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Reports on Scientific Meeting

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What's new in immunomodulation?

An appropriate response to the black-box warning: corrective, barrier repair therapy in atopic dermatitis

Speaker: Dr. Peter M. Elias
Dermatology Services, Veterans Affairs Medical Center, and Department of Dermatology, University of California, San Francisco, California, USA

The "black-box" warning about the potential toxicity associated with prolonged use of the immunosuppressive drugs, tacrolimus 0.1%/ 0.3% ointment (Protopic™) and pimecrolimus 1% cream (Elidel™), as well as the concerns about the adverse side effects of topical steroids, have resulted in a search for alternate forms of therapy in atopic dermatitis.

The current controversy centers on whether the long term topical use of these immunosuppressive drugs presents a risk of cancer. Small children with severe atopic dermatitis on tacrolimus and pimecrolimus have demonstrated high blood levels of these drugs with prolonged use. Cases have also been reported to the Food and Drug Administration (FDA) where cancers have developed either directly at sites of prolonged pimecrolimus and tacrolimus applications or in draining regional lymph nodes. The FDA advisory group pointed out that although blood levels do not necessarily reflect tissue levels of these drugs, the marketing companies did not, in their preclinical studies, provide enough information on drug tissue levels, or the possibility of absorption of these topical drugs into the lymphatics. Tumor incidence has also been linked to both the total applied dose and duration of calcineurin inhibitor therapy.

Rationale for barrier repair therapy

Recent genetic studies highlighted the primary role of a defective barrier to water loss and microbial invasion in the provocation of atopic dermatitis which led to the rationale of "barrier repair therapy". Studies in animal models and in patients showed that barrier repair interventions promote normal skin function and reduce the inflammatory component of the disease.

The clinical significance of barrier function begins with the large pool of pre-formed pro-inflammatory cytokines such as IL-1α and IL-β, which are stored in the stratum corneum. These molecules are released into the lower epidermis and dermis when barrier function is perturbed. In normal skin, the cytokine cascade helps to restore barrier function, but this is unsuccessful in atopic dermatitis, resulting in the recruitment of additional pro-inflammatory molecules. Failure of barrier function also triggers and aggravates atopic dermatitis by allowing repeated access of haptens, which ultimately stimulate the characteristic TH-2 cytokine response. These two mechanisms coupled

with the exotoxins released from colonizing *Staphylococcus aureus*, account for the downstream inflammation in atopic dermatitis.

Corrective barrier repair involves the topical applications of sufficient quantities and correct proportions of all three key lipids that mediate barrier function (i.e. cholesterol, free fatty acids and ceramides) to correct the underlying lipid biochemical abnormality in atopic dermatitis. Restoration of normal skin barrier function can then down-regulate inflammation in deeper skin layers.

EpiCeram™ cream is a recently FDA cleared new form of barrier repair therapeutics available for prescribing in USA since September 2008. In a recent, multicenter controlled clinical trial involving 113 children aged 6 months to 18 years with moderate to severe atopic dermatitis, EpiCeram™ was comparable to the mid-strength steroid cream (Cutivate™ cream) by 28 days of treatment.

Learning points:

Barrier initiated cytokine cascade and enhanced hapten access through a defective skin barrier contribute to TH-2 cells driven inflammation in atopic dermatitis. Barrier repair therapy utilizes topical application of specific combinations of the three epidermal lipids which comprise the epidermal permeability barrier to promote normal skin function and reduce skin inflammation in atopic dermatitis.

Etanercept use in childhood psoriasis

Speaker: Dr. Tor Shwayder
Director, Paediatric Dermatology, Henry Ford Hospital, Detroit, MI

Etanercept is a tumor necrosis factor (TNF) inhibitor produced by recombinant DNA in a Chinese hamster ovary mammalian cell expression system. It is a soluble TNF receptor fusion protein that antagonizes endogenous TNF-1. It had been widely used in the treatment of adult psoriasis and had been Food and Drug Administration (FDA) approved to control juvenile rheumatoid arthritis since 1998.

Paediatric onset of psoriasis i.e. onset on or before 16 years old is slightly more common among females. Triggering factors such as stress, pharyngitis, and trauma have been noted. Spontaneous remission does occur in 35.4% according to a review paper in 2000. No systemic therapy for psoriasis in children and adolescents is currently approved by the FDA, phototherapy and systemic therapies have limited use because of low tolerability in children and the fear of cumulative adverse effects.

Paller and her group assessed the efficacy and safety of etanercept (Enbrel™) in children and adolescents with moderate to severe plaque psoriasis in their study and was published in January 2008 in the New England Journal of Medicine.[1] In response to the results of the trial, FDA approved the use of etanercept for the treatment of moderate to severe psoriasis in the paediatric population in June 2008.

The study was a randomized, double-blind, placebo-controlled, phase 3 trial lasting a total of 48 weeks at 42 sites in the United States and Canada. The inclusion criteria were age of 4 to 17 years, moderate to severe plaque type psoriasis defined as PGA (Physician's Global Assessment 0 to 5) of more than or equal to 3, body surface area involvement of more than or equal to 10% and PASI (Psoriasis-Area-and Severity Index) of at least 12 for at least 6 months. Subjects must have failed topical therapy, and patients who had received previous phototherapy or other topical or systemic therapy would have to go through a washout period.

The trial had three phases, the first 12 weeks involved the double-blind placebo- controlled trial to establish drug efficacy, the next 24 weeks was the open label trial, the last 12 weeks

involved the randomized withdrawal/ retreatment period. Etanercept at a dose of 0.8 mg per kg of body weight up to a maximum of 50 mg or matching placebo was given to patients in once-weekly subcutaneous injections. A total of 211 patients were randomly assigned to receive placebo or etanercept. Seventy-five percent of the patients were white, the median age was 13 years old, the median PASI was 16.4, the median body-surface area affected was 20% and the median body weight was 58.2 kg.

At week 12, significantly more patients who received etanercept than those who received placebo achieved PASI 75 (57% vs 11%, $p<0.001$), a significant difference was observed as early as week 4. At week 12, 64% of patients receiving etanercept at a dosage of 0.8 mg/kg achieved PASI 75 as compared with 47% of patients receiving maximum dose of 50 mg. The finding suggested that a weight-based dosing may be more superior to fixed dosing due to the slightly higher body weight of paediatric psoriasis patients than their normal counterparts. The response rates in children and adolescents were comparable. At week 36, after 24 weeks of open-label etanercept, rates of PASI 75 were 68% and 65% for patients initially assigned to etanercept and placebo respectively. In the third phase of withdrawal/retreatment during week 36 to week 48, patients underwent a second randomization to continue etanercept or to switch to placebo, and 42% of those assigned to placebo lost their PASI 75 responses which were regained after 4-8 weeks of etanercept treatment. The mean percentage of PASI improvement in the group receiving 48 weeks of continuous etanercept plateaued consistently at 12 weeks and gradually declined.

The rates of infectious and non-infectious events were similar in the control and placebo group. Four serious adverse events, namely ovarian cyst removal in one patient, gastroenteritis and dehydration in one patient and pneumonia in one patient, occurred during the open label phase, all resolved with no sequel.

Along with its approval of etanercept for moderate to severe paediatric psoriasis, the FDA highlighted the need for efficacy data in a longer term, and more information on frequency of administration required maintaining disease control. The FDA also stated that data on the risk of malignancies noted in the patients using etanercept for other indications such as Crohn's disease and juvenile rheumatoid arthritis is not sufficient to understand the risk versus benefit of etanercept in paediatric plaque type psoriasis and future studies are necessary.

Reference

1. Paller AS, Siegfried EC, Langley RG, Gottlieb AB, Pariser D, Landells I, et al. Etanercept treatment for children and adolescents with plaque psoriasis. N Eng J Med 2008;358:241-52.

Learning points:

Etanercept, the tumor necrosis factor inhibitor has been shown to be effective and safe in children and adolescents, aged 4 to 17 years old with moderate-to-severe psoriasis in a multicenter, phase 3, randomized-controlled trial.

The management of acne scarring

Speaker: Dr. Gregory J. Goodman
Senior Lecturer, Monash University, Department of Community Medicine, Chief of Surgical Skin Care Foundation, Victoria, Australia

The combination of a large sebaceous gland and a small hair follicle in the presence of inflammation allows for follicular hyperkeratinisation, secondary colonization by *Pityrosporum acnes*, oil stagnation and intra-follicular abscess formation and finally a follicular explosion through the weakens side wall of the hair follicle. This consequent dermal inflammation induces atrophic scarring as the inflammation subsides and scar remodeling

retracts the skin surface. In some individuals, hypertrophic scarring occurs.

The factors to consider in the evaluation of the acne scarred patient include the activity of the acne, the Fitzpatrick skin type; with Type 1 and 2 patients being at risk of hypopigmentation with resurfacing procedures and visible demarcations between treated and non-treated areas. Type 3, 4 and 5 patients have the risks of prolonged erythema and prolonged hyperpigmentation with many resurfacing techniques. Other factors such as gender, age, physical health, psychological status and the specific type of acne scar should also be taken into account.

The classification of acne scarring has not reached consensus at the moment, technically acne scarring is difficult to measure. Three dimensional photography is available, but is expensive and not easily performed. Various techniques of classification have been attempted including scar counting and scoring, classification by presumed pathophysiology, morphological description and by burden of disease.

The speaker presented the qualitative classification system by Goodman and Baron and his suggestions on the management for the respective grades of acne scarring as follows:

Grade	Clinical features	Treatment
1	- erythematous hyperpigmented or hypopigmented flat marks - visible at any distance	- flashlamp pumped dye laser - low strength chemical peels - microdermabrasion - bleaching cream sunscreens - pigment transfer techniques e.g. autologous noncultured epidermal suspension (Re-Cell™) for white scars and marks
2	- small dish-like scars easily distensible and circular or linear in pattern - mild, either atrophic or hypertrophic - able to cover with makeup	- low strength chemical peels, microdermabrasion, non-ablative infrared laser - ablative and non-ablative fractional resurfacing
3	- moderate atrophic or hypertrophic disease - may be flattened by stretching of skin, not easily covered by makeup - obvious at conversational distance	- dermabrasion, laser resurfacing, skin rolling, chemical peeling - fractional resurfacing - dermal augmentation with mixture of botulinum toxin and fillers
4	- severe atrophic or hypertrophic scarring - deep ice pick scars, deep divots - obvious at conversational distance, not flattened by manual stretching - not adequately covered with makeup	- punch float or punch elevation technique - focal strong chemical peeling - spot strong trichloroacetic acid - excision of scar - fat transfer or deep volume enhancement by fillers - intralesional steroids, intralesional cytotoxics, vascular laser, silicon sheeting for hypertrophic scars and keloidal acne

It is important in the treatment of acne scarring to assess the entire patient, the type of scarring, the severity of scarring and to combine different modalities of therapies to optimally treat the patient.

Learning points:

Acne scarring may present with different shapes and sizes and vary greatly in severity. Classification according to the scar type and severity in both atrophic and hypertrophic scarring is useful in planning therapy. Many new and old therapies are available and are often best combined.

Advanced haemangioma management forum

Speakers: Dr. Maria C. Garzon,[1] Dr. Kimberly A. Horii,[2] Dr. Anita N. Haggstrom[3]

[1]Professor of Clinical Dermatology and Clinical Paediatrics, Columbia University, New York, USA; [2]Associate Professor of Paediatrics/Dermatology, Children's Mercy Hospitals & Clinics, Section of Dermatology, Kansas City, Missouri, USA; [3]Assistant Professor of Paediatrics, Department of Dermatology and Paediatrics, Indiana University, Riley Hospital for Children, Indianapolis, Indiana, USA

Introduction and update on clinical features of infantile haemangioma

The incidence of infantile haemangioma (IH) is commonly cited as 10%. High risk populations include females, Caucasians, premature infants, low birth weight infants, and multiple gestations. Advanced maternal age, history of preeclampsia and placental anomalies are the maternal risk factors for IH. Infantile haemangioma is becoming an emerging health issue as the prevalence of low birth weight and preterm infants is rising in the United States. There is a 40% increase in risk of infantile haemangioma for every 500 g decrease in birth weight. A cohort study by the Haemangioma Investigator Group (HIG) on growth characteristics of infantile haemangiomas followed the growth of 526 haemangiomas of 433 patients, reported the early proliferative stage to be complete in most by 5 months of age, i.e. reaching 80% of their final size. The overall growth stage is complete in most by 9 months of age. Three percent of the cohort study population showed growth beyond 9 months of age, and they are often haemangiomas of deep or segmental morphologies and of the head and neck regions.

Treatment options for infantile haemangiomas

The majority of infantile haemangiomas are treated with watchful waiting. However, therapy is indicated for high risk haemangiomas. The location, morphologic subtype, size, presence of ulceration or infection, risk of disfigurement and threat to vision or other vital functions dictates the risk and thus the need for treatment. Factors associated with a need for active treatment include segmental & multiple cutaneous morphology, facial location especially over lip, ear, nasal tip, glabella, periocular region, large size and presence of ulceration. Treatment should be initiated during the rapid proliferative phase in order to slow growth, and these patients with high risk haemangiomas should be followed closely during the early critical period in their first few months of life.

The treatment options of infantile haemangiomas include local wound care for ulceration, topical/intralesional/systemic steroids, interferon, vincristine, laser, excisional surgery and propranolol. There are no prospective randomized controlled studies looking at the efficacies of various modalities of treatment, only retrospective case series exist.

Intralesional steroids are best reserved for smaller and localized lesions and are not recommended for larger segmental lesions. Rapid and dramatic responses have been achieved but it carries the risk of central retinal artery occlusion in periocular lesions. Systemic

steroids have a rapid onset of action within hours to days. The dosing, duration and tapering vary in practice. Rebound is common if it is tapered too quickly. The initial recommended dose is 2-3 mg/kg/day of prednisolone in a single morning dose, keeping the initial dose for 4-12 weeks then slowly tapered. Most patients are treated for several months. Patients should be monitored closely every 1-4 weeks for haemangioma response and dose titration. Potential steroid toxicities to watch out for include hypertension, hyperglycemia, insomnia, gastric irritation, behaviour change, weight loss, growth and adrenal suppression. Interferon-alpha and the chemotherapeutic alkaloid vincristine are options in steroid-resistant aggressive infantile haemangiomas. Their use is limited by their potential toxicities and the lack of controlled data for their use in haemangiomas.

Propranolol, the nonselective beta-blocker is the newest addition to the treatment options for infantile haemangioma. A case series of 11 patients published by a European team in 2008 demonstrated excellent response of 11 out of 11 patients showing regression at their last follow up. The age of propranolol initiation varied from 2 to 6 months at a dose of 2-3 mg/kg/day in divided dose 3 times a day. The average duration of therapy was 8 months. The potential adverse effects are hypoglycemia and hypotension. The speaker stressed the importance of using appropriate infant size blood pressure cuffs for monitoring of blood pressure of those infants. Moreover, magnetic resonance imaging/magnetic resonance angiogram and cardiac echo is recommended in large facial haemangiomas to rule out cerebrovascular and cardiac abnormalities, which may result in more significant hypotensive episodes when propranolol is used.

Learning points:

Treatments are indicated in cases of infantile haemangiomas with secondary complications such as infection or ulceration, or when vital organ functions such as vision and feeding are compromised. Therapeutic options include steroids, interferon, vincristine, laser and excisional surgery. Propranolol has been shown in a recent case series to be a promising new treatment option.