Recent Advances in Atopic Dermatitis, Psoriasis and Rosacea

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Scientific Insights Report
Introductory Comment from
Dr. Charles Lynde - Past President CDA

It is difficult for physicians today to stay current with regard to recent publications. Focus on Dermatology brings to us a concise overview of recent clinical research combined with valuable clinical commentaries provided by our peers. This newsletter gives Canadian physicians a forum to share their experiences and to increase our collective understanding of new therapeutic options for treating our patients. The content included in the report will be chosen by an Editorial Advisory Board composed of dermatologists. Their goal is to provide a publication that will offer new and different therapeutic options for managing your patient’s conditions. I welcome this educational and informative report and look forward to the upcoming issues.

I would like to thank GlaxoSmithKline Consumer Healthcare for sponsoring this newsletter. GSK Consumer Healthcare has chosen to sponsor this Scientific Insights Report to help physicians keep current and understand the outcomes of some recent clinical trials in the dermatology field.
**Introductory Comment from the Editor Bonnie Kuehl PhD**

Welcome to the inaugural issue of Focus on Dermatology. This newsletter will provide you with an ongoing review of the literature, reporting recent dermatological clinicals from around the world. The content will come from peer reviewed journals as well as presentations from conferences and meetings. A clinical comment from our Editorial Board or one of your peers will appear with each abstract to help you understand the application of the information to your clinical practice. Each issue will focus on a specific aspect of dermatology with an emphasis on therapeutic options to manage the condition. The therapeutic options discussed will include emerging and traditional treatments (topical corticosteroids, immunomodulators, coal tar) and non-traditional treatments (emollient therapy, herbal remedies).

I am pleased to introduce you to the Editorial Board: Dr. Jerry Tan; Dr. Marni Wiseman; and Dr. Gordon Searles. Dr. Tan is an Adjunct Professor at the University of Western Ontario. Dr. Tan’s interests include epidemiological and clinical research in acne and rosacea. Dr. Marni Wiseman is the Director of Cutaneous Oncology at Cancer Care Manitoba. Dr. Wiseman’s interests include skin cancer, vulvar disease and hair disorders. Dr. Gordon Searles has an academic position at the University of Alberta. Dr. Searles’ interests include wound care and dermatologic manifestations of internal disease. I am also looking forward to working with this group and to asking dermatologists/physicians from across the country for their clinical comments on a variety of subjects. A very special thank you to Dr. Stuart Maddin for his assistance in getting this publication launched. Dr. Maddin is very excited about this new publication which will update Canadian physicians on recent clinicals and dermatological reports from around the world. He has agreed to provide on-going assistance to this new publication in order to make it easier for dermatologists to be more aware of new therapies for their patients.

This first issue will address recent advances in therapeutic options for a variety of skin diseases including atopic dermatitis, psoriasis, and rosacea. Clinical commentaries for this first issue have been supplied by Dr. Stuart Maddin, Dr. Jerry Tan, and Dr. Richard Thomas (Clinical Assistant Professor, University of British Columbia). I extend a special thanks to each of them for their valuable comments.

The study by Allen and colleagues (2003), demonstrates that pimecrolimus cream is effective and well tolerated when treating atopic dermatitis in children and infants. While the study, by Thiboutot and colleagues (2003), reports on two robust clinicals that clearly demonstrate the efficacy of azelaic acid gel as an effective treatment for moderate, papulopustular rosacea.

Other abstracts offer new options for the treatment of several skin conditions. Kang et al. (2003) found that there were significant improvements in both atopic dermatitis of the head/neck and non-head/neck treated areas following 12-weeks of treatment with 0.1% and 0.03% tacrolimus. Mark and colleagues (2003) found that intense pulse light treatment was effective in reducing rosacea associated blood flow, telangiectasia and erythema. This study was performed on a small number of patients but does offer an objective and quantitative measure of improvement of the patient’s rosacea and suggests why light therapy can be effective. Carboni et al. (2004) reported on the treatment of psoriasis with fumaric acid esters. This treatment was found to be safe, effective and well tolerated with over 82% of patients achieving remission.

All too often, clinicians struggle with choosing between drugs for the treatment of specific dermatoses. Such concerns are addressed in the studies comparing methotrexate with cyclosporine therapy for the treatment of moderate-to-severe psoriasis (Heydendael et al. (2003)) and comparing 15% azelaic acid with 0.75% metronidazole gel in the treatment of rosacea (Elwski et al. (2003)).

Another concern is whether combined therapy offers your patients any advantages over monotherapy in the treatment of psoriasis. Grundmann and colleagues (2004) found that combining UVB with PUVA had a higher efficacy than either monotherapy alone.

Finally, there are a few publications that discuss the importance of topical emollients, as a moisturizer or as the base for a pharmacological preparation, in repairing and restoring moisture skin barrier function. Goustras (2003) and Zhai and colleagues (2003) in their studies measured TEWL and found that the vehicle/base of a topical corticosteroid can have a significant effect on restoring skin hydration. Goustras, in his study on Eumovate, suggests that the cream base or vehicle can offer moisturizing potential that is complementary to the anti-inflammatory action provided by the topical corticosteroid.

This first issue of Focus on Dermatology brings an interesting mix of treatment options including combined therapies of new or existing drugs. This newsletter is a vehicle for sharing clinical information and experience. If you have any comments or thoughts on the content of the newsletter or input for future issues please send them to me at editor@sicg.ca.

Bonnie Kuehl
Atopic Dermatitis

1. Systemic exposure, tolerability, and efficacy of pimecrolimus cream 1% in atopic dermatitis patients.

Abstract: AIMS: To measure pimecrolimus blood concentrations and to evaluate tolerability and efficacy in children and infants treated topically for atopic dermatitis with pimecrolimus cream 1% for three weeks. METHODS: Three open label, non-controlled, multiple topical dose studies were conducted in children aged 8-14 years (study A, ten patients), and in infants aged 8-30 months (study B, eight patients) and 4-11 months (study C, eight patients). Pimecrolimus blood concentrations were determined on days 4 and 22 of treatment, and at end of study. Efficacy was assessed using the Eczema Area and Severity Index (EASI). RESULTS: Pimecrolimus blood concentrations were consistently low, typically (81%) below 1 ng/ml, with more than half of the measurements below the assay limit of quantitation (0.5 ng/ml) in studies A and B. The highest blood concentration measured throughout the three studies was 2.6 ng/ml. The cream was well tolerated, locally and systemically. The most common adverse event suspected to be related to study medication was a transient mild to moderate stinging sensation at the application site in 5/26 patients. There was no indication of any systemic adverse effect. The patients responded well to therapy with a rapid onset of action, usually within four days. Median reductions of EASI from baseline at day 22 were 55% (study A), 63% (study B), and 83% (study C).

CONCLUSION: Three weeks treatment of children and infants with extensive atopic dermatitis, using pimecrolimus cream 1% twice daily, is well tolerated and results in minimal systemic exposure, at which no systemic effect is expected.

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Even though these trials were open label and involved a range of ages (infants - up to 15 years), the results indicate a lack of systemic absorption. Furthermore, the brisk response to therapy, improvement within four days and the fact that this topical agent was well tolerated, are positive factors when treating younger age groups. (commentary Dr. Maddin)

2. Safe treatment of head/neck AD with tacrolimus ointment.

Abstract: BACKGROUND: Atopic dermatitis (AD) with head and neck involvement is common and therapeutically challenging. METHODS: Efficacy and safety data specific to treatment of head/neck regions with tacrolimus ointment (Protopic) from three double-blind, randomized, vehicle-controlled studies are reported. A total of 631 adult and 352 pediatric patients with moderate to severe atopic dermatitis applied the vehicle, 0.03% or 0.1% tacrolimus ointment twice daily to affected areas for up to 12 weeks. RESULTS: Significant improvements from baseline to end of treatment for signs of atopic dermatitis (erythema, edema, excoriation, oozing, scaling, and lichenification) were noted for head/neck and non-head/neck areas treated with either 0.03% or 0.1% tacrolimus ointment (p<0.001). Within each treatment group, the overall 12-week adjusted incidence rate of application site adverse events was similar for both head/neck and non-head/neck areas. The incidence of common adverse events such as pruritus, "skin burning", erythema, infection, and skin tingling in head/neck areas was comparable to that observed in non-head/neck areas within each treatment group. The overall prevalence of application site adverse events decreased rapidly during the first few days of treatment.

CONCLUSION: Tacrolimus ointment is a safe and effective treatment for atopic dermatitis on the head and neck.

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3. One-year follow up of children treated with Chinese medicinal herbs for atopic eczema.

VIEW THE ABSTRACT ONLINE:

4. The moisturisation potential of the emollient base of clobetasone butyrate cream and clobetasone butyrate 0.05% cream: results from two comparative studies.

Two small, laboratory-based, single-blind, and intra-individual studies involving volunteers with dry/normal skin were performed to evaluate the moisturisation potential of the emollient base of clobetasone butyrate (CB) cream (Eumo base) and Eumovate (CB 0.05%) cream. In Study A (n=20), when compared with untreated sites, 2 cm² sites on lower legs treated with Eumo base 10μL/cm² had statistically significant greater skin capacitance (i.e. hydration) over 6 h than sites treated with other emollient creams (E45, Unguentum M and Diprobase). In Study B (n=13), when compared with untreated controls, 5cm² sites on volar forearms treated with CB 0.05% 10μL/cm² cream had statistically significant greater skin capacitance over 24 h than four hydrocortisone-based creams (Eurax HC, Efertalan 0.5%, Efertalan 1.0% and Hc45). With their high concentration of glycerol (25% w/w), Eumo Base and CB 0.05% cream have better moisturising potential than the three other emollient- and four hydrocortisone-based creams, and the emollient base cream is cosmetically acceptable (as assessed by patient questionnaire in Study A (n=60)). The moisturising potential is complementary to the antiinflammatory action of CB 0.05% and may promote faster healing of skin flare-ups.

The loss of barrier function is important in many of the conditions that we treat especially atopic dermatitis. If we can assume that the increased hydration achieved by the clobetasone butyrate cream base (Eumo base) on normal skin also carries on to atopic skin it would be a very attractive product compared with the other bases. Cosmetic acceptability and therefore better compliance is very welcomed by many of my patients. (commentary Dr. Thomas)
Psoriasis


BACKGROUND: Psoriasis is a common, chronic, cell-mediated, inflammatory skin disease. Treatment limitations and a developing understanding of its pathogenesis on a molecular level have encouraged much interest in the field of immunomodulatory therapy. OBJECTIVE: To evaluate the efficacy and safety of fumaric acid esters, in particular dimethylfumarate (DMF), in the treatment of moderate to severe plaque psoriasis intolerant and/or resistant to other conventional systemic therapies. METHODS: A total of 40 patients were enrolled in this study. DMF was orally administered at the daily dose of 30 mg up to 360 mg for a minimum of 6 monthstreatment. Patients were followed-up with psoriasis area and severity index (PASI) score assessment, and clinical and photographic documentation. RESULTS: A total of 33 (82.5%) patients achieved complete clinical remission with DMF treatment: eight after 3 months and 25 after 6 months. Adverse events, such as intolerable abdominal cramps and incoercible diarrhoea, occurred in four patients who, for this reason, interrupted therapy.

CONCLUSION: The findings suggest that DMF is a safe, effective and well-tolerated long-term oral treatment worthy of consideration for selective patients.

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http://content.nejm.org/cgi/content/abstract/349/7/658?view=abstractpmid=12917302
Rosacea

9. A comparison of 15% azelaic acid gel and 0.75% metronidazole gel in the topical treatment of papulopustular rosacea: results of a randomized trial.

VIEW THE ABSTRACT ONLINE:
http://archderm.ama-assn.org/cgi/content/abstract/139/11/1444

Metronidazole has previously been considered to be the gold standard of topical rosacea therapy. This active comparator RCT demonstrated that 15% azelaic acid gel is statistically superior to 0.75% metronidazole gel twice daily over 15 wks in moderate, papulopustular facial rosacea. The magnitude of difference, however, may be of marginal clinical relevance. Of particular clinical interest to practitioners is the potential for enhanced clinical efficacy by combining the use of these agents. (commentary Dr. Tan)


VIEW THE ABSTRACT ONLINE:

This is one of few studies in rosacea using objective quantifiable evaluations of rosacea-associated erythema. Intense pulsed light treatment resulted in improvement in the three outcome parameters: blood flow, erythema intensity and area of telangiectasae. However, this study was small, and was not controlled - thus confounding factors cannot be excluded. A 1/2 face trial design may have provided greater validation in this small study. The duration of improvement and extent of patient satisfaction would also be of clinical interest. This small study should provide the impetus for pursuing a larger controlled clinical trial with relevant clinical endpoints. (commentary Dr. Tan)

VIEW THE ABSTRACT ONLINE:


These 2 large vehicle-controlled RCTs with a total of 664 patients demonstrated the efficacy of 15% azelaic acid (15%) gel in treatment of moderate inflammatory rosacea in reducing inflammatory lesions and erythema and in improving global rosacea assessments. Although typically mild and transient, 38% of subjects reported burning or stinging with active treatment. (commentary Dr. Tan)

Emollients


Factors in the treatment of atopic dermatitis include restoring skin moisture and reducing inflammation. This study evaluated a corticoid oil formulation and its components with respect to their skin hydration potential. Ten healthy Caucasians were enrolled. Five test sites on the left and right forearm of each subject were tested: one site served as a normal skin control (without treatment), whereas four were wetted by spraying distilled water (approximately 0.1 ml) over a 3 cm² skin surface area, and spraying was repeated every 5 min for a total of three applications. Five minutes after the final application, 0.2 ml of the corticoid oil formulation, moisturizing vehicle, and plain peanut oil were applied to each pre-designated site (3 cm²); one site was kept as a blank control (water saturation only). Thirty minutes later, test sites were gently wiped with paper tissues, and visual scoring, transepidermal water loss (TEWL), and capacitance were recorded and repeated at 2 and 3 h. The corticoid oil formulation, plain peanut oil, and moisturizing vehicle significantly increased skin hydration 30 min after each single application, with no statistically significant difference among the treatments at any point. The corticoid oil formulation and plain peanut oil slightly but not significantly elevated TEWL 30 min after application. The results support intuitive dermatologic judgment of advising patients to apply moisturizing medicaments after bathing.
Emollients and moisturizing creams are used to break the dry skin cycle and to maintain the smoothness of the skin. The term 'moisturizer' is often used synonymously with emollient, but moisturizers often contain humectants in order to hydrate the stratum corneum. Dryness is frequently linked to an impaired barrier function observed, for example, in atopic skin, psoriasis, ichthyosis, and contact dermatitis. Dryness and skin barrier disorders are not a single entity, but are characterized by differences in chemistry and morphology in the epidermis. Large differences also exist between moisturizing creams. Moisturizers have multiple functions apart from moistening the skin. Similar to other actives, the efficacy is likely to depend on the dosage, where compliance is a great challenge faced in the management of skin diseases. Strong odor from ingredients and greasy compositions may be disagreeable to the patients. Furthermore, low pH and sensory reactions, from lactic acid and urea for example, may reduce patient acceptance. Once applied to the skin, the ingredients can stay on the surface, be absorbed into the skin, be metabolized, or disappear from the surface by evaporation, sloughing off, or by contact with other materials. In addition to substances considered as actives, e.g. fats and humectants, moisturizers contain substances conventionally considered as excipients (e.g. emulsifiers, antioxidants, preservatives). Recent findings indicate that actives and excipients may have more pronounced effects in the skin than previously considered. Some formulations may deteriorate the skin condition, whereas others improve the clinical appearance and skin barrier function. For example, emulsifiers may weaken the barrier. On the other hand, petrolatum has an immediate barrier-repairing effect in delipidized stratum corneum. Moreover, one ceramide-dominant lipid mixture improved atopic dermatitis and decreased transepidermal water loss (TEWL) in an open-label study in children. In double-blind studies moisturizers with urea have been shown to reduce TEWL in atopic and ichthyotic patients. Urea also makes normal and atopic skin less susceptible against irritation to sodium laurilsulfate. Treatments improving the barrier function may reduce the likelihood of further aggravation of the disease. In order to have optimum effect it is conceivable that moisturizers should be tailored with respect to the epidermal abnormality. New biochemical approaches and non-invasive instruments will increase our understanding of skin barrier disorders and facilitate optimum treatments. The chemistry and function of dry skin and moisturizers is a challenging subject for the practicing dermatologist, as well as for the chemist developing these agents in the pharmaceutical/cosmetic industry.
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