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Journal Watch

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New topical photodynamic therapy for treatment of hidradenitis suppurativa using methylene blue niosomal gel: a single-blind, randomized, comparative study

Fadel MA, Tawfik AA.
Clin Exp Dermatol 2015;40:116-22.

Hidradenitis suppurativa (HS) is a chronic, relapsing and remitting condition principally affecting skin that contains apocrine glands. In severe disease, the condition imposes a major negative impact to the psychosocial well-being of the patients. Conventional treatments include antibiotics, anti-androgens, surgery and anti-tumour necrosis factor. Laser therapy (neodymium-doped-yttrium-aluminum-garnet) has also been employed to treat the disease by targeting the hair follicles. Photodynamic therapy using intense pulsed light (IPL) and aminolaevulinic acid (ALA) as photosensitiser have been used to treat HS with variable success. Undesirable adverse effects have been also reported with the treatment.

The aim of this study is to evaluate the clinical efficacy and safety profile of photodynamic therapy using IPL with methylene blue (MB) as photosensitiser. MB was delivered in form of a niosomal gel. In this study, 11 HS patients were recruited. All patients underwent a randomised split-body trial. Both sides of the patients were treated by phototherapy using the IPL (operated with a 630 nm filter). However, one side was treated with niosomal MB (NMB) gel while the other side with unloaded (free) MB (FMB) gel. Patients were followed up at 1, 3 and 6 months interval post-treatment. A statistically significant higher degree of lesional reduction was noted with NMB gel versus FMB gel (77.3% vs 44.1% reduction; $p<0.01$). Good safety profile was observed in both groups with no significant pain, erythema or hyperpigmentation in both treatment groups. The authors concluded that the use of IPL with MB as a sensitiser was a safe and efficacious way to treat HS. Drug delivery in niosomes was observed to provide more effective penetration into the dermis and may confer a greater clinical efficacy.

Allergy to dust mites may contribute to early onset and severity of alopecia areata

Li SF, Zhang XT, Qi SL, Ye YT, Cao H, Yang YQ, et al.
Clin Exp Dermatol 2015;40:171-6.

Alopecia areata (AA) is a recurrent, non-cicatricial alopecia with a presumably autoimmune aetiology. AA is associated with profound psychological and social disturbance to patients. The exact aetiology of AA is yet to be elucidated and is epidemiologically linked to allergic diseases such as allergic rhinitis, asthma and atopic dermatitis. However, the significance of the association of atopy with AA is largely unclear.

The current study aims to investigate the correlation between total serum IgE and allergen-specific IgE with the onset and severity of AA. In the study, 461 serological samples were collected from 351 AA patients and 110 healthy controls (HC). The samples were tested for the total serum IgE (tIgE) and allergen-specific IgE (sIgE) by a fluorescence enzyme immunoassay system (ImmunoCAP-100; Phadia, Uppsala, Sweden) and *in vitro* test. There was no significance difference of the prevalence rates of raised tIgE (>120 IU/mL) detected in both AA patients (29.3%) and HC

(21.8%). However, a statistically significant higher level of tIgE was observed in AA patients (235.2±575.1) than in HC (110.4±183.8) ($p<0.001$). Among the patients with AA, *Dermatophagoides pteronyssinus* and *Dermatophagoides farinae* were the two most common allergens with sensitisation (*Der p:*31.1%; *Der f:* 29.0%). The authors also compared the IgE levels between patients with early (0-19 yr) versus late-onset (20-59 yr) AA. The prevalence of tIgE and sIgE against dust mites (*Der p and Der f*) were significantly higher in the patients with early onset than those with late-onset AA (tIgE, $p<0.01$; sLgE, $p=0.001$). Importantly, the higher tIgE and sIgE were independent of background atopic history. The authors concluded that sensitisation to house dust mites may have a role in triggering the immune mechanism in the pathogenesis of AA, especially in patients with early onset disease and those of Chinese descent.

Association of metabolic syndrome and hidradenitis suppurativa

Miller IM, Ellervik C, Vinding GR, Zarchi K, Ibler KS, Knudsen KM, et al.
JAMA Dermatol 2014;150:1273-80.

Hidradenitis suppurativa (HS) is a chronic, localised inflammatory skin disease of apocrine gland-bearing skin. Metabolic syndrome (MeS) (diabetes mellitus, hypertension, dyslipidaemia, obesity) occurs more commonly with chronic inflammatory diseases such as rheumatoid arthritis and psoriasis. In contrast to psoriasis, HS may be considered as a more localised inflammation of the skin. An association between HS and MeS has been hypothesised. This is a cross-sectional study to explore the association of HS and MeS and assess its possible clinical relevance.

Two different groups of individuals with HS were recruited. The first group was identified in a general population sample (population HS group). The second was identified in a hospital-based sample (hospital HS group). Non-HS participants were defined as participants without HS from the general population. The definition of severity of HS was based on numbers and locations of boils and subsequent scarring (Hurley score/Sartorius score). The subjects were investigated for the presence of any co-morbidities (diabetes mellitus, hypertension, dyslipidaemia and obesity.).

A total of 32 individuals with HS from the hospital, 326 with HS from the general population and 14851 non-HS individuals from the general population were identified. When compared with the non-HS group, the odds ratios (ORs) for the hospital HS and population HS groups were 3.89 (95%CI, 1.90-7.98) and 2.08 (95%CI, 1.61-2.69), respectively, for MeS. The ORs were higher for the hospital HS group compared with the population HS group. The association between HS and MeS was not influenced by the degree of HS severity.

This population- and hospital-based study suggested an association between HS and MeS. When examining the MeS components individually, the ORs for diabetes mellitus indicated a significant positive association. The ORs for general and abdominal obesity were also found to be significant. Moreover, the association of an atherogenic lipid profile (increased TG levels and decreased HDL levels) was significant. Hypertension was only significant with regard to the hospital HS group. These co-morbidities indicate that HS patients require general medical attention beyond the skin. However, since this is a cross-sectional study, the causality between HS and MeS cannot be identified. Future longitudinal studies are needed to explore the temporal relationship of these associations.

Treatment of nail psoriasis: best practice recommendations from the medical board of the national psoriasis foundation

Crowley JJ, Weinberg JM, Wu JJ, Robertson AD, Van Voorhees AS.
JAMA Dermatol 2015;151:87-94.

Approximately 50% of patients with psoriasis have some nail involvement. Patients with psoriatic arthritis have rates of nail disease as high as 70%. Evidence also showed that nail psoriasis may be a predictor of joint disease developing later in life. The Nail Psoriasis Severity Index (NAPSI) was developed to measure changes in nail disease

over time. Various treatment options are available for nail psoriasis, including topical products, procedural interventions, oral systemic and biologic agents. This article critically reviewed the identified publications and proposed evidence-based practical treatment recommendations for nail psoriasis.

The authors performed PubMed search for articles on nail psoriasis from 1 January 1947 to 11 May 2014. Treatment recommendations for four types of clinical nail psoriasis were developed based on the evidence reviewed in this study and expert opinion from the Medical Board of the National Psoriasis Foundation. Treatment of nail psoriasis should include a comprehensive assessment of the extent of skin disease, severity of nail disease and psoriatic arthritis against any negative impact on the quality of life. All cases should be evaluated for onychomycosis. The treatment recommendations are as follows:

For patients with psoriasis limited to the nails, high-potency topical corticosteroids alone or in combination with calcipotriol were recommended. Intralesional corticosteroids were also recommended. Systemic and biologic treatments were not recommended.

Adalimumab, etanercept, intralesional corticosteroids, ustekinumab, methotrexate and acitretin were recommended (ranking order from highest to lowest) for patients with psoriasis limited to the nails in which topical therapy has failed.

Adalimumab, etanercept, ustekinumab, methotrexate, acitretin, infliximab and apremilast may be considered in patients with psoriasis of the skin and nails where topical therapies have not adequately controlled the disease.

For patients with skin, joint and nail disease, adalimumab, etanercept, ustekinumab, infliximab, methotrexate, apremilast and golimumab were recommended (ranking order from highest to lowest).

Association between malignancy and topical use of pimecrolimus

Margolis DJ, Abuabara K, Hoffstad OJ, Wan J, Raimondo D, Bilker WB.
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Pimecrolimus, a topical calcineurin inhibitor, was approved in December 2001 by the FDA for the treatment of mild to moderate atopic dermatitis (AD) in children at least two years old. Systemic calcineurin inhibitors were originally approved as immunosuppressive agents to be used after solid organ transplantation to prevent organ rejection. Adverse event associated with the use of these agents includes an increased risk of malignancy, especially skin cancer and lymphoma. A black box warning indicates a potential risk of malignancy associated with topical pimecrolimus in treating atopic dermatitis.

The Pediatric Eczema Elective Registry (PEER) study was established as part of the post-marketing commitments for the approval of this drug. It was a longitudinal cohort study and the purpose was to follow up children with AD for 10 years who had at least 6 weeks of exposure to pimecrolimus to determine their incidence of malignancy. The observed rates are compared with standardised rates from the Surveillance, Epidemiology, and End Results (SEER) program of the National Cancer Institute.

Overall 7,457 children were enrolled in the PEER, with a total of 26,792 person-years and a mean of 793g pimecrolimus was used. There were five malignancies reported up to May 2014 (two leukaemias, one osteosarcoma and two lymphomas). There were no skin cancers. The standardised incidence ratio for all malignancies based on the age-standardised SEER population was 1.2. The standardised incidence ratios were 2.0 (95%CI, 0.5-8.2) for leukaemia and 2.9 (95%CI, 0.7-11.7) for lymphoma. None of these findings reached statistical significance.

In conclusion, based on more than 25,000 person-years of follow-up, pimecrolimus as used in the PEER study did not appear to be associated with an increased risk of malignancy when compared to the SEER data and no skin cancer was recorded.

Evaluation of syndromic management of sexual transmitted infections within the Kisumu Incidence Cohort Study

Otieno FO, Ndivo R, Oswago S, Ondiek J, Pals S, McLellan-Lemal E, et al.
Int J STD AIDS 2014;25:851-9.

Syndromic approach for sexual transmitted infections (STI) management, theoretically, is suitable if the required clinical/diagnostic facilities are unavailable. To certain extent, this may prevent the spread of STIs and potentially avoid the loss of follow-up for laboratory results.

The aim of this study is to assess the correlation between the syndromic management and laboratory diagnosis. During the two-year study period in a primary care clinic, HIV-negative adults aged 18 to 34 years, who have had sexual intercourse at least once in the past three months were eligible for study. The participant completed an audio computer-assisted self-interview (ACASI) and the clinician completed the computer-assisted personal interview (CAPI) and performed a physical examination. Blood, urine and vaginal swabs were collected for laboratory testing of gonorrhoea, chlamydia, syphilis, HSV-2 serology and HIV.

A total of 864 participants were screened. Eighty-eight (10.4%) patients were diagnosed to have STIs by CAPI whereas 272 (32.2%) patients diagnosed to STIs by laboratory tests. The prevalence of STIs was greater in women than men by both CAPI (17.2% vs. 3.6% $p<0.0001$) and laboratory (48.6% vs. 15.6% $p<0.0001$). The agreement between CAPI and laboratory diagnosis had an overall kappa score of 0.09 (95% CI 0.03-0.15). The positive predictive value (PPV) of CAPI was 50.6% with syphilis being the lowest at 0% and HSV 2 being the highest at 63.6%. The PPV was dramatically dropped to 11.3% if syphilis and HSV 2 were not included. Syndromic approach was significantly associated with over diagnosis of gonorrhoea (9.5% vs. 2.4% $p<0.008$) when compared with laboratory diagnosis. For chlamydia, syndromic approach also tended to have over diagnosis than laboratory though not statistical significant (9.5% vs. 2.8% $p<0.27$). When ACASI was compared with CAPI, more patients reported symptoms on ACASI than CAPI in abdominal/scrotal pain (8.1% vs. 4.1% $p<0.0001$), genital ulcers (7.0% vs. 2.3% $p<0.0001$) and vaginal/urethral discharge (4.6% vs. 1.4% $p<0.0001$).

The authors commented that syndromic management of STIs was not sufficient in the primary care clinic and the high prevalence of asymptomatic infection may be one of the reasons behind.

Impact of genital warts on emotional and sexual well-being differs by gender

Vriend HJ, Nieuwkerk PT, van der Sande MA.
Int J STD AIDS 2014;25:949-55.

Genital wart (GW) is a common sexually transmitted infection (STI) that is caused by human papillomavirus (HPV). However, its impact on emotion and sexual well-being has not been assessed. The aim of this study is to assess the health-related quality of life (HRQoL) through two measurement tools: 1) the generic EQ-5D and 2) CECA-10 on patients diagnosed to have GW. EQ-5D stands for European Quality of Life that had previously been used in a wide range of clinical areas. It consists of a descriptive part in which the patient indicated the level of the problems on five dimensions: mobility, self-care, usual activities, pain/discomfort and anxiety/depression. There is a visual analogue scale from 0 (the worst) to 100 (the best) on the imaginable health state. CECA-10 stands for Specific Questionnaire for Condylomata Acuminata and was previously shown to be a valid measure of HRQoL in patients with GW. It consists of 10 statements on the impact of GW on emotional dimensions (6 statements) and sexual activity dimensions (4 statements). CECA scores were also standardised for a scoring system from 0 (the worst HRQoL) to 100 (the best HRQoL).

There were 104 patients diagnosed with GW: 50 women; 38 heterosexual men and 16 MSM. Women had more warts than men (median 4.5 vs. 3) but more men had larger warts than women (24% of heterosexual men, 19% of MSM vs. 16% of women) although not statistically significant. EQ-5D showed that women rated their health state

lower than men: 75.3% (95% CI 70.3-80.2) for women; 83.7% (95% CI 79.3-88.2) for heterosexual men and 82.1 (95% CI 75.4-88.9) for MSM. For emotional dimension CECA, the heterosexual men (60.9 with 95% CI 54.4-67.5) had a higher score than women (48.4 with 95% CI 42.3-52.4). For the sexual activity dimension CECA, the heterosexual men (71.5 with 95% CI 63.5-79.6) also had a high score than women (55.7 with 95% CI 48.3-63.0). Both were statistically significant. The MSM had highest emotional score (70.1 with 95% CI 57.4-82.7) and had similar sexual activity score with heterosexual men (70.8 with 95% CI 54.5-87.2). However, these were not significant in MSM patients. The more number of GW in women was significantly associated with lower CECA score.

The authors concluded that sexual and clinical factors influenced the impact of GW on the well-being in women whereas no such factors were found in men.

Topical rapamycin combined with pulsed dye laser in the treatment of capillary vascular malformations in Sturge-Weber syndrome: phase II, randomized, double-blind, intraindividual placebo-controlled clinical trial

Marqués L, Nùñez-Córdoba JM, Aguado L, Pretel M, Boixeda P, Nagore E, et al.
J Am Acad Dermatol 2015;72:151-8.

Sturge-Weber syndrome (SWS) is a congenital capillary-venous malformation (port-wine stain (PWS)) affecting the face, eyes and central nervous system. Pulsed dye laser (PDL) is the standard treatment for the facial lesions, yet complete resolution is rare and recurrence is common. It was believed that the local hypoxia induced after laser photo-thermolysis resulted in the increase in expression of multiple pro-angiogenic factors and stimulation of the mammalian target of rapamycin (mTOR) pathway, causing regeneration and revascularisation. Rapamycin is an immunosuppressive agent capable of inhibiting mTOR-mediated function and had been shown to be effective in treating various hypervascular anomalies.

In this study, the authors aimed at evaluating the efficacy of topical rapamycin alone and in combination with PDL in treating PWS in patients with SWS.

Patients with SWS were recruited. Four interventions on each subjects were evaluated: (1) placebo, (2) rapamycin, (3) PDL + placebo, (4) PDL + rapamycin. All patients received two sessions of PDL treatment at 6-week intervals and topical 1% rapamycin cream for 12 weeks. Patients were then assessed clinically using digital photographic computerised system at week 6, 12 and 18. Histological assessment was also performed at week 12 to evaluate the number of vessels at the treatment area.

Twenty-three adult patients were recruited with similar baseline digital photographic image scores. Most of them (91%) had prior PDL treatments. It was found that combination of PDL and rapamycin showed significantly lower scores than other treatment arms on each assessment visits. Histological assessment also revealed a significantly lower percentage of vessels in PDL and rapamycin group. The interventions were generally well-tolerated. Although systemic absorption of rapamycin was detected, no clinical abnormalities were found.

The authors concluded that combination of rapamycin with PDL seems to be an effective treatment for PWS in patients with SWS. However, the short follow-up period of this study cannot guarantee long-term efficacy. Moreover, the effectiveness of PDL may be compromised with the increased in thickness of PWS in these adult subjects and the prior treatments with PDL might have destroyed the more superficial, thinner vessels which made the subsequent PDL less effective. Hence, this combination therapy might be more effective in paediatric patients. Yet, the clinical relevance of systemic absorption of rapamycin in paediatic patients needs further evaluation.

Treatment of coexistent psoriasis and lupus erythematosus

Varada S, Gottlieb AB, Merola JF, Saraiya AR, Tintle SJ.
J Am Acad Dermatol 2015;72:253-60

Psoriasis and lupus erythematosus (LE) are both immune-mediated diseases. However, their coexistence, though rare, presents a significant clinical challenge. As the medication used in LE, might either be ineffective or even contraindicated for patients with psoriasis, and vice versa. Anti-tumour necrosis factor alpha (TNF-α) agents had been shown to be effective in LE patients in anecdotal reports, although it is commonly avoided as the concern of lupus flare.

In this retrospective study, the authors aimed at evaluated the epidemiology, clinical and serological characteristics of patient with co-existent LE and psoriasis and determined the risk of lupus flare with the use of TNF-α inhibitors.

Clinical records of patients with diagnosis of psoriasis or psoriatic arthritis (PsA) and at least one type of LE were retrieved from two tertiary-care academic institutions from 1990 to 2013. A total of 96 patients were recruited, 77.1% were white. A relatively higher prevalence (42.0%) of PsA was detected than the general cutaneous psoriasis-alone population. Among 25 of those who had received at least one biologic, TNF-α inhibitors (namely infliximab and etanercept), ustekinumab and abatacept, there was only one case of lupus flare after using TNF-α inhibitors and 9 patients had subclinical seroconversions without worsening of LE condition. Four of the five patients who had received ustekinumab and all three who received abatacept reported improvement in both cutaneous psoriasis and lupus symptoms, oral ulcers and haematological abnormalities.

The authors concluded that anti-TNF-α agents, ustekinumab and abatacept, may be a treatment option for patients with concomitant psoriasis and lupus. However, this study was limited by its retrospective nature, small sample size and incomplete documentation.

Spectrum of cutaneous manifestations of type 1 diabetes mellitus in 500 South Asian patients

Sawatkar GU, Kanwar AJ, Dogra S, Bhadada SK, Dayal D.
Br J Dermatol 2014;171:1402-6.

There has been very few data on the cutaneous manifestations of type 1 diabetes mellitus (DM). The aim of this study was to look at the spectrum of dermatoses in type 1 DM patients. In addition, it also studied the effects of long-term glucose control and disease duration on these dermatoses.

The authors performed clinical examination and relevant investigations in 500 subjects with type 1 DM which enrolled from July 2011 to June 2012 in India. Different dermatoses were found and their correlation with the duration of diabetes was studied.

Five hundred patients were recruited. The mean age was 16.9±6.9 years (range 1-25 years) and the mean total duration of diabetes was 4.43± 4.4 years. Three hundred and thirty-nine patients (67.8%) had one or more dermatoses and the cutaneous adverse effects related to insulin injections (CAII) were noted to be lipohypertrophy (41%), lipoatrophy (0.6%), post-inflammatory hyperpigmentation (3%), acanthosis nigricans (0.4%) which was most common in comparison to other adverse effects such as limited joint mobility (LJM) (16.8%), xerosis (15.8%) and scleroderma-like skin changes (10%). In addition, there was a significantly higher chance of lipohypertrophy ($p=0.000$), LJM ($p=0.000$), scleroderma-like skin changes ($p=0.000$), diabetic dermopathy ($p=0.000$), skin tags ($p=0.002$) and acanthosis nigricans ($p=0.005$) with a longer duration of DM (>4.4 years). The blood glucose level was shown to be significantly correlated to lipohypertrophy, LJM and scleroderma like skin changes.

In summary, the authors concluded that cutaneous changes are common in young Asian patients with type 1 DM. In order to prevent these dermatoses, doctors need to increase their awareness and provide information, education and counselling to patients and care givers.

Sunlight exposure behaviour and vitamin D status in photosensitive patients: longitudinal comparative study with healthy individuals at U.K. latitude

Rhodes LE, Webb AR, Berry JL, Felton SJ, Marjanovic EJ, et al.
Br J Dermatol 2014;171:1478-86.

People living in northerly latitudes often suffer from low vitamin D levels. Patients who suffer from photosensitive skin problems are recommended to avoid sun light, however, their sunlight exposure levels, photoprotective measures and vitamin D status are unknown. The aim of this study was to look at the seasonal vitamin D level in photosensitive patients relative to healthy individuals and to assess the demographic and quantitative behavioural contributors.

The authors conducted a longitudinal prospective cohort study examining year-round 25-hydroxyvitamin D [25(OH)D] levels, oral vitamin D intake and sun-exposure behaviour in photosensitive patients (n=53) diagnosed at a photoinvestigation unit located at 53.5 North unit, compared with healthy adults (n=109).

The results showed that photosensitive patients achieved seasonal 25(OH)D variation. Almost half (47%) of the patients was 25(OH)D level insufficient (<20 ng mLi^{-1}) in summer and rising to 73% in winter and even 9% of the patients was 25(OH)D deficient (<10 ng mLi^{-1}) in summer and increased to 32% in winter. After the adjustment for demographic factors, compared to healthy volunteers, the mean values of 25(OH)D level in patients were lower by 18% (95% CI 4-29) in summer (p=0.02) and 25% lower (95% CI 7-39) in winter (p=0.01). This difference in 25(OH)D between cohorts could be explained by behavioural factors. There was a smaller skin surface area exposure (p=0.004), lower weekend ultraviolet B doses (p<0.001)and greater sunscreen use (p<0.001) in study subjects, while average oral vitamin D intake was low in both groups but there was no significant difference in supplementation or diet (photosensitive: 2.94 mcg/day vs. healthy: 3.23 mcg/day). The 25(OH)D levels could be increased by the supplementation and summer surface area exposure. It was found that 1 mcg per day increment in supplementary vitamin D raised summer and winter 25(OH)D by 5% (95% CI 3-7) and 9% (95% CI 5-12), respectively (both p<0.001).

The authors concluded that photosensitive patients are at increased risk of year-round low vitamin D level. It is recommended that advice should be given on oral supplement to this group of patients.

Excision of fascia in melanoma thicker than 2 mm: no evidence for improved clinical outcome

Hunger RE, Seyed Jafari SM, Angermeier S, Shafighi M.
Br J Dermatol 2014;171:1391-6.

There were different ways among surgeons in obtaining the depth of wide excision for primary cutaneous melanomas due to lack of data. The aim of this study was to evaluate the clinical effect of excision of the deep fascia in melanomas thicker than 2 mm on patient outcome.

A retrospective cohort review (1996-2012) of patients with melanomas thicker than 2 mm was done on patients underwent excision with a 1-cm margin. Data such as sex, age, tumour location, tumour type, Breslow depth and presence of ulceration were collected. The data on loco-regional and distant metastases, local recurrences, and disease-free and overall survival were compared between the fascia-excised and the fascia-preserved groups.

This study recruited 2182 patients with malignant melanomas. There were 213 melanomas thicker than 2 mm. The mean Breslow depth was 4.2 mm and the mean age of the patients was 62.6 years. The median follow-up was 1547 days.

The analysis of data showed that there was no significant difference in the number of deaths attributable to melanoma (p=0.72), local recurrence (p=0.71), and locoregional (p=0.87) and distant metastases (p=0.34) between the study groups. In addition, Kaplan-Meier and Cox regression analysis of both groups showed no significant difference in disease-free [p=0.35; hazard ratio (HR) 1.25; 95% confidence interval (CI) 0.79-1.97] and overall survival (p=0.63; HR 1.18; 95% CI 0.61-2.27).

The authors commented that excision of the deep fascia did not improve the outcome of melanomas thicker than 2 mm.