

Journal Watch

Reviewed by AYP Fung 馮貽邦, FC Ip 葉方正, CK Kwan 關志強, KM Lam 林嘉雯,
WY Leung 梁偉耀

Pimecrolimus 1% cream versus betamethasone 17-valerate 0.1% cream in the treatment of facial discoid lupus erythematosus: a double-blinded, randomized pilot study

Barikbin B, Givrad S, Yousefi M, Eskandari F.
Clin Exp Dermatol 2009;34:776-80.

The most common form of chronic cutaneous lupus erythematosus is discoid lupus erythematosus (DLE). The main aim of treatment is to improve the appearance of the affected skin and to prevent new lesions development. The most common form of treatment options included topical corticosteroids and systemic antimalarials. The use of topical corticosteroids has been associated with various side effects including skin atrophy and telangiectases especially over facial area. Therefore, an alternative is necessary for this group of patients.

Topical calcineurin inhibitor (TCI) is an immunomodulator therapy. There are a variety of TCI that are useful for the treatment of inflammatory skin disorders. For example, tacrolimus has been shown to be effective in treating DLE in several studies. Pimecrolimus, being the newest type of TCI, is compared with a common therapeutic agent, betamethasone valerate in treating patients with DLE in this study.

This was a randomized double-blind pilot study performed in the outpatient clinics of two major referral hospitals in Iran. There were 10 patients with moderate to severe DLE of the face recruited and randomized into two groups for 8 weeks treatment and 8 weeks of follow up afterwards. One group used pimecrolimus 1% cream twice daily and the other used betamethasone valerate 0.1% cream twice daily to facial lesions. The patients were assessed on the degree of erythema,

infiltration and presence of scale. The results showed a decrease of 86% and 73% in clinical severity scores for pimecrolimus and betamethasone respectively. The difference in efficacy was not significant between the two groups of patients. There was no adverse effect seen in both groups of patients. The result showed that pimecrolimus 1% cream is comparable in terms of efficacy to betamethasone valerate 0.1% cream in treatment of facial DLE. This study however, is limited by the small sample size and further study with larger number of patients is necessary.

Autoantibodies against epidermal transglutaminase are a sensitive diagnostic marker in patients with dermatitis herpetiformis on a normal or gluten-free diet

Rose C, Armbruster FP, Ruppert J, Igl BW, Zillikens D, Shimanovich I.

J Am Acad Dermatol 2009;61:39-43.

Dermatitis herpetiformis (DH) is a cutaneous manifestation of gluten-sensitive enteropathy (coeliac disease). Patients with DH demonstrate circulating IgA antibodies against epidermal transglutaminase (eTG) and tissue transglutaminase (tTG). It has been suggested that eTG is the autoantigen of DH. The authors aimed to characterize the autoimmune response to eTG and tTG in patients with DH on a normal or gluten-free diet (GFD). Sera from 52 patients with DH were studied for the presence of IgA antibodies to eTG and tTG by enzyme-linked immunosorbant assay. In 38 patients, serum was obtained before initiation of a GFD, whereas 14 patients had been on a GFD for at least 2 years. The results showed that autoantibodies against eTG were detected in 36 of 38 patients (95%) and those against tTG in 30 of 38 patients (79%) with

DH on a normal diet. Of 14 patients on a long-term GFD, 7 patients were free of DH lesions and did not require dapsons treatment. None of these patients showed circulating antibodies against eTG or tTG. The remaining 7 patients on a GFD were not able to stop taking dapsons. All these patients demonstrated anti-eTG antibodies, whereas only 3 of them showed additional reactivity against tTG. The authors concluded that antibodies to eTG are the most sensitive serologic marker in treated and untreated patients with DH and confirm the central role of eTG in the pathogenesis of this disease. Ideally, the autoantibody levels against eTG and tTG before and after introduction of a GFD should also be examined in the same patients.

Randomized, double-blind, placebo-controlled evaluation of the efficacy of oral psoralen plus ultraviolet A for the treatment of plaque-type psoriasis using the Psoriasis Area Severity Index score (improvement of 75% or greater) at 12 weeks

Sivanesan SP, Gattu S, Hong J, Chavez-Frazier A, Bandow GD, Malick F, et al.
J Am Acad Dermatol 2009;61:793-8.

Psoralen plus ultraviolet A (PUVA) for the treatment of psoriasis has never been evaluated using the Psoriasis Area Severity Index (PASI) in a randomized, double-blind, placebo-controlled trial. The lack of such data limits our capacity to estimate PUVA's efficacy relative to other available treatment options. The authors aimed to evaluate the efficacy of PUVA therapy for patients with plaque-type psoriasis. Forty such patients were recruited of which thirty received PUVA and ten received UVA with placebo, both three times per week. PASI scores were assessed at baseline and every 4 weeks thereafter for 12 weeks. By non-responder imputation, 60% (18 of 30) in the PUVA group achieved 75% or more improvement in PASI score after 12 weeks of treatment compared with 0% (0 of 10) in the UVA plus placebo group ($P < 0.0001$). Using intent to treat with last observation carried forward analysis, 63% (19 of 30) in the PUVA group achieved 75% or more improvement in PASI score compared with 0%

(0 of 10) in the UVA plus placebo group ($P < 0.0001$). By per protocol analysis, 86% (18 of 21) in the PUVA group as compared with 0% (0 of 7) in the UVA plus placebo group reached 75% or more improvement in PASI score after 12 weeks ($P < 0.0001$). This study supports the observation that PUVA is a highly efficacious treatment for chronic plaque psoriasis. The study was relatively small with only 40 patients enrolled and 28 patients who completed the protocol. Further studies that involve head-to-head comparison of PUVA with other treatment modalities are needed. The authors also used many statistical models for data analyses including non-responder imputation, last observation carried forward with intent to treat, and per protocol analyses. Each has separate advantages and limitations when determining clinical significance.

Efficacy and safety of calcipotriol plus betamethasone dipropionate scalp formulation compared with calcipotriol scalp solution in the treatment of scalp psoriasis: a randomized controlled trial

Kragballe K, Hoffmann V, Ortonne JP, Tan J, Nordin P, Segaert S.
Br J Dermatol 2009;161:159-66.

A randomized double-blind controlled trial was conducted in 17 dermatology centres in Belgium, Canada, Denmark, France and Sweden. This study was carried out from September 2005 to May 2006 to compare the clinical efficacy and safety of calcipotriol plus betamethasone dipropionate scalp formulation with calcipotriol scalp solution in the treatment of scalp psoriasis.

A total of 312 patients with a clinical diagnosis of scalp psoriasis were recruited in the study, in which 207 were allocated to receive the two-compound scalp formulation and 105 patients to receive calcipotriol scalp solution. Of 272 patients completed the treatment phase, 190 were in the two-compound scalp formulation group and 82 in the calcipotriol scalp solution group.

Patients who were below 18 years old, had received systemic therapy, biological therapies,

phototherapy or very potent (WHO group IV) topical corticosteroids recently were excluded from the study. Clinical efficacy were assessed by the six-point Investigator's Global Assessment (IGA) scale for the severity of scalp psoriasis and the sum of the scores for the three signs constituted the Total Sign Score (TSS).

The proportion of patients with 'clear' or 'minimal' disease at week 8 was significantly greater in the two compound scalp formulation group (68.6%) than in the calcipotriol scalp solution group (31.4%; $p < 0.001$) in terms of IGA score. Improvement was also more rapid with the two compound scalp formulation than with calcipotriol scalp solution.

The authors thus concluded that the once-daily, two-compound scalp formulation, which combines calcipotriol with betamethasone dipropionate, was significantly more effective than twice-daily calcipotriol scalp solution in the management of scalp psoriasis.

Therapeutic effectiveness of various treatments for eosinophilic pustular folliculitis

Fukamachi S, Kabashima K, Sugita K, Kobayashi M, Tokura Y.
Acta Derm Venereol 2009;89:155-9.

Eosinophilic pustular folliculitis (EPF) is a rare dermatosis of unknown aetiology. Many treatments have been used for this condition without success.

This was a retrospective study conducted in a university hospital in Japan to assess the effectiveness of various therapies for eosinophilic pustular folliculitis between 1998 and 2007. Fourteen women and six men with EPF were enrolled during the study period. The effectiveness of each treatment was assessed by a severity score index for EPF based on five items of the essential features of EPF. Eleven patients were treated with oral indomethacin, and the severity scores of all patients were decreased after the treatment. Oral cyclosporine was markedly effective in all 11 patients treated, and topical tacrolimus ointment alleviated the condition in 3 of 7 with one patient

showing a remarkable reduction in the severity score.

The author concluded that oral cyclosporine and topical tacrolimus may be beneficial choices when patients have been resistant to indomethacin or other oral non-steroidal anti-inflammatory drugs. This study was limited by the small sample size and non-randomized design.

Pemphigoid gestationis: early onset and blister formation are associated with adverse pregnancy outcomes

Chi CC, Wang SH, Charles-Holmes R, Ambros-Rudolph C, Powell J, Jenkins R, et al.
Br J Dermatol 2009;160:1222-8.

It has been unclear whether clinical features of pemphigoid gestationis (PG) may affect pregnancy outcomes or whether the adverse outcomes in pregnancies complicated by PG are related to or worsened by systemic corticosteroid treatment. This is a retrospective study carried out in the St John's Institute of Dermatology and two tertiary hospitals in the United Kingdom and Taiwan to evaluate the associations of adverse pregnancy outcomes with clinical features of PG (including trimester of onset, extensive involvement, and presence of blisters), PG autoantibody titre, and systemic corticosteroid treatment.

In this study, the diagnosis of PG was confirmed with immunofluorescence studies and a total of 61 pregnancies complicated by PG in 59 women were included. The outcomes of interest in the study included gestational age at delivery, preterm birth before 37 completed weeks of gestation, low birth weight (LBW) defined as birth weight < 2500 g, small-for-gestational-age defined as birth weight below the 10th percentile for gestational age, fetal loss, congenital malformation and mode of delivery. Results showed that those with PG onset in the second trimester had a reduction in gestational age at delivery of 3.05 weeks compared with disease onset in the third trimester. Those with disease onset in the first and second trimesters of gestation had a reduction in newborn's birth weight of almost 600 g compared with disease onset in the third trimester of gestation. It was also evidenced

that disease onset in the first and second trimesters were 10 times more likely to have LBW children and all preterm births occurred in women with blisters and disease onset in the first and second trimesters. However, there was no significant association between systemic corticosteroid treatment and pregnancy outcomes in this study.

The author therefore concluded that onset of PG in the first or second trimester and presence of blisters should be considered high risk and appropriate obstetric care should be provided. Systemic corticosteroid treatment, in contrast, does not substantially affect pregnancy outcomes, and its use for PG in pregnant women is justified.

Association of cigarette smoking but not alcohol consumption with cutaneous lupus erythematosus

Boeckler P, Cosnes A, Frances C, Hedelin G, Lipsker D.

Arch Dermatol 2009;145:1012-6.

This is a case-control study to look at whether smoking and alcohol intake is associated with cutaneous lupus erythematosus (LE). Some epidemiological studies suggest that smoking is a risk factor in genetically predisposed person to develop LE while alcohol intake is associated with reduced risk. Most of these studies focused on systemic LE and most patients were female. The authors suggested that analysis of risk should not be restricted to patients who met four or more American College of Rheumatology (ACR) criteria in the diagnosis of LE and cutaneous LE should also be included. The study was performed in the form of a questionnaire to obtain data regarding the smoking and drinking habits of patients with cutaneous LE and controls.

A total of 108 patients and 216 controls were recruited. In the 79 patients with LE, 91.1% of them smoked before the onset of LE and the prevalence of smoking in LE patients was higher than controls in both sex. It was found that patients who smoked most were those with cutaneous LE, less than four ACR criteria for systemic LE and negative anti-ds DNA antibody. On the other hand, those with LE who met 4 or more ACR criteria with positive anti-ds DNA antibody smoked

least. Several hypotheses were suggested. Cigarette smoke contains aromatic amines that is known to associate with LE. Cigarette smoke is also found to be phototoxic and has complex immunomodulatory effect. The study concluded that smoking is a risk factor in predisposed patients to develop cutaneous LE but not in those with systemic LE with four or more ACR criteria. Alcohol consumption was not found to be associated with LE in this study. This study was limited by the relative small sample size.

Efficacy of leukotriene receptor antagonist with an anti-H1 receptor antagonist for treatment of chronic idiopathic urticaria

Wan KS.

J Dermatol Treat 2009;20:194-7.

This is a single-blinded randomized placebo control trial to study the efficacy of combination therapy of anti-histamine 1 and leukotriene receptor antagonist in the treatment of chronic idiopathic urticaria. A total of 120 patients with chronic idiopathic urticaria were randomly allocated to four groups to receive the treatment for four weeks. The treatment groups were 1) Oral hydroxyzine 25 mg and cetirizine 5 mg BID, 2) Oral hydroxyzine 25 mg and famotidine 20 mg BID, 3) Oral hydroxyzine 25 mg and montelukast 5 mg BID, 4) Oral placebo BID. A daily record of severity of whealing was collected and was presented as weekly aggregate urticaria activity score.

The study found significant percentage of improvement in Group 1: 23.3%, Group 2: 63.3% and Group 3: 53.3%. The efficacy of combination of anti-histamine 1 with anti-histamine 2 was higher than that of combination of anti-histamine 1 with leukotriene receptor antagonist. The author concluded that combination treatment with anti-histamine 1 and anti-histamine 2 for chronic idiopathic urticaria is the most efficacious but combination of anti-histamine 1 and leukotriene receptor antagonist has a role as alternative regimen. The side effect profile is mainly due the sedative effect of hydroxyzine. The study is limited by the single-blinded design and relative small sample size.

Consensus statement on the management of chronic hand eczema

English J, Aldridge R, Gawkrödger DJ, Kownacki S, Statham B, White JM, et al.
Clin Exp Dermatol 2009;34:761-9.

Hand eczema is common and it affects all age groups with different causes. There is no evidence-based guideline for chronic hand eczema currently. This statement is developed by a panel of dermatologists and a general practitioner with a special interest in dermatology. They discussed the published data and clinical practice in both primary and secondary care intended to guide the management of chronic hand eczema. As there are insufficient good-quality studies for critical review, this is not a systematic review.

A careful full history should be taken. Exclusion of other diagnoses including infection and infestation is necessary. They should be given advice on skin-protection programme like protecting the hands with gloves and/or barrier creams and avoiding likely irritants and allergens. Initial treatment should include the use of emollients and a trial of a potent and very potent topical steroid. The trial should last for a few weeks. The case should be referred to a dermatologist if the response is not satisfactory. The management should be reviewed for the referred patients including history, patient education and assessment of skin condition and treatment. Other appropriate investigations should be done like patch test, prick testing, swabs, serum IgE and specific IgE tests and cutaneous allergic investigations. The initial treatment should be continued or modified. If the condition does not improve, systemic treatment should be tried according to the need of different patients even though there is lack of adequate evidence from comparative randomized trials. Topical psoralen UVA (PUVA) is used in case of hyperkeratotic hand eczema which is relatively safe. There are other options like oral steroid (if a rapid control is needed), ciclosporine and azathioprine. Acitretin

is effective in hyperkeratotic hand eczema. Alitretinoin is the only treatment specifically licensed for the treatment of hand eczema and its efficacy has been shown in a randomized controlled trial.

A comprehensive review of biomarkers in psoriasis

Rashmi R, Rao KS, Basavaraj KH.
Clin Exp Dermatol 2009;34:658-63.

Psoriasis is a common chronic recurrent skin disorder with inflammatory changes in the epidermis and dermis. The pathogenesis is still not clear. It is suggested that psoriasis is a multifactorial disease with genetic predisposition. Some factors like stress, drug, trauma, infections and climate are found to trigger psoriasis. Its response to treatment with T-cell depletion and antitumour necrosis factor (TNF- α) implied involvement of T-cells and TNF- α in the pathogenesis of psoriasis. In psoriatic lesions, there is overexpression and underexpression of certain proteins. These can be classified as abnormal keratinocyte differentiation, keratinocyte hyperproliferation and inflammation. Oxidative stress and abnormal lipid metabolism are found to be associated. There are aberrant expression of antigens associated with hyperproliferation and induced expression of major histocompatibility complex class II antigens and intercellular adhesion molecules. Dermal mast cells and dendritic cells are increased in psoriatic skin lesions. There are reports of involvement of neuropeptides and various autoantibodies such as antistratum corneum antibody, antikeratin antibody and antilipocortin-I antibody in patients with psoriasis.

The authors reviewed the current evidence of various markers for psoriasis that can aid in better understanding of the disease. Further studies are necessary for the biomarkers targeted for effective treatment.

Implications of replacing the existing diagnostic strategy for *Neisseria gonorrhoeae* and *Chlamydia trachomatis* infections with sole molecular testing of urine specimens in a sexually transmitted infection clinic setting

Ho KM, Lo YCJ, Lo CTA, Cheng KF, Chan FK.
Sex Trans Dis 2009;85:322-5.

The Social Hygiene Clinics (SHC) in Hong Kong nowadays use urogenital swabs for *Neisseria gonorrhoeae* culture (NG) and for *Chlamydia trachomatis* (CT) polymerase chain reaction (PCR) in making the diagnosis of gonorrhoea and chlamydial urogenital tract infections. The authors of this paper evaluate the nucleic acid testing of urine samples by Aptima Combo 2 (AC2) against conventional NG culture and CT PCR tests by urogenital swabs in a public SHC in Hong Kong.

Urogenital swabs and urine samples of 414 patients were collected. In the conventional side, the swabs were subjected to on-site Gram stain microscopy and then inoculated onto modified Thayer Martin medium for NG culture. The swabs were also used for the CT PCR testing by Amplicor test. In the testing side, urine samples were subjected to NG and CT nucleic acid testing by AC2. The sensitivity and specificity of AC2 for NG were 100% (35/35) and 98.4% (373/379) respectively with the reference to NG culture as the standard. On the other hand, the sensitivity and specificity of AC2 for CT were 98.7% (78/79) and 97.5% (313/321) respectively with the reference to CT Amplicor test as the standard. Fourteen samples of CT Amplicor test yielded uninterpretable results because of the presence of inhibitors.

The authors concluded that nucleic acid molecular testing of urine samples for NG and CT yielded comparable results to the existing conventional diagnostic strategy in Hong Kong SHC.

Adequacy of testing, empiric treatment, and referral for adult male emergency department patients with possible chlamydia and/or gonorrhoea urethritis

Merchant RC, DePalo DM, Stein MD, Rich JD.
Int J STD AIDS 2009;20:534-9.

Since 1993, the Centres for Disease Control and Prevention (CDC) has issued guidelines for sexually transmitted diseases (STD) on testing, treatment and referral. The guidelines suggested that men with suspected chlamydia and/or gonorrhoea urethritis should be tested to determine the specific cause of infection even if empiric treatment is initiated. In addition to an accurate diagnosis, specific diagnosis may improve the treatment compliance and partner notification. This study reviewed the adequacy of testing, empiric treatment and referral for further evaluation of adult male patients who suspected to have chlamydial and/or gonococcal urethritis in an urban, academic emergency department (ED).

Total 968 patients' medical records were included for the analysis retrospectively. The median age was 29 years old. Forty-two percent had discharge and dysuria, 16% had discharge only, 24% had dysuria only, 16% had no symptoms. Total 84% of the patients were tested for chlamydia and gonorrhoea, only 16% were tested for HIV and 27% for syphilis. A positive syphilitic test was found in 3% of patients tested. There were still 16% of patients who did not receive chlamydia and gonorrhoea testing. Moreover, the screening for HIV and syphilis in suspected chlamydia and/or gonorrhoea ED attendees was poor. Therefore, the authors suggested that more explicit guidance from CDC regarding syphilis and HIV testing is needed. The CDC recommends empiric treatment should be considered when the prevalence of infection in the community is high, compliance with treatment is not assured and after exposure to known or suspected chlamydia and/or gonorrhoea infected sources. Vast majority (92%) of male ED patients with suspected chlamydial and/or gonococcal urethritis received empiric treatment but only 29% were actually infected with chlamydia, gonorrhoea and both. Therefore, the authors also suggested that better methods of choosing which patient to receive empiric antibiotics in ED such as by determining the prevalence of the disease and taking more detail history are needed.