Hong Kong J. Dermatol. Venereol. (2017) **25**, 91-94

Reports on Scientific Meeting

The 75th American Academy of Dermatology Annual Meeting

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Date: 3-7 March 2017
Venue: The Orange County Convention Centre, Orlando, Florida, U.S.A.
Organiser: The American Academy of Dermatology

What's new in atopic dermatitis

Speakers: Lawrence Eichenfield,[1] Amy Paller,[2] Eric Simpson[3]
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Atopic dermatitis (AD) is a complex disease with immune and barrier abnormalities. It is the most common inflammatory disease in adults (3-7%) and children (15-25%), with up to one-third being moderate or severe. The epidermal barrier is defective with decreased proteins and lipids, associated with the filaggrin mutation. The inflammatory lesions are associated with immune and cytokine activation of the Th2 (IL4, 13, consistently), Th22 (IL22), or Th17 pathways. There is a large unmet need for safe and effective treatments in all age groups.

Food allergy is estimated to be present in 15% of patients with children with mild to moderate AD. However, excluding foods in unselected patients is found to offer no additional benefit. Non-discriminatory food allergen or IgE testing, except for peanut, is not advisable with high possibility of false positives. The latest guidelines on food allergy recommend that infants with mild to moderate eczema should be introduced age-appropriate peanut-containing foods as early as 4-6 months of age to reduce future risk of peanut allergy. If they have severe eczema, egg allergy, or both, a serum IgE screen for peanut allergy is useful. If positive, referral to allergy clinic is recommended, otherwise introduction of peanut-containing foods is advised in accordance with family preference and cultural practices. In high risk infants born to AD parents, it has been shown in randomised control studies that early use of full-body emollient therapy reduces the cumulative incidence of eczema by a relative risk reduction of 50% at 6 months, and 32% at 32 weeks. The risk of parabens as preservatives in moisturisers is considered not to be substantiated at this juncture.

Regarding topical therapy, various epidemiological studies of over 6000-8000 children over five to 10 years on topical calcineurin inhibitors have refuted the black-box warning risk of cutaneous malignancy and lymphoma. They are important adjuncts in the management and prevention of AD. Pro-active maintenance therapy with medium-strength steroid or calcineurin inhibitor two to three times a week improves outcome and compliance. A novel, non-steroidal topical phosphodiesterase

4 inhibitor (PDE4I), has been approved by FDA, for treatment of mild to moderate AD in children and adults. By increasing the intracellular cyclic AMP, pro-inflammatory cytokines are suppressed in AD. Crisaborole 2% ointment, a PDE4I with boron ring integration, used twice a day for 28 days, was shown to be safe in adults and children older than two years, with slight improvement in pruritus and Investigators Global Static Assessment (IGA) scores compared to vehicle. Local side effects are pain and irritation. Topical tofacitinib, a JAK inhibitor involved in Th2/IL4-signalling, has been shown to be effective in phase 2 studies.

For severe AD, the off-label use of existing biologics (interferon gamma, anti-IgE, anti-TNF, antiIL12/23) is shown to be not successful. New biologics targeted at IL4, IL13 have emerged with moderate efficacy. Dupilumab is a humanised monoclonal antibody that blocks the interleukin-4 receptor alpha subunit which in turn blocks IL4 and IL13 pathway. It has been shown in two randomised, placebo-controlled studies (SOLO1, SOLO2 studies) with over 700 patients of moderate to severe eczema with no topical steroid allowed, to be efficacious after 16 weeks of treatment, in reducing IGA scores by 37%, Eczema Assessment Severity Index 75 (EASI 75) scores by 44-50% and itch by 44-50%. There was no significant difference in efficacy with different dosing intervals (300 mg weekly or every two weeks). Serious adverse event rates including were not higher than placebo. The most common side effects were injection site reactions and conjunctivitis. The EASI 75 was achieved at 60-70% on usage up to one year, in combination with topical steroid (CHRONOS study). Other biologics targeting at IL13 (lebrikizumab) and IL31 (nemolizumab) have shown promising results in phase 2 studies. The latter has significant reduction in itch (90%) and moderate reduction in inflammation.

Learning points:

AD is a disease with defective epidermal barrier and inflammation. Topical and systemic anti-inflammatory targeted therapies are emerging with promising results.

Psoriasis: Biologics update

Speakers: Mark Lebwohl[1] and Richard Langley[2]
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Psoriasis is a common chronic immune-mediated inflammatory disorder which primarily affects the skin. It is associated with increased risk of metabolic syndrome, cardiovascular disease and depression. It poses significant disfiguration and disability to our patients. There is so far no cure for the disease, but advances in treatment provide much better symptom control and improvement in quality of life for psoriatic patients. Traditional treatment includes topical agents such as topical steroid, coal tar, salicylic acid, and Vitamin D3 analogue; phototherapy; and systemic treatment such as oral retinoids, methotrexate, and cyclosporine. With better understanding of the underlying pathogenesis of psoriasis, biologic agents have been developed and are being increasingly used for patients who do not respond to first-line therapy. The current Food and Drug Administration (FDA) have approved biologic agents for the treatment of psoriasis which include etanercept, infliximab, adalimumab, ustekinumab, secukinumab and ixekizumab. This article aims to review the clinical trials of the newer biologic agents.

Anti-IL-17 (Secukinumab, Ixekizumab, Brodalumab)

1. Secukinumab:
   - ERASURE trial: this was a randomised, double blind, placebo-controlled phase 3 study involving 738 adults with moderate-to-severe plaque psoriasis. Patients were randomly assigned in a 1:1:1 ratio to receive secukinumab (300 mg), secukinumab (150 mg), or placebo. The proportion of patients who achieved PASI-75 at 12 weeks was 81.6% with 300 mg of secukinumab, 71.6% with 150 mg of secukinumab, and 4.5% with placebo. In another similar trial (FIXTURE trial) which compared secukinumab with etanercept and placebo, the rates of PASI-75 were 77.1% with 300 mg secukinumab, 67% with 150 mg secukinumab, 44% with etanercept, and 4.9% with placebo (P<0.001 for each dose secukinumab dose vs comparators). Secukinumab showed superiority over etanercept and placebo.
   - CLEAR trial: this was a double blind randomised control trial which compared secukinumab with ustekinumab in patients with moderate-to-severe plaque psoriasis. At week 16, secukinumab showed superiority over ustekinumab, with PASI-90 of 79% in secukinumab group vs 58% in ustekinumab group.
2. Ixekizumab:
   - UNCOVER-2 and UNCOVER-3 trials: these were two identical-designed phase III double blind, randomised control trials which compared ixekizumab (4-weekly dose and 2-weekly dose) with etanercept and placebo in patients with moderate-to-severe plaque psoriasis. At week 12, ixekizumab showed superiority over etanercept and placebo, with PASI-75 of 87.3%-89.7% in 2-weekly ixekizumab group; 77.5%-84.2% in 4-weekly ixekizumab group, 41.6%-53.4% in etanercept group; and 2.4%-7.3% in placebo group (all p<0.0001 vs etanercept and placebo).
   - IXORA-S trial: this was a double blind randomised control trial which compared ixekizumab with ustekinumab in patients with moderate-to-severe plaque psoriasis. At week 24, ixekizumab showed superiority over ustekinumab, with PASI-90 of 83.1% in ixekizumab group vs 59% in ustekinumab group.
3. Brodalumab:
   - AMAGINE-2, AMAGINE-3 trials: these were two identical-designed phase 3 double blind, randomised control trials which compared brodalumab (210 mg and 140 mg) with ustekinumab and placebo in patients with moderate-to-severe plaques psoriasis. At week 12, brodalumab (both doses) showed superiority over placebo, with PASI-75 of 85%-86% in 210 mg brodalumab group, 67%-69% in 140 mg brodalumab group, and 6%-8% in placebo group (all p<0.001). At week 12, brodalumab (210 mg) showed superiority over ustekinumab, with PASI-100 of 37%-44% in 210 mg brodalumab group and 19%-22% in ustekinumab group (P<0.001). The PASI-100 response rates with 140 mg of brodalumab were 26% in AMAGINE-2 (P=0.08 vs ustekinumab) and 27% in AMAGINE-3 (P=0.007).

Anti-IL-23 (Tildrakizumab, Guselkumab)

1. Tildrakizumab:
   - RESURFACE-1, RESURFACE-2 trials: two phase III double blind, randomised control trials compared tildrakizumab (100 mg and 200 mg) with etanercept and placebo in patients with moderate-to-severe plaque psoriasis. At week 12, tildrakizumab (both doses) showed superiority over etanercept and placebo, with average PASI-90 of 37% in 100 mg tildrakizumab group, 36% in 200 mg tildrakizumab group, 21% in etanercept group and 2% in placebo group. The average rates of PASI-90 in 100 mg and 200 mg tildrakizumab groups increased to 54% and 59% respectively at week 28 (vs etanercept 31%).

2. Guselkumab:
   - VOYAGE trial: this was a double blind phase 3 randomised control trial which compared guselkumab with adalimumab and placebo in patients with moderate-to-severe plaque psoriasis. At week 16, guselkumab showed superiority over placebo and adalimumab, with PASI-90 of 73.3% in guselkumab group, 49.7% in adalimumab group and 2.9% in placebo group. The response was maintained through week 48 (PASI-90 76.3% in guselkumab group vs 47.9% in adalimumab group).

Learning points:

Novel biologic agents were shown to be highly effective in treating plaque psoriasis. However, long term safety data is lacking. Treatment modalities should be chosen according to disease severity, relevant comorbidities, patient preference, efficacy and safety of treatment.