Dermatology Research Review™

Making Education Easy

Issue 30 - 2016

In this issue:

Abbreviations used in this issue:

ADD/ADHD = attention deficit (hyperactivity) disorder; **OR** = odds ratio; **QOL** = quality of life.

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Welcome to issue 30 of Dermatology Research Review.

The last issue for this year begins with preliminary research evaluating genetically corrected autologous epidermal grafts for treating recessive dystrophic epidermolysis bullosa. Two papers focus on infantile haemangioma, one describing sequelae and their risk factors following regression, and the other reporting superiority of topical timolol over ultrapotent corticosteroids for their treatment. Data from US population-based surveys confirmed that AD is associated with ADD/ADHD (attention deficit [hyperactivity] disorder) in adults as well as children. We end 2016 with promising results from a study of alitretinoin for the treatment of severe chronic hand eczema.

I hope you have enjoyed your copies of Dermatology Research Review this year. I look forward to bringing you more dermatology-related research in 2017.

Kind Regards,

Dr Warren Weightman

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Safety and wound outcomes following genetically corrected autologous epidermal grafts in patients with recessive dystrophic epidermolysis bullosa

Authors: Siprashvili Z et al.

Summary: This phase 1 clinical trial evaluated genetically corrected autologous epidermal grafts in four men with recessive dystrophic epidermolysis bullosa with an estimated affected body surface area of 4–30%. A total of 24 type VII collagen gene-corrected grafts (~35 cm^2) were transplanted onto six wounds for each participant. Tolerability of the grafts was good with no serious adverse events. Immunofluorescence microscopy revealed type VII collagen expression at the dermal-epidermal junction on the graft sites in 90%, 66% and 42% of biopsy samples at 3, 6 and 12 months, respectively, including correct type VII collagen localisation to anchoring fibrils. Wounds with recombinant type VII collagen graft sites exhibited ≥75% healing at 3, 6 and 12 months (87%, 67% and 50% of evaluable wound sites), respectively, compared with baseline wound sites.

Comment: This was a preliminary study of four patients and a follow-up of 12 months, but the results are encouraging and provide hope that improvements on this technique will lead to better long-term outcomes for patients with epidermolysis bullosa. These results are a significant improvement compared with previous studies of nongenetically modified allogenic keratinocyte grafts where only 22% showed healing at 18 weeks. Although the benefit was lost over 12 months, 50% showed better healing at 12 months compared with baseline wounds. If there can be further advances with this technique and other gene defects than type VII collagen replaced, this may represent a major breakthrough in the treatment of epidermolysis bullosa.

Reference: JAMA 2016;316(17):1808–17

Abstract

Clinical significance of serum soluble CD molecules to assess disease activity in vitiligo

Authors: Speeckaert R et al.

Summary: The value of sCD27 (soluble CD27), sCD25 and sCD40L as biomarkers of disease activity and progression in vitiligo was explored in this cross-sectional, prospective study of 83 patients with nonsegmental vitiligo and 10 with segmental vitiligo. Both sCD27 and sCD25 levels were significantly associated with active disease, and sCD27, but not sCD25, level was significantly associated with disease progression after 3–6 months. Correlations were also seen between sCD25 level and interferon-γ (r=0.562 [p=0.005]), IL-10 (r=0.453 [p=0.03]) and sCD27 secretion (r=0.549 [p=0.007]) in additional *in vitro* experiments. There were no associations detected for sCD40L levels.

Comment: The difficulty with vitiligo is that active inflammation is not seen clinically and a benefit can only be seen when melanin is produced. A biomarker would be valuable in deciding the activity of vitiligo and guide appropriate treatment. This was a large trial that enabled subset analyses of disease activity and treatment response. sCD25 levels were significantly lower in patients treated with topical immunosuppressants and sCD27 levels were lower in patients with recent pigmentation, indicating their usefulness in monitoring response to treatment. Only a higher level of sCD27 was associated with disease progression, which is an indicator of response to treatment. It would be beneficial to know likely response in the early months of treatment when little is seen clinically and whether to persist with a treatment or change to an alternative. sCD25 and sCD27 are not specific to vitiligo and are elevated in other inflammatory conditions, so their use may be limited to patients with no other inflammatory conditions. Other chemokines CXCL9 and CXCL10 have also been shown to reflect disease activity and treatment response in other studies of vitiligo, and using several of these inflammatory markers could optimise treatment decisions.

Reference: JAMA Dermatol 2016;152(11):1194–200
Abstract

Risk factors for degree and type of sequelae after involution of untreated hemangiomas of infancy

Authors: Baselga E et al.

Summary: These authors reported sequelae of infantile haemangiomas after natural involution, and characteristics for their prediction, for a retrospective cohort of 184 infantile haemangiomas that had not been treated systemically and with follow-up photographic images until regression. Sequelae occurred in 54.9% of the haemangiomas, with the most common after involution being telangiectasias (84.3%), fibrofatty tissue (47.1%) and anetodermic skin (32.6%). The haemangiomas completed involution at an average age of 3.5 years. Sequelae were more common with superficial versus deep and combined haemangiomas (respective ORs 1.6 [0.6–3.8] and 3.3 [1.7–6.3]) and for deep versus combined haemangiomas (2.1 [0.9–5.1]). More severe sequelae were seen with haemangiomas with a step or abrupt versus smooth border, and with superficial haemangiomas with a cobblestone appearance or rough surface versus a smooth surface (p<0.001 for both). A multivariate analysis revealed more sequelae with combined haemangiomas with a superficial component and a step border.

Comment: Propranolol has revolutionised treatment for infantile haemangiomas with complete regression without sequelae in 60% of cases. Systemic corticosteroids had a poor risk-to-benefit ratio and many infantile haemangiomas were left untreated. Indications for treating infantile haemangiomas have now changed to include those at high risk of permanent sequelae as well as the old indications of rapid growth, impinging on vital structures and interference with breathing, vision, eating or hearing. This study has identified the features that lead to a poor cosmetic outcome and will help in identifying which infantile haemangiomas are worthwhile treating with propranolol.

Reference: JAMA Dermatol 2016;152(11):1239–43
Abstract

Topical timolol maleate 0.5% for infantile hemangioma: its effectiveness compared to ultrapotent topical corticosteroids

Authors: Danarti R et al.

Summary: These researchers reported on 278 prospective outpatient cases of superficial infantile haemangioma from a single centre. They categorised these patients into those treated with topical ultrapotent corticosteroids, those treated with 0.5% timolol maleate solution and those treated with 0.5% timolol maleate gel. Follow-up was 6 months. Compared with ultrapotent corticosteroids, the two timolol maleate products were associated with significantly greater reductions in infantile haemangioma size after treatment ($p<0.001$), with no significant difference between the solution and gel formulations ($p=0.744$).

Comment: β-blockers have now replaced both systemic and topical corticosteroids for treatment of infantile haemangiomas. This article showed both timolol maleate solution and gel to be equally effective and significantly more effective in treatment of superficial infantile haemangiomas than ultrapotent topical corticosteroids. An effective treatment without systemic effects widens the types of infantile haemangioma considered for topical use, and would include smaller and more superficial infantile haemangiomas than those considered for oral propranolol.

Reference: Dermatology 2016;232(5):566–71
Abstract

Association between atopic dermatitis and attention deficit hyperactivity disorder in U.S. children and adults

Authors: Strom MA et al.

Summary: The relationship between atopic dermatitis and ADD/ADHD was explored using US population-based survey data for 354,416 children and 34,613 adults. Multivariate models revealed associations between atopic dermatitis and ADD/ADHD in children and in adults (respective adjusted ORs 1.14 [95% CI 1.03–1.26] and 1.61 [1.25–2.06]), with the association particularly strong for children with both severe atopic dermatitis and only 0–3 nights of adequate sleep per week (16.83 [7.02–40.33]), compared with those with 0–3 nights of adequate sleep per week only (1.83 [1.47–2.26]) and mild-to-moderate atopic dermatitis only (1.56 [1.22–1.99]). A strong association was also seen between atopic dermatitis and severe ADHD, and the risk of ADD/ADHD remained increased when atopic dermatitis in children was not accompanied by other allergic diseases. The increased likelihood of ADD/ADHD in children with atopic dermatitis was further increased in those with a history of anaemia, headaches and obesity, and in adults it was increased in those with asthma, insomnia and headaches but reduced in those who were underweight.

Comment: The association of ADD/ADHD with atopic dermatitis has been confirmed in children but not studied well in adults. This study confirms this association in both children and adults. The main reason is likely to be sleep disturbance, which is worse with more severe atopic dermatitis. The lack of sleep may lead to difficulty with attention and concentration, and effective treatment of atopic dermatitis may lead to improvement or resolution of the ADD/ADHD. This study showed that even atopic dermatitis patients who didn't have significant sleep disturbance had an increased incidence of ADD/ADHD, although not as much when the atopic dermatitis was severe enough to cause sleep disturbance. Other studies though have found that atopic dermatitis without sleep disturbance did not have an increase in ADD/ADHD, so this needs to be explored further. ADD/ADHD is also increased in allergic rhinitis and asthma alone, but higher again if asthma and atopic dermatitis occur together. Headaches, obesity and anaemia further increase the risk of ADD/ADHD in children with atopic dermatitis, but are factors associated with ADD/ADHD in patients without atopic dermatitis. This study shows that ADD/ADHD needs to be thought of in patients with atopic dermatitis and that treatment of atopic dermatitis may reduce it.

Reference: Br J Dermatol 2016;175(5):920–9
Abstract

Adult female acne and associated risk factors

Authors: Di Landro A et al., the Group for Epidemiologic Research in Dermatology Acne Study Group

Summary: This research explored the role of personal and environmental factors in 248 outpatient cases of adult female acne, with 270 women diagnosed with different conditions serving as controls. A multivariate analysis revealed that factors associated with acne were a history of acne in parents (OR 3.02) or siblings (2.40), history of acne during adolescence (5.44), no previous pregnancies (1.71), hirsutism (3.50), being an office worker versus being unemployed or a housewife (2.24), having a high degree of psychological stress (2.95), a low weekly dietary fruit/vegetable intake (2.33) and low fresh fish consumption (2.76).

Comment: This study looked at adult female acne over the age of 25 years and showed an association with several lifestyle factors. There was no association with high intake of milk and skimmed milk or with body mass index (in contrast to adolescent acne), which may indicate a different pathogenesis of acne in female adults compared to adolescent acne. Seventy-five percent of patients had inflammatory acne, truncal involvement was present in 30%, 68% had adolescent acne and the mean age was 32.2 years, confirming that adult female acne is still a young adult disease. Correction of these lifestyle factors, particularly increasing consumption of fish, vegetables and fruit and reducing stress, may be worthwhile trying, but confirmation by other trials is needed.

Reference: J Am Acad Dermatol 2016;75(6):1134–41
Abstract

Intralesional triamcinolone for flares of hidradenitis suppurativa (HS)

Authors: Riis PT et al.

Summary: Outcomes associated with routine intralesional triamcinolone acetonide 10 mg/mL for the treatment of acute hidradenitis suppurativa flares were reported in this prospective case series. Intralesional triamcinolone was associated with significant reductions in physician-assessed erythema, oedema, suppuration and size at follow-up ($p<0.0001$ for all), and significant reductions in patient-reported pain after 1 day and from day 1 to day 2 ($p\leq0.005$).

Comment: Treatment of hidradenitis suppurativa is difficult and systemic treatment is usually needed, although it is not always effective. Intralesional corticosteroids have been recommended in the literature but have not been assessed systematically or in a trial. Incision and drainage is not usually suitable for a solid process such as a hidradenitis nodule. Intralesional steroids are a simple and relatively easy way to manage these patients, and in this study were effective for the short-term management of flares. Discomfort is minimal in most patients and several lesions could be done. The improvement did not correlate with the volume of triamcinolone injected, so lower amounts may be able to be used with equal effect.

Reference: J Am Acad Dermatol 2016;75(6):1151–5
Abstract

A multicenter, randomized, split-face clinical trial evaluating the efficacy and safety of chromophore gel-assisted blue light phototherapy for the treatment of acne

Authors: Antoniou C et al.

Summary: This trial enrolled 98 patients with moderate-to-severe acne vulgaris to receive 6 weeks of twice weekly treatment with an LED blue-light device using specific photoconverter chromophores (KLOX BioPhotonic System) applied to a randomly selected hemiface, but not the contralateral hemiface; all participants also applied a cleanser and a noncomedogenic cream with ultraviolet protection to their entire face during the treatment period, and were followed for a further 6 weeks. At 12 weeks, IGA (Investigator's Global Assessment) scale severity scores had reduced by ≥2 grades in 51.7% of participants, with 45.3% and 61.1% of those with baseline IGA grades of 3 and 4, respectively, experiencing this level of improvement. Lesion count decreases of >40% were seen in 81.6% of treated hemifaces at 12 weeks. The participants also reported a decrease of acne-related pain and improved QOL at 6 weeks. There were no serious adverse events or adverse event-related study discontinuations.

Comment: New treatments for acne are needed with the high incidence of bacterial resistance making antibiotic therapy less suitable and many acne patients are not severe enough to warrant isotretinoin with its high side effect profile. Light phototherapy for acne has advantages, as it is a noninvasive, in-office method with no systemic side effects. There has been a lack of well-designed randomised controlled studies evaluating light therapy for acne. This was a multicentre, randomised, split-face study although a double blind study would have been preferable. There is no long term follow up in this or other similar studies, which would be useful to know. A comparison study with systemic antibiotic therapy would give more confidence in knowing which therapy is more effective. There was a continued improvement between the 6 week and 12 week visits and a high proportion of patients with severe acne (baseline IGA 4) benefited from this treatment. The jury is still out as to whether it is more effective than antibiotics and it is likely to be more expensive.

Reference: Int J Dermatol 2016;55(12):1321–8
Abstract

Use of Er:YAG for the treatment of recalcitrant facial verruca plana

Authors: Balevi A et al.

Summary: Forty-six patients with recalcitrant facial verruca plana underwent 1–4 Er:YAG laser treatment sessions at 4-week intervals in this research – 550 lesions were treated with 1–3 passes. The complete response rate was 62.5%, with 83.3% and 5.5% of treated lesions being completely and partially healed, respectively. Postinflammatory hyperpigmentation and mild scar formation were seen following treatment. The recurrence rate was 26.0%. Twenty-six participants reported they were completely satisfied with the treatment and nine reported they were mostly satisfied.

Comment: Plane facial warts are difficult to treat, as all treatments have a potential to cause scarring or postinflammatory pigmentary changes. Often reassurance that they will clear over time is the best management. In this study although over 80% were completely cleared, there was recurrence in 26%, so about 60% remained cleared. There was hyperpigmentation and mild scarring, and only just over 50% were completely satisfied with the treatment. These results may be better than cryotherapy and other treatments, but are not ideal and no treatment may still be the best option.

Reference: J Dermatolog Treat; Published online Oct 24, 2016
Abstract

Effectiveness of alitretinoin in severe chronic hand eczema

Authors: Thaçi D et al.

Summary: Patients with severe chronic hand eczema (n=631) received alitretinoin once daily for ≤24 weeks in the open-label, real-world, observational PASSION study; the dropout rate was 44.2%. A Physician Global Assessment rating of clear or almost clear at week 24 was achieved for 29.8% of the intent-to-treat population. QOL improved, with increases in mean baseline EQ-5D utility and visual analogue scale scores by week 24 (from 0.76 to 0.94 and from 53.6 to 80.8, respectively), and the proportions of participants reporting strong and very strong workplace impairment decreased from 49.4% to 8.5% and from 29.1% to 1.4%, respectively, over the same period. Adverse events occurred in 18.4% of participants, with no new safety concerns emerging.

Comment: Chronic hand eczema is difficult to treat and often only partially responsive to various treatments with frequent flares. Alitretinoin is not available in Australia, but there was a significant improvement with almost 30% achieving clear or almost clear results. There was a high dropout rate of almost 45%, and most of these had unspecified reasons with 6% withdrawing due to side effects and 6% withdrawing because of lack of effect. There were also significant improvements in disability, QOL and work incapacity. Alitretinoin would be a worthwhile addition to the treatments available in Australia, and ways should be explored to make it available.

Reference: J Dermatolog Treat 2016;27(6):577–83
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.

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