World Congress of Dermatology
Conference Review

Making Education Easy

May 24-29, 2011, Seoul, Korea

In this review:

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Research Review is an independent medical publishing organisation producing electronic journals in several specialist areas. These journals provide summaries of the 'must see' studies from the most respected medical journals in the world together with a local specialist commentary indicating why they matter. Research Review publications are intended for New Zealand medical professionals.

Welcome to this review of the World Congress of Dermatology held in Seoul May 24–29, 2011.

The World Congress of Dermatology is hosted every 4 years by the International League of Dermatological Societies, which currently has 127 member societies globally. Amanda Oakley and Ian Coutts attended the Congress held in Seoul in May this year and identified the following presentations as being of particular interest. We hope you also find them interesting, and useful in your current practice.

Kind Regards,

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Adalimumab treatment of psoriasis patients following suboptimal responses to etanercept, methotrexate, or phototherapy: efficacy across subgroups in an open-label study

Presenter: Bruce E Stober, New York University School of Medicine, New York, USA

Summary: This study evaluated the efficacy of adalimumab in chronic plaque psoriasis patients with prior suboptimal responses to systemic therapy. 152 patients with prior suboptimal responses to etanercept (n=82), methotrexate (n=41), or narrow-band ultraviolet B (n=29) were enrolled. At week 16, response (Physician's Global Assessment [PGA] "clear" or "minimal") was achieved in 48.8%, 61.0%, and 48.3% of patients in the respective groups. Results for subgroup analyses (e.g. age, sex, disease duration, presence/absence of psoriatic arthritis, bodyweight) were similar to those overall. In conclusion, about 50% patients with suboptimal response to systemic therapy achieved a clinically relevant improvement 16 weeks after transitioning to adalimumab.

Comment: It is interesting to compare the results of this study that found PGA clear or minimal at 16 weeks in nearly half of 82 patients on adalimumab in patients that had inadequate response to etanercept with a study that evaluated efficacy of etanercept in the treatment of 10 psoriasis patients who had inadequate response to adalimumab (Vender R et al. J Drugs Dermatol. 2011;10(4):396-402). The latter reported 50% had PGA clear or minimal at 12 weeks and 80% had PGA clear or minimal at 24 weeks. It was initially thought one TNF-α inhibitor would not show efficacy after loss of efficacy or failure of another TNF-α inhibitor with a similar mechanism of action. However, it is known that TNF inhibitors have different mechanisms of action, pharmacokinetics, pharmacodynamics and safety profiles. PGA was clear or minimal at 16 weeks in 61% of patients that had had methotrexate; failure of methotrexate is one of the criteria for treatment with biologics in New Zealand. *AO*

http://www.ncbi.nlm.nih.gov/pubmed/21414495

Melanoma: do we need a new classification?

Presenter: Stephan N. Wagner, Medical University of Vienna, Austria

Comment: The melanoma genome atlas has already identified numerous genetic alterations involving hundreds of 'driver' and 'passenger' genes. Currently, melanoma is classified clinically, dermoscopically and histopathologically. The AJCC TMN classification [http://www.ncbi.nlm.nih.gov/pmc/articles/PMC2793035/] published in 2009 is used worldwide for staging melanoma. In the future we will need to identify molecular subtypes to detect the disease early, to analyse it, to type the cancer, and to treat it with targeted therapy. We might be able to get cells for analysis by tape stripping. The relevance today is that current clinical trials targeting BRAF+ melanoma (50%) are showing promising results in metastatic disease. Numerous drugs are under development for other molecular targets. *AO*

Atopic Dermatitis

Numerous papers about atopic dermatitis (AD) were presented at this year's World Congress of Dermatology. Exciting new discoveries about epidermal barrier function should soon lead to more effective treatments for AD, and ways to prevent it.

Skin barrier in atopic dermatitis: filaggrin and ceramides

Presenter: Eric Simpson, Dept of Dermatology, Oregon Health & Sciences University, USA

Summary: Mutations in the gene encoding filaggrin have been shown to be strongly associated with the development of AD, having been identified in up to 50% of patients with mild to severe AD. Filaggrin deficiency compromises skin barrier function, not only leaving skin vulnerable to irritants and allergens but also reducing Natural Moisturising Factor (NMF) in the stratum corneum. Ceramides are one of the main lipids in the stratum corneum and act to maintain skin barrier function and ensure optimal hydration. Reduced ceramide levels lead to a compromised skin barrier and dehydration. Correction of these skin barrier abnormalities can reduce the likelihood of flares, reduce the need for steroids, and may also prevent disease onset.

Comment: It is clear that AD starts with skin barrier defects. Numerous abnormal genes have been identified in several components of the skin barrier. The stratum corneum or horny layer of the skin may be described as a brick wall. The corneocytes (bricks) are held together by corneodesmosomes (mortar). Mutations in filaggrin, a structural protein, and ceramides, an epidermal lipid, result in breakdown of the corneodesmosomes. The stratum corneum is 35% thinner and it is dry and leaky, resulting in increased transepidermal water loss. Microbes and irritants such as house dust mite and sweat may then penetrate through the weakened epidermis. These activate the innate immune system, resulting in inflammation.

The hope is that effective emollients containing filaggrin and ceramides can be developed to improve barrier function. Several papers and posters describing new emollients and their benefits in eczema were presented at the meeting. The new vehicles will also be used to reformulate topical corticosteroids and calcineurin inhibitors. It won't be long until some of these effective evidence-based products are on the market in New Zealand. *AO*

Skin barrier dysfunction in atopic dermatitis: the role of environmental factors

Presenter: Michael J Cork, Academic Unit Of Dermatology Research, University Of Sheffield Medical School, UK

Summary: Breakdown of the skin barrier in AD can occur via an increased pH in the stratum corneum, which in turn leads to increased protease activity. Proteases are most active at pH 7.0–7.5 and cause enhanced desquamation and a thinning of the stratum corneum barrier. Protective lipid synthesis enzymes work best at pH around 5. A high skin pH (7.0–7.5) can therefore lead to breakdown of the skin barrier, making it vulnerable to irritant and allergen penetration. Reducing exposure of the skin to soaps and harsh detergents such as sodium lauryl sulphate that increase skin pH will improve the control of AD.

Comment: Filaggrin breakdown products contribute to NMF, which maintains an acid pH on the skin surface. Both proteases and protease inhibitors are present in normal skin. Increased protease activity can be due to genetic upregulated proteases or downregulated protease inhibitors. There are also more proteases if the pH is higher, i.e. if the acid mantle is disturbed by filaggrin mutations, sweat, soap, harsh detergents, toiletries and inappropriate moisturisers (including aqueous cream, which includes a small amount of the irritant sodium lauryl sulfate). Bacteria such as Staphylococcus aureus and Propionibacterium acnes produce proteases as well. The proteases destroy skin proteins and lipids such as filaggrin and ceramides, leading to further weakening of the skin barrier. Unfortunately, topical corticosteroids also increase protease activity – a reason why they should only be used for short-term control rather than long-term prevention of AD flares. Study of proteases and protease receptors may lead to more effective treatments for AD. Serum protease inhibitors and proteinase-activated receptor-2 antagonists could be included in emollients. These may be helpful in the restoration of the epidermal barrier, as well as the suppression of inflammatory reactions. *AO*

Looking at the underlying inflammation of atopic dermatitis

Presenter: Thomas Bieber, Dept of Dermatology and Allergy, University of Bonn Medical Center, Germany

Summary: In recent years, the pathophysiology of AD has become clearer. Polymorphisms in the filaggrin gene predispose individuals to skin barrier abnormalities. The impaired skin barrier becomes susceptible to penetration by high-molecular-weight allergens that in turn drive dendritic cells to enhance TH2 polarisation. Patients with AD have subclinical inflammation in the skin, even in the absence of visible lesions, which makes it difficult for the immune system to manage microbial skin infections. Autoimmune responses may play a role in the pathogenesis of AD, as approximately 30% of adults with AD have been found to have IgE autoantibodies to keratinocytes and endothelial cell proteins that correlate with disease severity. This appears to be under the control of Fcε-receptor-positive dendritic cells, which play a critical role in the control of IgE synthesis. Strategies that control inflammation at the earliest possible stage of AD may therefore be disease modifying.

Comment: 'Extrinsic' atopic eczema is associated with an acute TH2 inflammatory response (cytokines IL4, 5, 10 and 13) and elevated total and specific IgE. Immune gene polymorphisms may be partly responsible. But defective barrier function is probably more important, as IgE-mediated allergy is not a feature of early infantile eczema or late-onset adult 'intrinsic' eczema. Nonlesional skin shows histological signs of subclinical inflammation between flares and on adjacent unaffected sites. Potential allergens, such as house dust mite and pollens, penetrate the defective skin barrier activating the innate immune system through Toll-like receptors and keratinocyte pattern recognition receptors. They also result in cellular immunity through interaction with epidermal dendritic cells. The dendritic cells activate T-cells, releasing proinflammatory and immunosuppressive cytokines, neuropeptides and growth factors. The stage is set for autoimmunity, which perpetuates the inflammation and results in chronic disease. Effective barrier creams applied to the entire skin surface in early infancy may actually prevent the development of AD. *AO*

Independent commentary by Associate Professor Dr Amanda Oakley
MBChB FRACP PGDipHealInf

Professor Amanda Oakley is specialist dermatologist in Hamilton and is a Clinical Associate Professor at Waikato Clinical School (Auckland University School of Medicine).

Independent commentary by Ian Coutts MBChB, MRCP (UK), FRACP

Dr Ian Coutts is the Lead Consultant Dermatologist at Wellington Hospital and also practices at the NZ Dermatology & Skin Cancer Centre in Wellington.

Long-term active maintenance therapy in moderate and severe atopic dermatitis: latest advances

Presenter: Diamant Thaci, Dept of Dermatology and Venereology, Johann Wolfgang Goethe University, Germany

Summary: The CONTROL studies investigated the efficacy of long-term active maintenance treatment with the calcineurin inhibitor tacrolimus in patients with mild to severe AD. The use of twice weekly tacrolimus ointment (0.1% in adults and 0.03% in children) was compared with flare treatment only (twice daily) over a 12-month treatment period. A sub-analysis in patients with moderate-to-severe AD found fewer major flares ($p<0.001$), and a delay in time to first major flare with twice-weekly treatment in both adults and children. In conclusion, twice-weekly tacrolimus ointment may have several clinical advantages over flare treatment only in patients with moderate-to-severe AD.

Comment: European guidelines (J Eur Acad Dermatol Venereol. 2010;24(3):317-28) for the management of AD recommend that basic skin care should include nonirritating cleansers, bath oils and hydrating emollients, and avoidance of provoking agents. Flares should be treated with generous topical corticosteroid – mild to moderate potency for mild disease, and moderate to strong for more severe involvement. Anti-inflammatory treatment with calcineurin inhibitors is preferred in certain countries e.g. pimecrolimus cream (unfunded in New Zealand) and tacrolimus ointment (not easily obtained here). Dr Thaci described several studies comparing corticosteroids and calcineurin inhibitors. Equipotent agents appear to be equally effective at reducing inflammation in short-term use (twice daily to active lesions for 2 to 4 weeks), and in reducing flares with intermittent use (to the same areas once daily, 2 days per week). However, barrier function returns to normal with intermittent calcineurin, whereas it remains poor with intermittent corticosteroid. This may be a good reason to promote the use of calcineurin inhibitors, which are well tolerated (after initial stinging) and have few adverse effects. *AO*

Antimicrobial peptides: more than epidermal antibiotics

Presenter: Juergen Schauber, Dept of Dermatology and Allergy, Ludwig-Maximilian-University, Munich, Germany

Summary: Cutaneous production of antimicrobial peptides (AMPs) such as cathelicidins and defensins is a primary system for protection of the skin barrier. Cathelicidins and defensins protect the skin via direct antimicrobial activity, and by initiation of a host response. Antimicrobial peptide dysfunction is a central factor in the pathogenesis of several cutaneous diseases including AD, rosacea and psoriasis. Vitamin D3 has recently been identified as a major factor involved in the regulation of cathelicidin, which may explain the beneficial effects of topical treatment with vitamin D analogs or UV phototherapy. Therapies that target the control of cathelicidin and other AMPs may offer new approaches to the management of infectious and inflammatory skin diseases.

Comment: AMPs such as cathelicidins and defensins protect the skin against infection. They are normally expressed in response to injury, microbial invasion or exposure to UV radiation. They work in two ways, by killing the pathogen and by releasing cytokines enhancing cellular response. Cathelicidin regulation is disturbed in inflammatory conditions such as rosacea and psoriasis. The benefits of topical vitamin D analogues in psoriasis may be based in part on their effect on AMPs. But vitamin D analogues are irritants and may cause an inflammatory reaction in AD. Interestingly, AMP levels may be reduced, normal or increased in AD. Their role in colonisation or infection of eczema is unknown. Excessive washing can however lead to a reduction in AMPs and impair the natural protective functions of the skin. Several manufacturers have reported improvement in barrier function and in dermatitis after the application of emollients containing AMPs. *AO*

Systemic treatment for atopic dermatitis

Presenter: Mette S. Deleuran, Dept of Dermatology, Aarhus University Hospital, Denmark

Summary: A combination of topical and systemic therapy is often necessary to control AD. Systemic corticosteroids work rapidly, but must only be used short-term because of the many adverse events associated with long term use. Alternate systemic immunosuppressants e.g. cyclosporin, azathioprine, methotrexate and mycophenolate mofetil may therefore be considered in chronic, severe cases. Close patient follow-up is mandatory for a positive outcome in patients with severe AD.

Comment: When education, barrier creams, topical anti-inflammatories and antibiotics have failed, dermatologists may treat patients with severe eczema by hospitalisation, oral glucocorticosteroids, phototherapy and systemic immunosuppression. The literature about response rates is scant and non-evidence based. No new data were presented in this paper. Corticosteroids work quickly but in most cases should only be used short-term for acute exacerbations because of many long-term side effects. Cyclosporin, azathioprine, methotrexate and mycophenolate are all effective in some patients but not in others. It is disappointing that most currently available biologics have not proven useful in AD. Some benefit has been reported with rituximab. Immunoapheresis can also help, possibly by removing IgE. *AO*

Acute and chronic photocarcinogenic effects of UV radiation

Presenter: Elma D Baron, Dept of Dermatology, Case Western Reserve University, USA

Summary and comment: UV radiation has acute and chronic effects. Acute effects include erythema and pigmentation and sunscreen is often evaluated on its ability to prevent acute endpoints. Chronic effects include carcinogenesis. Epidemiological evidence is strongest that SCC is caused by chronic UV exposure both to UVB and UVA. However there is evidence to support the hypothesis that chronic UV exposure causes BCC and melanoma. UVB is directly absorbed by DNA resulting in cyclopyrimidine dimers, and insufficient repair by nucleotide repair mechanisms leads to mutagenesis. UVB also causes direct mutations to tumour suppressor genes such as p53. UVA can also cause DNA damage indirectly via UVA photoproducts. Therefore full spectrum of UV radiation is carcinogenic. Also, UV spectrum is immunosuppressive leading to poor immune surveillance. Sun protection including broad spectrum UV protection is necessary in order to prevent skin cancer development. *IC*

Photoaging

Presenter: Jin Ho Chung, Department of Dermatology, Seoul National University, Seoul

Summary and comment: Skin aging can be divided into two processes, intrinsic and photoaging. Intrinsic aging is characterised by smooth, dry, pale and finely wrinkled skin. Photoaging is characterised by severe wrinkling, loss of elasticity and irregular pigmentation. The changes of dermal connective tissue fibres by chronic UV exposure account for the aged appearance of skin. Collagen deficiency in photoaged skin involves a number of regulatory pathways in collagen turnover and synthesis and finding strategies for regulating these pathways may be beneficial in prevention and rejuvenation of skin photoaging. Further research into the complex biology and mechanisms of skin aging is being driven by cosmeceutical companies to try and identify novel strategies to halt and reverse this fascinating process. *IC*

New technologies in dermatosurgery: potential pitfalls

Presenter: Moshe Lapidoth, Tel-Aviv University, Israel

Comment: The use of new devices such as lasers and intense pulse light has become established practice in dermatology. This increased use has been accompanied by a sharp increase in number of case reports of professional errors. Dermatologists needs to recognise the stages of adoption of a technology namely innovators (2.5%), early adoptors (13.5%), early majority (34%), late majority (34%), and laggards (16%). The recommendation is to move to purchase and use of technologies in the early majority stage, buy well known brand names, ask for upgrades to be part of purchase contract and be provided with clear training and standards. *IC*

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Asian dust storm particles exert toxicological effects on human skin through the activation of the cellular detoxification system and the production of pro-inflammatory cytokines

Presenter: Hyun Choi, Amorepacific Corporation Bora-Dong R&D Center, Republic of Korea

Summary: This study evaluated the toxicological effects of Asian dust storm particles on human skin. Dust particles were collected during 4 periods of Asian dust storms in Seoul and their effects on the various gene expressions in normal human keratinocytes (NHKs) were evaluated. Exposure to Asian dust particles significantly increased the expression of the cytochrome P450 1A1 (CYP1A1), CYP1A2, and CYP1B1 genes, implying the activation of aryl hydrocarbon receptor. Gene transcription of pro-inflammatory and immunomodulatory cytokines such as IL-6, IL-8, and GM-CSF was also increased. The protein extract of pollen, often found on Asian dust particles, increases expression of IL-6, CYP1A1, CYP1A2 and CYP1B1 in NHK. In conclusion, Asian dust particles exert toxicological effects on human skin via activation of a cellular detoxification system and the production of pro-inflammatory cytokines.

Comment: The effects of the phenomenon of Asian dust storms on skin toxicology and defence mechanisms are driving a different field of research into the biology of skin and may produce a range of cosmetics with novel properties on skin aging. *IC*

What are the standards of treatment of rosacea?

Presenter: Lajos Kemeny, Dept of Dermatology and Allergy, University of Szeged, Hungary

Summary: Rosacea is a chronic inflammatory disease that requires continuous management. Treatment can be tailored to the subtype and may involve various combinations of therapies. Patients need to avoid triggers, perform proper skin care, and protect their skin from sun. There are camouflaging cosmetic options available, as well as standard topical treatments such as metronidazole, azelaic acid and sodium sulfacetamide-sulfur. Patients with moderate-to-severe rosacea, or those with ocular involvement, need systemic therapy with tetracycline, doxycycline or metronidazole. Severe rosacea may require low dose isotretinoin therapy. Telangiectasias and persistent erythema can be treated with intense pulsed light or the pulsed-dye laser but surgery is the only treatment for patients with rhinophyma.

Comment: There was no novel treatment solution offered but a reminder that the doctor should always ask about eye symptoms as they may be very symptomatic and the patient will not often recognise the connection between their skin and eye symptoms. *IC*

Strategies for reduction of anxiety and pain during facial surgery under local anesthesia

Presenter: Murad Alam, Northwestern University Feinburg School of Medicine, Chicago, USA

Summary: This study reviewed methods used to alleviate pain and anxiety during minimally invasive facial surgery under local anesthesia. Strategies include a comprehensive preoperative consultation, preoperative communication of expectations, covering the eyes, relaxing music, conversational banter, verbal reassurance, hypnosis and guided imagery. Comfort aids (e.g. pillows) for positioning are also used. Further research is needed to determine the most effective methods.

Comment: This paper gave a good overall reminder of some practical and novel tips for improving the patient journey in the dermatologist's operating theatre. Simple choice of theatre bed and positioning, appearance of a clean and modern environment, importance not to appear rushed and good nurse support all are likely to reduce patient anxiety and hence the patient's pain experience. *IC*

Publication of this Conference Review was supported by an educational grant from Abbott Laboratories NZ Ltd. The content and opinions expressed in this publication do not necessarily reflect the views of Abbott unless so specified.