

Journal Watch

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Adherence to acitretin and home narrowband ultraviolet B phototherapy in patients with psoriasis

Yentzer BA, Yelverton CB, Pearce DJ, et al.
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In the treatment of psoriasis, patient adherence to oral medications is poor and even worse for topical therapy. However, few data exist about adherence rates to home phototherapy, adding to concerns about the appropriateness of home phototherapy as a psoriasis treatment option. The authors sought to assess adherence to both oral acitretin and home ultraviolet B phototherapy for the treatment of psoriasis.

In all, 27 patients with moderate to severe psoriasis were treated with 10 to 25 mg of acitretin daily, combined with narrowband ultraviolet B, 3 times weekly at home, for 12 weeks. Five subjects were lost to follow up. Three of them failed to return to scheduled visit. Another two subjects withdrew from the treatment of which one had worsening psoriasis and the other one developed Ramsay Hunt Syndrome. Adherence to acitretin was monitored by an electronic monitoring medication bottle cap, and to phototherapy by a light-sensing data logger. Adherence data were collected on 22 patients for acitretin and 16 patients for adherence to ultraviolet B. Mean adherence to acitretin decreased steadily during the 12-week trial (slope -0.24), whereas mean adherence to home phototherapy remained steady at 2 to 3 d/wk. Adherence was similar between patients who reported side effects and those who did not.

They concluded that adherence rates to home phototherapy were very good and higher than adherence rates for the oral medication. Side effects of treatment were well tolerated in this small

group and did not affect use of the treatment. Home phototherapy with acitretin may be an appropriate option for some patients with extensive psoriasis. The small sample size and lack of follow-up on some patients were limitations of this study.

Topical methyl-aminolevulinate photodynamic therapy using red light-emitting diode light for treatment of multiple actinic keratoses: a randomized, double-blind, placebo-controlled study

Pariser D, Loss R, Jarratt M, et al.
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The use of light-emitting diode light offers practical advantages in photodynamic therapy (PDT) with topical methyl-aminolevulinate (MAL) for management of actinic keratoses (AK). The authors sought to evaluate the efficacy of MAL PDT using red light-emitting diode light by a multi-center, double-blind, randomized study.

A total of 49 patients with 363 AK lesions had 16.8% MAL cream applied under occlusion for 3 hours, and 47 patients with 360 AK lesions had vehicle cream similarly applied. The lesions were then illuminated (parameters as follows: 630 nm, light fluence 37 J/cm²). The illumination time was calculated automatically, with an average period of illumination approximately 8 minutes. The treatment was repeated treatment 1 week later. Complete lesion and patient (all lesions showing complete response) response rates were evaluated 3 months after last treatment. The results showed that MAL PDT was superior ($p < 0.0001$) to vehicle PDT with respect to lesion complete response (86.2% vs 52.2%, odds ratio 6.9 [95% confidence interval 4.7-10.3]) and patient complete response (59.2%

vs 14.9%, odds ratio 13.2 [95% confidence interval 4.1-43.1]).

They concluded that MAL PDT using red light-emitting diode light is an appropriate treatment alternative for multiple AK lesions. Nevertheless, the population studied may not be representative of all patients with AK.

A new scalp formulation of calcipotriene plus betamethasone compared with its active ingredients and the vehicle in the treatment of scalp psoriasis: a randomized, double-blind, controlled trial

Jemec GB, Ganslandt C, Ortonne JP, et al. *J Am Acad Dermatol* 2008;59:455-63.

New topical treatments in scalp psoriasis are needed because many current topical treatments are disliked by patients and associated with poor compliance. The authors compared the efficacy and safety of once-daily, two-compound scalp formulation containing calcipotriene plus betamethasone dipropionate with the individual components in the same vehicle and the vehicle alone.

In this 8-week, multicenter, randomized, double-blind study, patients with scalp psoriasis were randomized to treatment with the two-compound scalp formulation (calcipotriene 50 microg/g plus betamethasone 0.5 mg/g, as dipropionate) (n=541), betamethasone dipropionate 0.5 mg/g in the same vehicle (n=556), calcipotriene 50 microg/g in the same vehicle (n=272), or vehicle alone (n=136). The results showed that more patients achieved "absent" or "very mild" disease at week 8 with the two-compound scalp formulation (71.2%) compared with betamethasone dipropionate in the same vehicle (64.0%, $p=0.011$), calcipotriene in the same vehicle (36.8%, $p<0.0001$), or the vehicle (22.8%, $p<0.0001$).

The authors concluded that calcipotriene plus betamethasone dipropionate scalp formulation was more effective than either of the individual components or the vehicle alone. The study was

limited by the fact that the efficacy of the active comparators in the study has not been established in relation to calcipotriene and betamethasone formulations available for clinical use.

Nail changes in pemphigus vulgaris

Habibi M, Mortazavi H, Shadianloo S, et al. *Int J Dermatol* 2008;47:1141-4

Nail involvement in pemphigus vulgaris (PV) is frequently caused by bullae close to the nail, but the frequency and types of nail changes are unclear. The aim of this study was to determine the frequency and types of nail changes and their correlation with the number of skin and periungual bullae.

Seventy-nine patients who were diagnosed to have PV during December 2004 to September 2005, including 59 new patients and 20 patients in relapse, were recruited. All subjects were examined by three experienced dermatologists. All abnormal nails were photographed and examined directly in potassium hydroxide and cultured for fungus.

Twenty-five (34.2%) patients had nail changes and 8 patients had more than one manifestation. The changes included: paronychia (n=8), onychomadesis (n=6), Beau's lines (n=5), discolouration (n=4), onycholysis (n=3), nail splitting (n=2), subungual hyperkeratosis (n=2), subungual haemorrhage (n=1), ripping (n=1), longitudinal ridges (n=1) and pitting (n=1). Seventy percent were the fingernails and 30% were toenails. The thumbs and index fingers were most commonly affected. Of 1580 nails examined, 71 nails had bullae adjacent to the nail fold with 22 (31%) leading to nail changes. Among 1509 nails without periungual bullae, only 78 (5.2%) had nail changes ($p<0.005$). The number of skin bullae was higher in patients with nail changes than in those without nail changes (mean number of skin bullae was 55.4 vs 36.6 respectively; $p<0.05$). The mean duration of disease was 26.2 months with nail changes and 10.6 months without nail changes ($p<0.05$). Finally, all nail had healed completely with the clearance of the skin and mucosal lesions.

The authors concluded that nail changes in PV are common and related to the number of skin bullae and the presence of periungual bullae.

A comparison between BSA, PASI, PLASI, SAPASI as measures of disease severity and improvement by therapy in patients with psoriasis

Henseler T, Schmitt-Rau K.

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Many measures have been established to evaluate the severity of psoriasis. These include body surface area (BSA), psoriasis area and severity index (PASI), psoriasis log-based area and severity index (PLASI) and self-administrated PASI (SAPASI). This study aimed to investigate the four measures of disease severity in patients with psoriasis, both before and after therapy.

Thirty-three patients with moderate to severe chronic plaque psoriasis were treated with 1 mg/kg/week efalizumab subcutaneously in 18 dermatologic outpatient centres for total 12 weeks (63.6% of patients were male). More than 60% of patients used at least four different systemic treatments such as PUVA, methotrexate, retinoids and cyclosporin A before efalizumab. The attending dermatologists assessed the treatment result according to three categories – "very good", "good" and "poor". These categories were used to compare with the changes of individual measures. In the category of "very good" and "good", there was statistical significant in percentage change of PASI and PLASI. The percentage change of SAPASI in the category of "good" was also significant. Each possible correlation between the parameters BSA, PASI, PLASI and SAPASI were found to be highly significant ($p < 0.001$). However, all correlations between PASI, PLASI and SAPASI were significantly stronger than any correlation involving BSA.

Comparing the slopes and intercepts of the regression lines revealed PLASI as the most reliable measures for the severity and therapeutic improvement. PLASI also proved to be marginally

more accurate than PASI and much more accurate than SAPASI and BSA.

Evaluation of autologous serum skin test results in patients with chronic idiopathic urticaria, allergic/non-allergic asthma or rhinitis and healthy people

Taskapan O, Kutlu A, Karabudak O.

Clin Exp Dermatol 2008;33:754-8

The autologous serum skin test (ASST) based on intradermal injection of autologous serum is a simple screening diagnostic procedure used in chronic urticaria. Recent data showed that ASST had a high rate of reactivity not only in chronic idiopathic urticaria (CIU) but also in case of non-allergic asthma and rhinitis (NAAR), multiple drug allergy syndrome (MDAS) and even in some healthy people. A positive test suggests that there are autoantibodies or histamine-releasing factors present in the serum. The aim of the study was to evaluate ASST reactivity in patients with CIU, allergic/non-allergic asthma or rhinitis and in healthy controls.

The investigators studied 80 patients with CIU, 40 non-atopic patients NAAR, 57 patients with allergic rhinitis (AR) and allergic bronchial asthma (ABA), and 45 healthy controls. Pure physical urticaria and urticaria lasting <6 weeks were excluded in CIU group. ASST was performed in all patients and controls, and it was considered positive when a serum-induced wheal with a diameter of 1.5 mm greater than the negative (saline) control, surrounded by an erythema, was present.

In total, 42 (52.5%) patients with CIU showed ASST reactivity. ASST was found positive in 8 of 40 patients with NAAR (20%). The rate was similar (17.5%) in the patients with allergic rhinitis (AR)/bronchial asthma (ABA). The overall rate of ASST positivity in patient group (CIU, NAAR, AR/ABA) was 39.9% while 55.5% of healthy controls had a positive result.

The authors concluded that data in patients and controls suggest that ASST positivity might be a non-specific phenomenon.

Ceftibuten resistance and treatment failure of *Neisseria gonorrhoeae* infection

Lo JY, Ho KM, Leung AO, et al.

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Neisseria gonorrhoeae continues to be an important bacterial agent that causes sexually transmitted infections. In Hong Kong, penicillin was the treatment of choice for *N. gonorrhoeae* infections until 1985, when rising resistance resulted in its replacement by ofloxacin, which in turn became obsolete in 1997. It was empirically replaced by a single oral 400 mg dose of ceftibuten. Following anecdotal reports of the treatment failure of gonorrhea with oral extended-spectrum cephalosporins, the current study was undertaken to determine the antimicrobial susceptibility pattern and molecular characteristics of isolates of *N. gonorrhoeae* among patients with putative treatment failure in a sexually transmitted disease clinic setting.

Between October 2006 to August 2007, 44 isolates of *N. gonorrhoeae* were studied from patients identified clinically to have treatment failure with empirical ceftibuten. The ceftibuten MICs for three strains were found to have been 8 mg/liter. These strains were determined by *N. gonorrhoeae* multiantigen sequence typing (NG-MAST) to belong to sequence type 835 (ST835) or the closely related ST2469. The testing of an additional eight archived ST835 strains revealed similarly elevated ceftibuten MICs. The penA gene sequences of these 11 isolates all had the mosaic pattern previously described as pattern X. Of note is that the ceftriaxone susceptibility results of these strains all fell within the susceptible range. In addition, all isolates with reduced susceptibility to ceftibuten remain susceptible to the injectable agent spectinomycin.

The authors concluded that ceftibuten resistance may contribute to the empirical treatment failure of gonorrhea caused by strains harboring the mosaic penA gene. Screening for such resistance in the routine clinical laboratory may be undertaken by the disk diffusion test. The continued monitoring of antimicrobial resistance and molecular characteristics of *N. gonorrhoeae* isolates are important to ensure that control and prevention strategies remain effective.

Impact of small reductions in plasma HIV RNA levels on the risk of heterosexual transmission and disease progression

Modjarrad K, Chamot E, Vermund SH.

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Antiretroviral medications are typically very effective in reducing the plasma HIV RNA. However, a large proportion of the world's HIV-infected population is still not being treated due to logistic impediments, lack of antiretroviral medications or a relatively early stage of illness. It is not known if a small reduction of HIV RNA resulting from relatively simple interventions, such as clearing coinfections, can translate into large benefits in transmission and survival. The authors sought to estimate the impact of small changes in plasma levels of HIV-1 RNA on the risk of heterosexual transmission or disease progression to an AIDS-defining event or death by systemic review of the published literature.

Medline and PubMed databases for studies published from January 1987 to July 2008 were searched. Articles prior to 1987 were excluded because reliable and reproducible HIV RNA assays were not yet available. Search words consists of "HIV-1", "HIV RNA", "viral load", "risk", "heterosexual transmission", and "disease progression". The authors reviewed titles and abstracts of 435 articles and identified 22 articles for full review. Nine studies reported risk estimates of HIV heterosexual transmission and disease progression. The authors calculated risk estimates of transmission and disease progression for each 0.3, 0.5 and 1.0 log viral load increment.

It was found that every 0.3 log, 0.5 log and 1.0 log increment in HIV RNA increased the likelihood of transmitting HIV via heterosexual contact by 20%, 40% and 100% respectively. Similarly, a 0.3 log, 0.5 log and 1.0 log increment in HIV RNA was associated with 25%, 44% and 113% increased risk of progression to AIDS or death respectively.

Antiretroviral therapy continues to be unavailable or not-yet-indicated for 72% of the world's HIV-infected persons. Mounting evidence that treatment of coinfections may reduce HIV viral load, even modestly, suggests the priority of

improved adjunctive care for HIV infected person even without antiretroviral therapy. This relatively simple strategy would slow disease progression and reduce infectiousness.

Single-dose fluconazole versus standard 2-week therapy for oropharyngeal candidiasis in HIV-infected patients: a randomized, double-blind, double-dummy trial

Hamza OJ, Matee MI, Bruggemann RJ, et al.
Clin Inf Dis 2008;47:1270-6.

Oropharyngeal candidiasis (OPC) is the most common opportunistic infection affecting HIV-infected patients. Owing to convenience, less cost, and less likelihood of drug-drug interaction, a single-dose fluconazole may be a more favorable regimen than two-week standard dose fluconazole in treatment of OPC. The authors conducted a prospective, randomized, double-blind, placebo-controlled trial to compare the clinical and mycological response, relapse rates, and safety of a single 750-mg dose and a 14-day course of treatment with fluconazole.

A total of 220 HIV-infected patients with clinical and mycological evidence of OPC were randomly assigned in a 1:1 ratio to receive either a 750-mg single dose orally administered fluconazole or 14-day daily 150 mg orally administered fluconazole.

The single-dose fluconazole was equivalent to a 14-day course of fluconazole in achieving clinical and mycological cure, with clinical cure rates of 94.5% and 95.5% respectively (odds ratio 0.83; 95% confidence interval 0.24-2.79; $p=0.99$) and mycological cure rates of 84.5% and 75.5% respectively (odds ratio, 1.78; 95% confidence interval, 0.24-0.29; $p=0.13$). Drug-related adverse events were uncommon and were not different between the treatment groups.

The authors concluded that a single dose of 750 mg of fluconazole was safe, well tolerated, and as effective as the standard 14-day fluconazole therapy in HIV-infected patients who had OPC coinfection.

Combination therapy of cyclosporine and methylprednisolone on severe alopecia areata

Kim BJ, Min SU, Park KY, et al.
J Dermatol Treatm 2008;19:216-20.

Conventional therapy for severe alopecia areata (AA) such as topical, systemic and intralesional steroid are usually ineffective. Although cyclosporine appears to be one of the treatment options for chronic severe AA, the high rate of recurrence after discontinuation and the side effect profile limit its use. This study tried to determine whether the combination therapy of cyclosporine and methylprednisolone could be effective for treatment of severe AA.

Total 46 patients with severe AA were recruited, and of them, 14 (30.5%) suffered from alopecia totalis and universalis. All patients were treated with a combination of cyclosporine (200 mg twice daily) and methylprednisolone (24 mg twice daily for men, 20 mg twice daily for women and 12 mg twice daily for children). The doses of methylprednisolone were diminished by 4 mg/day weekly, and the dose of cyclosporine was decreased gradually after cessation of administration of methylprednisolone. The duration of treatment with steroid was 3-6 weeks. The total duration of treatment with cyclosporine was 9-14 weeks in adult and 7-11 weeks in children.

There were 33 (76.7%) patients with complete remission and 5 (11.6%) patients with partial remission. Treatment failure occurred in 5 (11.6%) patients, and three patients discontinued treatment due to side effects. The average duration of induction of vellus hair was 3.3 weeks to 4.1 weeks in the response group. Nine (23.7%) of the responders relapsed during the 12 months follow-up. Side effects such as gastrointestinal disturbance, edema, weight gain, menstrual disturbance and acne were generally tolerated with three patients discontinued the treatment. Hypertrichosis was reported in 3 patients of whom 2 withdrawn.

In summary, combination treatment with cyclosporine and methylprednisolone can be useful to severe AA. However, this study result was limited by uncontrolled character. The high

recurrence rate after discontinuation of therapy and long term side effects of continuous treatment also needed to be addressed.

Psoriasis independently associated with hyperleptinemia contributing to metabolic syndrome

Chen YJ, Wu CY, Shen JL, et al.
Arch Dermatol 2008;144:1571-5.

Leptin, a 16 kDa adipocyte-derived hormone, stimulates endocrine activity in adipose tissue and regulates energy homeostasis, metabolism and inflammatory process. Leptin has been implicated in the pathogenesis of autoimmune inflammatory diseases. An elevated level of leptin was associated with psoriasis. This case-control study aimed to evaluate the role of leptin in the development of metabolic dysregulation of psoriasis.

Serum leptin levels and proportions of comorbidities (including hypertension, diabetes mellitus, metabolic syndrome, hypertriglyceridemia, and reduced high-density lipoprotein cholesterol concentrations) in cases versus age and sex matched controls were compared.

The study included 77 psoriasis patients and 81 controls. Significantly more obesity (odd ratio [OR] =2.67; $p=0.04$) and hypertension (OR=2.17; $p=0.04$) were observed in subjects with psoriasis. High serum leptin levels ($> \text{ or } =7397 \text{ pg/mL}$) were significantly associated with female subjects (OR=6.05; $p<0.001$), obesity (OR=3.45; $p=0.01$), hypertension (OR=2.19; $p=0.04$), metabolic syndrome (OR=3.58, $p=0.08$) and psoriasis (OR =2.25; $p=0.02$). On multivariate analysis, psoriasis (OR=4.57; $p=0.009$) was significantly associated with hyperleptinemia independently. Other independent risk factors for hyperleptinemia were female sex (OR=26.36; $p<0.001$) and metabolic syndrome (OR=4.37; $p=0.04$). In addition, patients with psoriasis who had hyperleptinemia tended to be female ($p<0.001$) and manifested obesity ($p=0.002$) and metabolic syndrome ($p=0.003$).

It is postulated that chronic inflammation process of psoriasis could cause a high leptin level. This was evident by the production of leptin by inflammatory regulator cells. In summary,

hyperleptinemia was found to be associated with psoriasis and metabolic syndrome. Further causal relationship needed to be elucidated.

Role of thiopurine methyltransferase activity in the safety and efficacy of azathioprine in the treatment of pemphigus vulgaris

Firooz A, Ghandi N, Hallaji Z, et al.
Arch Dermatol 2008;144:1143-7.

Thiopurine methyltransferase (TPMT) is the enzyme responsible for the inactivation of the toxic metabolite 6-mercaptopurine of azathioprine. Previous study recommended that patients put on azathioprine should be evaluated for the enzyme activity to avoid toxic effect or suboptimal dosing. This study aimed to determine the relationship between TPMT activity and the outcome of azathioprine treatment in patients with pemphigus vulgaris.

This is a cross sectional study that included 139 patients with pemphigus vulgaris treated with azathioprine. A total of 127 patients (91.4%) had normal TPMT activity and 11 patients (7.9%) had low TPMT activity and 1 patient had supranormal activity. Fourteen patients discontinued azathioprine because of adverse effects: elevated liver enzyme, leukopenia, anemia and pancreatitis. Of the 14 patients withdrawn from the study, only one had low TPMT activity. No significant relationship ($p=0.29$) was found between the development of adverse effects and TPMT activity. Fifty-two patients who had been treated with a combination of prednisolone and azathioprine for at least 1 year were included in the study. There was no correlation found between TPMT activity and clinical response. There was no relationship observed between the TPMT activity and time needed to taper prednisolone dosage.

In summary, this study found that no correlation between TPMT activity and adverse effect and efficacy of azathioprine treatment in patients with pemphigus vulgaris. There might be factors other than TPMT activity to determine the adverse effect and efficacy of azathioprine treatment. The prevalence of complete absence of TPMT activity is very low. Larger prospective studies are needed to determine the clinical significance of TPMT test.