Dermatology Research Review™

Making Education Easy

Issue 113 - 2024

In this issue:

- Botox vs. microwave thermolysis for primary axillary hyperhidrosis
- Botox for rosacea: positive impact on QOL and self-esteem
- Nonablative fractional laser vs. minoxidil for androgenetic alopecia
- Cysteamine-nicotinamide for melasma
- Topical triamcinolone vs. sulfur cream for hand eczema
- CV risk with TNF inhibitors vs. conventional therapies for immune-mediated inflammatory diseases
- Excision margins for head/neck melanoma *in situ*
- HLAs and sulfamethoxazole-cotrimoxazole-induced severe cutaneous adverse reactions
- Topical statins as antifungals
- Biologics for pityriasis rubra pilaris

Abbreviations used in this issue:

CV = cardiovascular;
DRESS = drug reaction with eosinophilia and systemic symptoms;
HLA = human leucocyte antigen; **IL** = interleukin; **QOL** = quality of life;
SJS/TEN = Stevens-Johnson syndrome/toxic epidermal necrolysis;
TNF = tumour necrosis factor.

Welcome to issue 113 of Dermatology Research Review.

The issue begins with two papers investigating botulinum toxin A (Botox®), with the first comparing it with microwave thermolysis for the treatment of primary axillary hyperhidrosis, and the second reporting positive impacts on QOL and self esteem when used to treat rosacea. There is also research suggesting a lower rate of adverse CV events when TNF inhibitors are used to treat immune-mediated inflammatory diseases compared with use of conventional systemic nonbiologics. Other included research has reported on associations of HLA genotypes with severe cutaneous adverse reactions after sulfamethoxazole-cotrimoxazole exposure. The issue concludes with a review of biologics as a potentially favourable treatment option for patients with pityriasis rubra pilaris.

Thank you for your valuable feedback on our reviews. We look forward to more of your input.

Kind Regards,

Dr Warren Weightman
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Botulinum toxin A versus microwave thermolysis for primary axillary hyperhidrosis

Authors: Grove GL et al.

Summary: Thirty patients with axillary hyperhidrosis had axillae treated with botulinum toxin A or microwave thermolysis in a randomised contralateral manner in this trial. Both treatments were associated with significant objective reductions in sweat, with a greater reduction seen with botulinum toxin A at 6 months but no significant difference at 1 year; there was no significant difference between treatments at either timepoint for subjective sweat assessments. Both treatments were also associated with significant reductions in odour, with a significant difference favouring microwave thermolysis at 1 year but not at 6 months. Microwave thermolysis was also associated with significant visible hair reduction at 1 year, whereas botulinum toxin A was not. Around three-quarters of participants reported a preference for microwave thermolysis.

Comment: Botulinum toxin A for many years has been the standard of care for axillary hyperhidrosis after failed topical treatment, but is now being challenged by physical modalities such as microwave thermolysis and radiofrequency ablation. This article compared botulinum toxin A and microwave thermolysis using each modality on either side of each patient. At 1 year, there was no difference in the reduction of sweating, although there was more odour in the botulinum toxin A group. Hair reduction only occurred with microwave thermolysis, and may be a beneficial side effect. Microwave thermolysis requires two treatments and causes irreversible damage to the sweat glands with likely permanent reduction in sweating compared with Botox where the benefit wears off over 4–9 months. Procedural pain was worse in the botulinum toxin A group with a median value of 4.5/10 compared with microwave thermolysis of 3, but postprocedural pain on day 2 was light to moderate with microwave thermolysis but no pain in the botulinum toxin A group. Most patients (76%) showed a preference for microwave thermolysis. This article provides a good comparison of the risks and benefits of the two treatments and will inform patients as to what choice to make, but a permanent treatment may be the preferred option in many patients.

Reference: JAAD Int 2024;15:91–9
Abstract

Dermatology Research Review™

Independent commentary by Dr Warren Weightman

Dr Warren Weightman has practiced Dermatology for more than 30 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 keratoases 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.

Efficacy and safety of botulinum toxin for rosacea with positive impact on quality of life and self-esteem

Authors: Takahashi KH et al.

Summary: Thirty-three patients with rosacea treated with standard therapeutic options were administered botulinum toxin A injections on days 1 and 14 in this study. Improvements in the clinical signs of rosacea were recorded for 94% of the participants after receiving the botulinum toxin A injections. The participants also had significant improvements in QOL scores and significant increases in self-esteem scores. Adverse events were infrequent.

Comment: Erythema in rosacea remains difficult to treat, and two botulinum toxin A injections one fortnight apart showed improvement in QOL and self-esteem. In this study, 'micro-Botox' was used, where botulinum toxin A is hyperdiluted compared with the standard dilution, and microboluses given. This study had low numbers, no controls (although this would be difficult to do) and did not measure improvement in erythema directly, so the benefits are uncertain. Botulinum toxin A is expensive and needs to be repeated, but some patients with erythema and flushing may benefit from it. Further comparison studies are needed against laser and IPL (intense pulsed light) therapy.

Reference: Int J Dermatol 2024;63:590–6
Abstract

Investigator-blinded, controlled, and randomized comparative study on 1565nm non-ablative fractional laser versus 5% minoxidil for treatment of androgenetic alopecia

Authors: Qu H et al.

Summary: Thirty patients with androgenetic alopecia were randomised to four sessions of laser therapy (1565nm nonablative fractional laser 10mJ, 250 spots/cm^2) at 2-week intervals or to receive 1mL of topical 5% minoxidil solution twice a day. Both treatments were associated with significant increases from baseline in hair density and diameter at week 10, but there were significantly greater improvements in total hair number and density, terminal hair number and density, number of hair follicle units and average hair number/number of hair follicle units with the laser therapy than with minoxidil.

Comment: Four treatments of 1565nm nonablative fractional laser at 2-week intervals was more effective than 5% minoxidil lotion in treating androgenic alopecia. The potential mechanisms include increase in local blood flow, and stimulation of growth factors and cytokines. Most patients complained of mild-to-moderate, but tolerable, pain during laser treatment, but the pain resolved within a few hours. Local anaesthesia and analgesics were not required before or during laser treatment. The initial hair loss often seen with topical minoxidil may last up to 4 months, so 10 weeks is too early for a valid comparison and would be better done at 6 months. Topical minoxidil is the least effective treatment for androgenic alopecia, so longer comparison trials with oral anti-androgens are needed.

Reference: J Cosmet Dermatol 2024;23:1638–44
Abstract

Combination of 5% cysteamine and 4% nicotinamide in melasma

Authors: Crocco EI et al.

Summary: Thirty-five patients with melasma were treated with a combination cream of 5% cysteamine and 4% nicotinamide for 60, 120 and 180 min in the first, second and third months, respectively; 35 of 53 enrolled participants completed the study. The treatment was associated with significant reductions in modified MASI (Melasma Area and Severity Index) and MelasQoL scores, significant improvements in brightness, luminosity, homogeneity and spot intensity, and smaller spots and improved homogeneity on photographic and colorimetric analyses.

Comment: Alternative treatments are needed for melasma in patients who have failed or need a break from hydroquinone preparations. Cysteamine inhibits tyrosinase, and has long been known to be a potent depigmenting agent but has an offensive odour, and only in recent years has an odourless formulation been developed. Nicotinamide has anti-inflammatory properties and suppresses the transfer of melanosomes to keratinocytes. Previous studies have shown erythema and burning occurred in 20–43% of patients and was severe in 18–20%. Most side effects were transient and mostly cleared after the first week of treatment, and most resolved after the first month. Prior studies of 5% cysteamine cream showed a reduction of 51% to 58% in three studies and 21% and 38% in two other studies. One study compared 5% cysteamine cream with a modified Kligman's formula, and 5% cysteamine cream performed slightly better, but the results weren't significant. This trial showed a 58% reduction in MASI score. The 5% cysteamine and 4% nicotinamide cream is a worthwhile depigmenting cream, as it is safe, effective and tolerable in most patients.

Reference: J Cosmet Dermatol 2024;23:1703–12
Abstract

Comparison of the effect of topical triamcinolone 0.1% cream with sulfur 2.0% cream in the treatment of patients with hand eczema

Authors: Asilian A et al.

Summary: Seventy patients with bilateral hand eczema were treated with topical 0.1% triamcinolone or 2.0% sulfur applied to randomly allocated contralateral hands every 12 hours for 4 weeks. Both treatments resulted in significant reductions in Hand Eczema Severity Index score, itching, dryness, burning sensation and erythema, with all therapeutic effects lasting for ≥4 weeks after treatment cessation.

Comment: Topical sulfur is an old treatment used for dermatitis, and has antifungal, antibacterial, keratolytic and anti-inflammatory properties with few side effects. Sulfur cream was significantly more effective at the end of 4 weeks of treatment, but at the end of follow-up 4 weeks later, there was no significant difference. Most of the improvement at follow-up was maintained, with no difference between the two groups. Patient satisfaction with both treatments was the same. The sulfur cream also was effective in reducing itching, dryness and erythema. There were no side effects with the sulfur cream. From this study, it is worthwhile using topical sulfur as a cost-effective, steroid-sparing cream that is suitable for long-term use in chronic hand eczema.

Reference: J Cosmet Dermatol 2024;23:1753–7
Abstract

Reducing cardiovascular risk in immune-mediated inflammatory diseases: tumour necrosis factor inhibitors compared to conventional therapies

Authors: Galajda NÁ et al.

Summary: This systematic review with meta-analysis included 56 studies (randomised controlled, cohort and case-control studies) reporting on the incidence of CV events with TNF inhibitors versus conventional therapies in the treatment of immune-mediated inflammatory diseases; 29 articles were eligible for the meta-analysis, with the remaining systematically reviewed, and most were observational, contributing to overall high heterogeneity. Compared with conventional systemic nonbiologics, TNF inhibitors were associated with a significantly reduced risk of major adverse CV events across all immune-mediated inflammatory diseases (incidence rate ratio 0.77 [95% CI 0.67–0.88]) and for patients with psoriasis/psoriatic arthritis (0.79 [0.64–0.98]).

Comment: This large meta-analysis of observational studies showed that TNF inhibitors reduced the risk of CV events compared with conventional systemic nonbiologics. Whether there is an absolute risk of reduction in cardiac risk is still not proven. Large meta-analyses of observational studies suggested that methotrexate reduced cardiac risk in patients with rheumatoid arthritis and psoriasis, but a large-scale randomised placebo-controlled trial of methotrexate in high-risk patients showed no benefit of methotrexate on CV events. A large, randomised placebo-controlled study of TNF inhibitors would be needed to confirm an absolute risk, but is unlikely to be done. The new biologics in psoriasis, including IL-17 and IL-23 inhibitors, weren't assessed, so it's difficult to extrapolate the results to these biologics.

Reference: J Eur Acad Dermatol Venereol 2024;38:1070–88
Abstract

Excision margins for melanoma in situ on the head and neck

Authors: Tate JA et al.

Summary: This 10-year retrospective review of Mohs micrographic procedures performed at a single centre sought to define excision margins required for optimal cure of 807 primary and 39 recurrent head and neck melanomas *in situ*, and investigate factors for achieving tumour clearance when >5mm margins were required. When 5mm margins were used, 62% of melanomas were cleared, and 15mm margins were required to achieve 97% clearance, with a significant difference in clearance rates between margin thresholds. There were significant correlations between both tumour location on the cheek and larger preoperative size with a >5mm margin being needed to achieve tumour clearance.

Comment: Mohs surgery detects accurately the lateral spread of tumour cells, and this article indicated that only 62% of melanomas *in situ* were cleared with 5mm margins, 90% with 10mm margins, and 15mm margins were needed to achieve 97% clearance. Their recommendation is that at least 10mm margins are needed for head and neck *in situ* melanomas, especially for large lesions. On these results, it could be argued that all melanomas *in situ* on the face should all be excised by Mohs. Frozen sections with H and E and melanoma antigen staining are sufficient. If Mohs surgery is not available, this article provides useful guidance for determining excision margins.

Reference: J Am Acad Dermatol 2024;90:1226–31
Abstract

Human leukocyte antigens and sulfamethoxazole/cotrimoxazole-induced severe cutaneous adverse reactions

Authors: Wu P-C et al.

Summary: This was a systematic review and meta-analysis of six studies in 322 patients who had experienced severe cutaneous adverse reactions following sulfamethoxazole or cotrimoxazole exposure, including 236 with SJS/TEN and 86 with DRESS, along with 8448 healthy controls and 229 tolerant controls. Compared with tolerant controls, the risk of severe cutaneous adverse reactions was greater for patients expressing the *HLA-A*11:01, HLA-B*13:01, HLA-B*15:02, HLA-B*38:02* and *HLA-C*08:01* genotypes (respective odds ratios 2.10 [95% CI 1.11–4.00], 5.96 [1.58–22.56], 2.23 [1.20–4.14], 3.47 [1.42–8.48] and 2.63 [1.07–6.44]). The *HLA-B*15:02* and *HLA-B*38:02* genotypes were significantly associated with SJS/TEN (respective odds ratios 3.01 [95% CI 1.56–5.80] and 5.13 [1.96–13.47]), and the *HLA-A*68:01, HLA-B*13:01* and *HLA-B*39:01* genotypes were significantly associated with DRESS (12.86 [1.09–151.34], 23.09 [3.31–161.00] and 4.56 [1.31–15.82]).

Comment: Severe cutaneous adverse reactions are more likely in certain HLA types, and the most well-known associations are *HLA-B*15:02* and *HLA-A*31:01* with carbamazepine-induced SJS/TEN in the Han Chinese population. This article has shown that several HLA genotypes are associated with severe cutaneous adverse reactions to sulfamethoxazole and cotrimoxazole, when used in combination. It is believed that the sulfamethoxazole component is the more likely allergen, but not in all cases. This review showed that in patients taking sulfamethoxazole-cotrimoxazole, *HLA-B*15:02* and *HLA-B*38:02* genotypes were significantly associated with SJS/TEN, while the *HLA-A*68:01* and *HLA-B*39:01* genotypes were associated with DRESS, and the *HLA-B*13:01* allele showed associations with both SJS/TEN and DRESS. This article looked at different populations, and *HLA-B*15:02* was associated with higher risks among Han Chinese, Korean, Malaysian and Thai populations while *HLA-A*31:01* was seen more in European, Korean and Japanese individuals. Dapsone, another well-known sulfone drug, has also been associated with severe cutaneous adverse reactions in patients carrying the *HLA-B*13:01* genotype. This article helps to guide the need for HLA testing when starting sulfamethoxazole-cotrimoxazole in different populations.

Reference: JAMA Dermatol 2024;160:525–34
Abstract

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Topical statins as antifungals

Authors: Khoury DM et al.

Summary: The authors of this review discussed *in vitro* studies reporting that systemic statins confer antimycotic effects against many fungal species, regardless of whether they are used as monotherapy or combined with other typical antifungal agents. They also discuss the shift towards the use of topical rather than systemic statins due to drug-drug interactions and well-known side effects with the latter. They also note the potential benefits for patients receiving systemic statins for dyslipidaemia who develop a topical fungal infection, but note that initiation of systemic statins for topical fungal infections only is not indicated. The authors also reviewed the different formulations that have been studied to enhance the efficacy of topical statins, as well as the differential effects of topical statins on different dermatological fungal infections.

Comment: This is an interesting article showing that statins have activity against a range of fungi including tinea, *Candida, Aspergillus* and mucormycosis, with the different statins having different ranges of actions. Many fungi are dependent on HMG-CoA reductase for the synthesis of their cell walls, and since human HMG-CoA reductase enzymes have 76% homology to fungi, statins can have an antifungal effect. There are drug interactions between statins and antifungals that use the cytochrome P450 pathway, including itraconazole and fluconazole but not terbinafine, so using both together would be relatively contraindicated, but used alone oral statins, may have some benefit. Topical statin creams may be helpful and different formulations have been looked at. With increasing resistance, it will be useful to have other alternative antifungal treatments.

Reference: Int J Dermatol 2024;63:747–53
Abstract

Biologics for treatment of pityriasis rubra pilaris

Authors: Chandy RJ et al.

Summary: These authors compared biologics for efficacy in pityriasis rubra pilaris and discussed the benefits and risks when choosing a biologic for patients. They mention that TNFα inhibitors have been reported to be effective in patients with pityriasis rubra pilaris, but more recently, anti-IL-17 and anti-IL-23 therapies (e.g. ustekinumab, secukinumab, ixekizumab) have also emerged as new options that have provided mean improvements in Area and Severity Index scores, as well as changes in the severity of erythema, scaling and thickness of pityriasis rubra pilaris lesions. Initial findings from clinical trials also suggest that secukinumab and ixekizumab are promising for achieving remission.

Comment: The pathogenesis of pityriasis rubra pilaris is not fully understood, but the IL-23/Th17 axis may play an important role. TNFα, IL-17 and IL-23 inhibitors including ustekinumab have all shown promise in pityriasis rubra pilaris, but as patient numbers are small and there have been no comparison trials, it is difficult to know if one is more effective than the other. About 80% of patients with the classical type go into spontaneous remission over 3 years, making it more difficult to assess the benefit of any treatment. It is reasonable to start a biologic treatment after failure of either acitretin or methotrexate.

Reference: J Cutan Med Surg 2024;28:269–75
Abstract

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