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Journal Watch

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Influence of smoking on disease severity and antimalarial therapy in cutaneous lupus erythematosus: analysis of 1002 patients from the EUSCLE database

Kuhn A, Sigges J, Biazar C, Ruland V, Patsinakidis N, Landmann A, et al.
Br J Dermatol 2014;171:571-9.

The role of smoking in the activity of the cutaneous lupus erythematosus and the efficacy of antimalarial drugs have not been well understood. This study was aimed to investigate the impact of smoking on the disease severity and antimalarial treatment in patients with cutaneous lupus erythematosus using the Core Set Questionnaire of the European Society of Cutaneous Lupus Erythematosus (EUSCLE).

This was a cross-sectional study in 14 countries which recruited a total of 1002 patients (234 male, 768 female) with different cutaneous lupus erythematosus subtypes. EUSCLE Core Set Questionnaire was employed to assess the smoking behaviour in 838 patients. The results were analysed with the Cutaneous Lupus Erythematosus Disease Area and Severity Index (CLASI) and the efficacy of antimalarial treatment was investigated.

It was found that a large proportion (87.2%) of the 499 patients with cutaneous lupus erythematosus, had already smoked at the time when the diagnosis was first made. The results showed that patients with intermittent cutaneous lupus erythematosus had smoked significantly more than patients with subacute cutaneous lupus erythematosus ($p<0.05$) and chronic cutaneous lupus erythematosus ($p<0.05$). The total CLASI activity and the damage score of patients with cutaneous lupus erythematosus was 6.6±7.1 and 2.6±4.3, respectively. Besides, the total CLASI activity was higher in patients who had smoked than that in nonsmokers.

The study showed that antimalarial treatment was effective in 84.3% of cases, and had a significantly higher successful rate in nonsmokers than in patients with cutaneous lupus erythematosus who had smoked before ($p<0.05$).

In summary, the authors concluded that smoking had a negative impact on cutaneous lupus erythematosus disease severity and reduced the efficacy of the antimalarial treatment.

High prevalence of circulating autoantibodies against thyroid hormones in vitiligo and correlation with clinical and historical parameters of patients

Colucci R, Lotti F, Dragoni F, Arunachalam M, Lotti T, Benvenga S, et al.
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In the normal population, autoantibodies against thyroid hormones (THAbs) directed towards triiodothyronine (T3-Ab) or thyroxine (T4-Ab) are uncommon. However, they could be found elevated in certain nonthyroidal autoimmune diseases and they tend to correlate with future autoimmune thyroid disorders. This study was meant to see if there was any prognostic role of the autoantibodies in patients suffered from vitiligo.

This study assessed the prevalence of THAbs in patients with vitiligo and analysed these antibodies to find out if they would correlate with the clinical and historical parameters.

A total of 79 patients with nonsegmental vitiligo and 100 normal people as controls were recruited. Information such as the physical findings of vitiligo and family and personal medical history were collected. Thyroid autoantibodies, antinuclear antibodies and thyroid hormones were evaluated. A radioimmunoprecipitation technique was used to measure IgM T3-Ab, IgG T3-Ab, IgM T4-Ab and IgG T4-Ab.

The study found that 77 out of 79 patients (97%) had one or more types of THAb (11 T3-Ab, 10 T4-Ab, 56 both). For comparison, there was only one person (1%) having THAbs in the control group. For patients with vitiligo, T3-Abs was significantly associated with leucotrichia (IgM+IgG, $p=0.033$; IgG, $p=0.039$; IgM, $p=0.005$) and thyroglobulin autoantibodies (IgM+IgG, $p=0.031$; IgG, $p=0.058$). On the contrary, when T3-Ab was not detected, it was correlated to a history of cancer (IgM+IgG, $p=0.021$; IgG, $p=0.039$). Besides, T4-Abs were significantly associated with the activity of vitiligo (IgM+IgG, $p<0.001$; IgM, $p=0.037$) and its duration (IgG, $p=0.013$).

In summary, THAb was commonly found in patients with vitiligo. The associations may suggest a pathogenetic role in vitiligo. Future large studies with longer follow-up are required.

Herpes simplex virus reactivation as a trigger of mucous lesions in pemphigus vulgaris

Kurata M, Mizukawa Y, Aoyama Y, Shiohara T.
Br J Dermatol 2014;171:554-60.

There are many factors that could exacerbate pemphigus vulgaris (PV) and infection is one of them. However, the definite role of the micro-organisms has not been fully investigated.

The aim of this study was to look at the association between PV and herpes simplex virus (HSV). The saliva of the patients after onset of PV was examined for the presence of HSV DNA. In addition, the conventional serological tests and immunohistochemistry were examined.

The results showed that high levels of HSV DNA were found in the saliva samples from six of 16 patients with PV, who had no signs of active herpes simplex. Although the numbers of the HSV DNA copies in PV patients were more than those with herpes labialis and with eczema herpeticum, the prevalence (37.5%) of HSV DNA detected in the patients was lower compared to that of eczema herpeticum (56.5%), but similar to that in patients with herpes labialis (30.0%). The detection of HSV DNA in the saliva was temporary and limited to the initial stage of the disease. Furthermore, anti-HSV immunoglobulin G titres in patients suffered from PV were significantly higher than those in patients with virologically confirmed HSV induced diseases. In this study, all patients with the presence of HSV DNA in saliva with PV had a poorer disease control and were more resistant to treatment.

The authors concluded that the detection of HSV DNA in saliva was a feasible, noninvasive and quantitative way of supporting the role of HSV in the pathogenesis of PV. It was also useful for finding patients with PV who would have a poorer prognosis.

Anal cytology and p16 immunostaining for screening anal intraepithelial neoplasia in HIV-positive and HIV-negative men who have sex with men: a cross-sectional study

Arora R, Pandhi D, Mishra K, Bhattacharya SN, Yhome VA.
Int J STD AIDS 2014;25:726-33.

The presence of multiple sexual partners, low CD4 count in HIV-positive people, smoking, anogenital warts, syphilis and homosexual sexual contact are all related to the increased risk of anal dysplasia. Anal cytology with p16 immunostaining may be used for the screening of anal intraepithelial neoplasia. The aim of this study is to screen men who have sex with men (MSM) for HPV related anal dysplasia by Pap smear along with immunochemical staining of p16 protein. This is a cross-sectional study conducted on age ≥18 MSM attending the sexually transmitted infection clinic of an urban hospital without any history of

anal cancer or anal ulceration. Anal cytology was classified according to Bethesda classification 2001 and two experienced pathologists who were blinded from clinical details read the cytology and p-16 stained slides independently. Discrepant cases were reviewed together to obtain a consensus diagnosis.

A total of 65 patients were included, 31 were HIV positive while 34 were HIV negative. The mean age was 29.2 years. The exposure to commercial sex workers was significantly higher in the HIV+ve group than HIV-ve group (64.5% vs 23.5%; p= 0.003) but there was no increase in the risk of anal dysplasia (p=0.163). There was also no increase in anal dysplasia in patients who had anogenital warts (57%, p=0.794). The nadir CD4 count in HIV+ve group was not significantly associated with anal dysplasia. Overall, 18 patients (27.7%) had abnormal anal cytology which was more common in the HIV+ve group (35%) than the HIV-ve group (20%) but the difference was not significant (p=0.180). Similarly, it was more common for the HIV+ve group than the HIV-ve group to have both low grade (25.8% vs 17.6%, p=0.549) and high grade (8.3% vs 4.8%, p=0.341) anal dysplasia but the differences were not significant statistically. Thirteen (20%) patients were p-16 staining +ve with the sensitivity and specificity of anal dysplasia of 72.3% and 100% respectively. There was a positive correlation for p-16 score and the grade of anal dysplasia (R=0.671, p=0.00). Therefore, the authors concluded that anal cyotology may be used for the screening of anal dysplasia in MSM irrespective of HIV status and the addition of p-16 staining can further improve the diagnostic accuracy.

High prevalence of asymptomatic sexually transmitted infections in HIV-infected men who have sex with men: A stimulus to improve screening

Keaveney S, Sadlier C, O'Dea S, Delamere S, Bergin C.
Int J STD AIDS 2014;25:758-61.

It is always recommended to offer sexually transmitted infection (STI) screening to asymptomatic HIV-infected patients regularly to provide opportunity for early intervention and controlling the spread of STIs from asymptomatic individuals. The aim of this study was to investigate the prevalence of asymptomatic bacterial STIs, *Neisseria gonorrhoeae* (GC) and *Chlamydia trachomatis* (CT) in HIV-infected men who have sex with men (MSM) in the largest HIV centre in Ireland so as to improve the screening strategy. In the first part of the study, all asymptomatic HIV-infected MSM attending the centre for HIV care were offered nucleic acid amplification test for GC and CT. The urine sample and the healthcare provider-performed pharyngeal and rectal swabs were collected during March and April 2012. The second part of the study was implemented in August and September 2012 to offer an option of self-performed or healthcare provider performed rectal swab to all HIV-infected MSM while attending the centre.

In the first part of the study, 50 HIV-infected MSM with a mean age of 38 years were included in the study. Thirty-eight percent always used condoms and 4% reported never using condoms. Only 78% were on highly active antiretroviral therapy (HAART). GC was found in eight patients (16%) with four from rectal swab and four from pharyngeal swab. Among them, two cases (4%) were co-infected with rectal CT. Two patients (4%) were not on HAART. The mean age of infected patients was significantly younger (29 vs 40 years) than the non-infected group (p<0.001). In the second part of the study, 71 HIV-infected MSM were included and 65 (92%) opted for a self-performed rectal swabs. One patient (1.4%) was found to be co-infected with rectal GC and CT. Five patients (70%) had rectal CT. One patient (1.4%) had pharyngeal CT and 2 patients (2.8%) had urethral CT. All rectal infections were detected by self-performed rectal swabs.

The authors commented that although CT is still the most prevalent STIs in Ireland, GC is on an increasing trend and it is worthwhile to perform screening test in asymptomatic HIV infected MSM. The fact that 92% of patients opted for self-performed rectal swabs supported its introduction as a standard of care in HIV-infected MSM patients.

Severity of acute and chronic urticaria correlates with D-dimer level, but not C-reactive protein or total IgE

Baek YS, Jeon J, Kim JH, Oh CH.
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Assessment of urticaria has been difficult as most scoring systems for measuring the severity of urticaria rely on the subjective grading of symptoms such as wheals and pruritus. Objective criteria with inclusion of laboratory markers are much in need for clinical comparison and may facilitate researches in urticaria. Previous studies have shown positive correlation between severity of urticaria with laboratory markers involved in the coagulation/fibrinolysis pathway (e.g. prothrombin fragments, fibrin degradation products [FDP] and D-dimer levels). Also, C-reactive protein (CRP) and total IgE level have been shown to associate with the severity of chronic urticaria.

The authors conducted a retrospective study on 94 patients with a diagnosis of urticaria (acute or chronic). The study aimed to evaluate the role of D-dimer, CRP and total IgE levels in the assessment of disease severity in acute and chronic urticaria. The authors also attempted to correlate these markers with the established Urticaria Activity Score (UAS) measured at initial visit and follow-up visit (7-10 days later). They observed that a significant proportion of patients with urticaria had elevated D-dimer levels (i.e. 43.5% in acute urticaria; 39.6% in chronic urticaria). In addition, a positive correlation between the serological D-dimer level and the UAS was identified in this study ($p<0.001$ for acute urticaria; $p<0.05$ for chronic urticaria). Similar findings were not observed for CRP and total IgE levels.

The authors concluded that D-dimer level could be used as a potential marker for indicating the disease severity in urticaria. Future studies with a larger population size and investigations on other markers of the coagulation / fibrinolysis pathways (e.g. FDP) are required.

Transforming growth factor-β1 gene polymorphism in mycosis fungoides

Zayed AA, Abdel-Halim MR, Sayed KS, Mohammed FN, Hany DM, Amr KS.
Clin Exp Dermatol 2014;39:806-9.

Mycosis fungoides (MF) is the most common form of cutaneous T-cell lymphoma. Regulatory T cells (Tregs) are proven to play an important role in the suppression of anti-tumour responses in various types of neoplasms. Tregs produce transforming growth factor (TGF)-β1, which is an immunosuppressive cytokine responsible for the proliferation and differentiation of Tregs. TGF-β1 has suppressive effects on the growth of many cell types, including the haematopoietic cells. It is therefore postulated that dysfunction of the TGF-β1 signalling pathways may predispose to the development of MF. This study aimed to investigate the correlation between single nucleotide polymorphisms (SNPs) of the TGF-β1 gene and the occurrence of MF.

The authors investigated 55 patients with MF by using restriction fragment length polymorphism analysis to assess the SNPs in the TGF-β1 gene. There were 100 healthy subjects set as control in the study. Statistically significant difference was observed in the distribution of different TGF-β1 genotypes between the case and control groups. A higher proportion of patients presented with the mutant forms (T/C, T/T) were observed in the study ($p<0.001$). The authors found that heterozygous genotype (T/C) was more frequently observed in the patch phase of MF, while the homozygous genotype (T/T) was associated with the tumour phase of MF ($p=0.001$). The authors concluded that mutant TGF-β1 genotypes are positively correlated with the development of MF in a local population in Egypt. This finding may help to shed light on the genetic background of MF. Future larger multi-centre studies involving different races are needed to confirm the results.

Effect of psoriasis severity on hypertension control. A population-based study in the United Kingdom

Takeshita J, Wang S, Shin DB, Mehta NN, Kimmel SE, Margolis DJ, et al.
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It has been suggested that psoriasis is associated with an increased risk of major adverse cardiovascular events independent of traditional cardiovascular risk factors. This is a population-based cross-sectional study determining the association between uncontrolled blood pressure and psoriasis. Uncontrolled hypertension was defined as a systolic blood pressure of 140 mmHg or higher or a diastolic blood pressure of 90 mmHg or higher.

A total of 1,322 patients with psoriasis and hypertension were recruited. It was found that there was a significant positive dose-response relationship between uncontrolled hypertension and psoriasis severity as objectively measured by the affected body surface area in patients adjusted for age, sex, body mass index, smoking and alcohol use status, presence of comorbid conditions, and current use of antihypertensive medications and nonsteroidal anti-inflammatory drugs (adjusted OR 1.10 (95%CI 0.98-1.24) p=0.01). It was also noted that the likelihood of uncontrolled hypertension among psoriasis was increased.

In conclusion, this study demonstrated a significant and increasing likelihood of uncontrolled hypertension among patients with more severe psoriasis, independent of other risk factors for poor blood pressure control. There is a need for more effective blood pressure management, particularly among patients with more severe psoriasis. The authors suggested that further studies are required for better understanding of the mechanisms underlying poor blood pressure control among patients with psoriasis and to determine whether an improvement in hypertension management affects psoriasis severity.

Intralesional injection of *Mycobacterium w* vaccine vs imiquimod, 5%, cream in patients with anogenital warts. A randomized clinical trial

Kumar P, Dar L, Saldiwal S, Varma S, Upadhyay AD, Talwar D, et al.
JAMA Dermatol 2014;150:1072-8.

Activation of cell-mediated immunity appears to be the primary mechanism responsible for the regression and clearance of human papillomavirus (HPV) related lesions, including anogenital warts (AGWs). Topical imiquimod stimulates both innate and adaptive immune responses, inducing cytokine production such as interleukin 2 (IL-2), interferon alpha-1 and -2, interferon beta, interferon gamma, and transforming growth factor alpha and thus it is accepted as one of the treatment modalities of AGWs. *Mycobacterium w* (Mw; revised nomenclature, *Mycobacterium indicus pranii*) is a nonpathogenic, soil-derived, rapidly growing atypical mycobacterium. A heat-killed Mw vaccine contained $0.5x10^9$ bacilli per 0.1 ml. This vaccine generates strong cytokine responses involving IL-2, IL-4, IL-5 and interferon gamma. In view of its immunomodulatory action, complete clearance of cutaneous warts in patients who received intralesional Mw vaccine has been reported.

This double-blind randomised study compared the efficacy and safety of intralesional Mw vaccine with that of 5% imiquimod cream in the treatment of AGWs, as well as the changes in HPV-6 and HPV-11 viral loads. Eighty-nine patients with AGWs received either 5% imiquimod cream and an intralesional vehicle (n=44) or vehicle cream and intralesional Mw vaccine (n=45).

It was found that 59% of the patients in the imiquimod group and 67% of those in the Mw vaccine group had complete resolution of AGWs. There was a significant decline in the mean viral loads of HPV-6 and HPV-11 after treatment in the Mw vaccine group but only in the viral load of HPV-6 in the imiquimod group. No recurrence of AGWs in patients with complete clearance up to three months and no serious adverse events in both treatment groups were reported.

In conclusion, 5% Imiquimod and the Mw vaccine were equally effective in achieving clinical and virologic clearance for HPV-6. A significant decline in the HPV-11 viral load was achieved only with the Mw vaccine. It was found that the efficacy and safety of intralesional Mw vaccine is comparable to that of 5% imiquimod in the treatment of AGWs despite the fact that intralesional Mw vaccine therapy is invasive and may associate with local immunological reaction. The authors also suggested that further studies concerning the efficacy of the Mw vaccine in AGWs that fail to respond to 5% imiquimod and other conventional therapies should be carried out.

An oral phosphodiesterase inhibitor (apremilast) for inflammatory rosacea in adults: a pilot study

Thompson BJ, Furniss M, Zhao W, Chakraborty B, Mackay-Wiggan J.
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Apremilast, an oral phosphodiesterase 4 inhibitor, modulates multiple proinflammatory and anti-inflammatory pathways through targeted phosphodiesterase type 4 inhibition, resulting in increasing interleukin 10 production, which in turn suppresses other proinflammatory cytokines. Phosphodiesterase type 4 inhibitors have been tested for the treatment of many inflammatory dermatologic diseases but never for rosacea. This is an open-label pilot study investigating the safety and efficacy of apremilast for the treatment of moderate to severe inflammatory rosacea.

Ten patients with moderate to severe inflammatory rosacea were administered apremilast, 20 mg orally twice daily, for 12 weeks. They were assessed every two weeks during treatment (weeks 2, 4, 6, 8, 10, and 12), and one month after discontinuation of treatment (week 16). It was found that there was a statistically significant improvement in ratings on the Physician Global 7-Point Assessment, Physician Overall Erythema Severity, erythematotelangiectatic rating and non-transient erythema. However, when baseline ratings were compared with those at follow-up one month after discontinuation of treatment, measures that reached statistical significance were Physician Overall Erythema Severity and non-transient erythema only. Apremilast was well tolerated and no adverse effects requiring treatment alteration or discontinuation were reported. Limitations of this study include the small sample size and the absence of a control arm.

The authors concluded that apremilast may represent a novel alternative treatment for rosacea and rosacea-associated erythema and larger randomised clinical studies are needed to more adequately evaluate the drug's efficacy and safety.

Two decades of using the combination of tetracycline derivatives and niacinamide as steroid-sparing agents in the management of pemphigus: Defining a niche for these low toxicity agents

McCarty M, Fivenson D.
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Pemphigus is a chronic immunobullous disorder and usually requires long-term immunusuppresants, especially corticosteroids. Hence, effective steroid-sparing agents are necessary to minimise long-term toxicities. Tetracycline, doxycycline or minocycline and niacinamide (TCN/NAM) had been shown to inhibit and reduce various inflammatory cytokines. Its combination (TCN/NAM) had also been shown to be as efficacious as steroid in treating bullous pemphigoid. However, data on pemphigus treatment was limited.

This was a retrospective study in a private dermatology clinic. The authors reviewed patients who had received TCN/NAM as steroid-sparing agents and determined its efficacy as well as effect on autoantibody level. Patients with newly diagnosed or flare of pemphigus were treated with TCN/NAM (tetracycline 500 mg 4 times/day, doxycycline 100 mg twice daily or minocycline 100 g twice daily) after active blistering were halted by initial oral steroid induction therapy (1-2 mg/kg/day). Oral steroids were tailed off over 2-3 months, unless they were taking other immunosuppressants or TCN/NAM were previously proven ineffective. TCN/NAM were

maintained for one year after all symptoms of pemphigus resolved and slowly weaned off over six months. Disease activity was assessed clinically (i.e. remission, control on minimal therapy, transient lesions, or active disease) and responders were classified as disease remission, control on minimal therapy, or only transient lesions within three months of starting the regime. Side effects related to TCN/NAM therapy were documented and serological assessment of anti-desmoglein 1 (DSG1) and anti-desmoglein 3 (DSG3) using ELISA method were performed.

A total of 51 pemphigus patients were analysed (43 with pemphigus vulgaris, 7 with pemphigus foliaceous, and 1 pemphigus erythematosus). Forty-six out of 51 patients achieved disease control, with a duration of response from 1-13 years (mean, 3.14±2.97 years). Of which, 13 patients achieved complete remission while 33 needed intermittent topical clobetasol or short courses of oral steroids for flare, and there were five non-responders. TCN/NAM was generally well tolerated with good safety profile. Serological response was highly variable but the relative titre reduction seemed to be a predictor of response.

The authors concluded that the efficacy of TCN/NAM therapy was comparable with other pemphigus treatment, but with a good safety profile and make it favourable for long-term maintenance. However, this study was limited by the retrospective data analysis from a single centre.

Systemic treatment and narrowband ultraviolet B differentially affect cardiovascular risk markers in psoriasis

Sigurdardottir G, Ekman AK, Stahle M, Bivik C, Enerback C.
J Am Acad Dermatol 2014;70:1067-75.

Psoriasis is a chronic inflammatory disorder affecting not only the skin and joints, but also associated with metabolic syndrome and cardiovascular disease. Previous studies had shown that ongoing systemic inflammation in psoriasis, as evidenced by high circulating chemokines, might play a role in cardiovascular comorbidities in these patients. However, specific cardiovascular biomarkers analysis in psoriatic patients was lacking. In this case-control study, the authors aimed at assessing the plasma levels of selected cardiovascular risk molecules in psoriatic patients and studied the effect of systemic treatment (tumour necorsis factor-alpha inhibitor, TNF-α) or local treatment (phototherapy) on these markers.

In this case-control study, 28 patients with psoriasis were included together with 28 age-, gender-matched controls, some of whom were BMI- and WHR-matched. Clinical severity were measured using PASI score and six cardiovascular markers (i.e. sVAM-1, sICAM-1, sE-selectin, MMP-9, MPO and tPAI-1) were measured before and after either 12-week of NB-UVB or etanercept treatment.

Five of the 6 markers were significantly higher in psoriatic patients, which were not correlated with PASI score, signifying systemic inflammation instead of local inflammation in the skin. Four of these markers correlated with BMI and WHR, yet tPAI-1 remained elevated despite controlling for these factors. Both groups demonstrated significant improvement in PASI scores clinically after treatment, but the patients who received 12-week phototherapy had a sustained high level of circulation markers while those who received etanercept showed a significant reduction.

The authors concluded that the choice of treatment in psoriasis might influence the cardiovascular risk. Although NB-UVB failed to reduce studied cardiovascular markers, the relationship between local and systemic inflammation was complex. Previous studies had shown that phototherapy reduce hs-CRP, which is a systemic marker for cardiovascular risk. Moreover, despite the fact that the studied markers are strongly associated with cardiovascular risk, additional mediators may also contribute to the risk.