* infection (1.04 [0.96–1.13]) or small intestinal bacterial overgrowth (0.71 [0.18–1.86]).

Comment: Rosacea was significantly associated with coeliac disease, Crohn's disease, ulcerative colitis, irritable bowel syndrome and, in some, *H. pylori* infection, and may serve as a diagnostic marker of unrecognised GI disease. These results have been supported in another large UK population-based study that showed that more patients with rosacea than controls suffered from inflammatory bowel disease, with high disease activity around the time of the first rosacea diagnosis. The mechanism is unknown, but there are shared genetic loci and a common infectious aetiology is also possible. Rosacea was diagnosed by either a documented past history of rosacea or two prescriptions of topical metronidazole, so some patients with rosacea may have been missed. It is worthwhile asking patients with rosacea about GI tract symptoms and investigating accordingly.

Reference: Br J Dermatol 2017;176(1):100–6
Abstract

What's new in atopic eczema? An analysis of systematic reviews published in 2014. Part 2. Treatment and prevention

Authors: Lloyd-Lavery A et al.

Summary: This review, which is part of a series of annual updates on the evidence base for atopic eczema, highlighted key findings from 12 systematic reviews from 2014 focussing on treatment and prevention. The authors noted that while phototherapy and a variety of systemic medications are commonly used to treat atopic eczema, many have not been robustly assessed in head-to-head RCTs. Atopic eczema severity and quality of life may also be improved by educational interventions. Although pre- and postnatal probiotic intake may help prevent atopic eczema, little evidence exists to support a role for treatment. Allergen avoidance was associated with no benefit for preventing atopic eczema, but immunotherapies for treating atopic eczema-associated aeroallergen sensitivity require further evaluation. Evidence for vitamin D supplementation for treating atopic eczema is insufficient.

Comment: This article only summarised the reviews from 2014 but shows the difficulty in effectively treating atopic eczema. Although cyclosporin, azathioprine and methotrexate are commonly used to treat atopic eczema, evidence supporting their relative efficacy is limited. There was insufficient evidence to support use of vitamin D supplements, alpine climate treatment or probiotics for the treatment of atopic eczema. Sublingual immunotherapy for patients with atopic eczema and aeroallergen sensitivity may be beneficial, but requires further evaluation and are not commonly available. The use of probiotics prenatally and continued postnatally may help prevent atopic eczema. There is currently no evidence for the role of allergen avoidance in the prevention of atopic eczema. The treatment options for severe atopic eczema still remain limited, with cyclosporin the best option based on current data, but its long-term use is limited by its side effects. There is some evidence to support educational interventions, phototherapy and topical sodium cromoglycate cutaneous emulsion. There are newer treatment options being studied, including IL-4 and IL-13 inhibitors and phosphodiesterase inhibitors, so further options will be available in the future.

Reference: Clin Exp Dermatol 2017;42(1):3–7
Abstract

Histological examination confirms clinical clearance of actinic keratoses following treatment with ingenol mebutate 0.05% gel

Authors: Ulrich M et al.

Summary: Adults with AKs (actinic keratoses) within a 25cm^2 contiguous area on the trunk and extremities (n=108) were treated with 0.05% ingenol mebutate gel for 2 consecutive days in this research; a subset of participants had a single AK randomly preselected on day 1 for clinical and histological evaluation at week 8 and for RCM (reflectance confocal microscopy). The observed agreement rate for clinical and histological assessments of single AK clearance was 81.9%, and the positive predictive value of a clinical assessment of clearance was 87%. The two pathologists had an agreement value of 88%. The common composite 8-week complete clearance rate was 41%, with respective observed agreement rates between RCM and pathologist 1 and 2 assessments of clearance of 72.9% and 81.4%. Thirty patients experienced 38 adverse events, with the most common treatment-related adverse event inside the treatment area being application-site pain (four participants).

Comment: Clinical clearance has been used as an endpoint in most trials for Picato®, but this study shows that histological clearance is achieved too and is associated with both clinical and RCM clearance. RCM is a good surrogate for tissue diagnosis, but this modality will have to await further technological advancements (reduction in size and cost) before it can be utilised in the general clinical setting. Five to nine discrete AKs within a contiguous 25cm^2 treatment area on the trunk and extremities, except the back of the hand, were selected and one was biopsied at week 8. The result may have been different if all AKs were biopsied, but with the correlation with RCM the results are likely to be accurate. The complete clearance rate was 41%, which is consistent with the results from other studies. If there is clinical clearance of AKs on the extremities or trunk following 0.05% ingenol mebutate gel, there is histological resolution of lesions, and dermatologists can be assured that the AKs have cleared.

Reference: Br J Dermatol 2017;176(1):71–80
Abstract

A popular myth – low-histamine diet improves chronic spontaneous urticaria – fact or fiction?

Authors: Wagner N et al.

Summary: Fifty-six patients with chronic spontaneous urticaria accompanied by GI symptoms consumed a low-histamine diet for ≥3 weeks in this research. Benefits were recorded for 75% of the participants, with 61% achieving an improvement in urticaria activity score of ≥3 points (primary endpoint) and an overall reduction from 9.05 to 4.23 points (p=0.004). Moreover, participants from a strongly affected subgroup had a reduction in urticaria activity score of 8.59 points (p<0.001). Activity of diamine oxidase, a histamine-degrading enzyme, remained stable.

Comment: A low-histamine diet looks to be useful in chronic urticaria. Although there was a significant reduction in the urticaria score, the average reduction was from 9.05 to 4.23 points, so disease activity persisted in most patients. Patients were allowed to take antihistamines when needed, and 39% reduced their intake with almost half of these stopping altogether, although 14% increased their intake of antihistamines. The lack of a control group in a disease that may show improvement over time is a failing of this study, but a low-histamine diet is a safe and cost-effective treatment that could be used in addition to other measures.

Reference: J Eur Acad Dermatol Venereol; Published online Oct 7, 2016
Abstract

Gabapentin: a promising therapy for uremic pruritus in hemodialysis patients

Authors: Nofal E et al.

Summary: Haemodialysis patients with uraemic pruritus were randomised to receive gabapentin 100mg titrated up to a maximum of 300mg (n=27) or placebo (n=27) after each haemodialysis session for 1 month. The response rate was greater in the gabapentin arm than the placebo arm (88.9% vs. 22.2% [p<0.001]). The low gabapentin dosage of 100mg thrice weekly was used significantly more frequently than other dosages (p<0.0001). Adverse events were mild and tolerated.

Comment: Currently the most effective treatment for pruritus of renal failure is phototherapy, especially NB-UVB. As many of these haemodialysis patients may be candidates for a renal transplant and subsequent immunosuppressive therapy, there is concern of an increased risk of skin cancer, especially with prolonged or frequent courses. There was a significant benefit in 88.9% of patients after gabapentin, which makes it a suitable first choice for therapy, with phototherapy reserved for resistant cases.

Reference: J Dermatolog Treat 2016;27(6):515–5
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.

