

## Journal Watch

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### **Terbinafine hydrochloride oral granules versus oral griseofulvin suspension in children with tinea capitis: results of two randomized, investigator-blinded, multicenter, international, controlled trials**

Elewski BE, Cáceres HW, DeLeon L, et al.  
J Am Acad Dermatol 2008;59:41-54.

Although griseofulvin is currently considered the primary antifungal agent used to treat tinea capitis in many countries, increasingly higher doses and longer durations of treatment are becoming necessary to achieve effective treatment. Alternative antifungal therapies with shorter/simpler treatment regimens may be important to develop for this indication. The authors compare the efficacy and safety of a new pediatric formulation of terbinafine hydrochloride oral granules with griseofulvin oral suspension in the treatment of tinea capitis.

Children (4-12 years of age) with clinically diagnosed and potassium hydroxide microscopy-confirmed tinea capitis were randomized in two identical studies (trial 1, trial 2) to once-daily treatment with terbinafine (5-8 mg/kg; n=1040) or griseofulvin administered per label (10-20 mg/kg; n=509) for a period of 6 weeks followed by 4 weeks of follow-up. End-of-study complete cure (negative fungal culture and microscopy with Total Signs and Symptoms Score [TSSS]=0), and mycologic (negative culture and microscopy) and clinical cure (TSSS=0) were primary and secondary efficacy assessment endpoint, respectively. Efficacy analysis was based on pooled data using modified intent-to-treat population (those who received at least one dose of study drug and had positive baseline fungal culture, N=1286). Safety assessments included monitoring of the frequency and severity of adverse events (AEs).

The results showed that rates of complete cure and mycologic cure were significantly higher for terbinafine than for griseofulvin (45.1% vs 39.2% and 61.5% vs 55.5%, respectively;  $P<0.05$ ). A majority (86.7%) of patients received griseofulvin, 10 to 19.9 mg/kg per day; complete cure rate was not found to be higher among patients who received griseofulvin more than 20 mg/kg per day compared with those who received less than 20 mg/kg per day. Complete cure rate was statistically significantly greater for terbinafine compared to griseofulvin in trial 1 (46.23% vs 34.01%) but not in trial 2 (43.99% vs 43.46%). On the basis of pooled data, clinical cure was higher for terbinafine than for griseofulvin, but the difference was not found to be statistically significant ( $P=0.10$ ). Subgroup analyses revealed that terbinafine was significantly better than griseofulvin for all cure rates--mycologic, clinical, and complete--among patients with *Trichophyton tonsurans* but not *Microsporum canis* ( $P<0.001$ ). For *M. canis*, mycologic and clinical cure rates were significantly better with griseofulvin than with terbinafine ( $P<0.05$ ). Approximately 50% of patients in each group reported an AE; almost all were mild or moderate in severity. Nasopharyngitis, headache, and pyrexia were most common in both groups. There were no drug-related serious AEs, no deaths, and no significant effects on weight or laboratory parameters, including liver transaminases.

A difference in the distribution of infecting microorganisms between the two trials was a limitation. Stringent adherence to griseofulvin doses recommended by prescribing information but smaller than those used in current clinical practice, and exclusion of adjuvant therapies such as shampoos or topical agents, which are routinely used in practice, are other limitations.

It was concluded that terbinafine is efficacious and well tolerated in the treatment of tinea capitis. Terbinafine is an effective alternative to griseofulvin against *T. tonsurans* tinea capitis.

### **National Psoriasis Foundation consensus statement on screening for latent tuberculosis infection in patients with psoriasis treated with systemic and biologic agents**

Doherty SD, Van Voorhees A, Lebwohl MG, et al. *J Am Acad Dermatol* 2008;59:209-17.

Chronic immunosuppression is a known risk factor for allowing latent tuberculosis (TB) infection to transform into active TB. Immunosuppressive/immunomodulatory therapies, while highly efficacious in the treatment of psoriasis and psoriatic arthritis, may be associated with an increased rate of active TB in patients receiving some of these therapies. The authors aimed to arrive at a consensus on screening for latent TB infection in psoriasis patient treated with systemic and biologic agents.

Reports in the literature were reviewed regarding immunosuppressive therapies and risk of TB. The results showed that screening patients for latent TB infection before commencement of treatment is of utmost importance when beginning treatment with the tumor necrosis factor-alpha inhibitors, T-cell blockers, cyclosporine, or methotrexate. The currently recommended method for screening is the tuberculin skin test. It is preferable that positively screened patients be treated with a full course of latent TB infection prophylaxis before immunosuppressive/immunomodulatory therapy is initiated. However, in the opinion of many experts, patients may be started on the immunosuppressive/immunomodulatory therapy after 1 to 2 months, if their clinical condition requires, as long as they are strictly adhering to and tolerating their prophylactic regimen. Limited by the fact that there are few evidence-based studies on screening for latent

TB infection in psoriasis patients treated with systemic and biologic agents, the authors concluded that the biologic TNF-alpha inhibitors are very promising in the treatment of psoriasis. However, because TNF-alpha is also an important cytokine in preventing TB infection and in keeping latent TB infection from becoming active disease, the use of TNF-alpha inhibitors has been associated with an increased risk of developing active TB. A higher incidence of TB has also been reported with other immunosuppressive/immunomodulatory treatments for psoriasis.

It is, therefore, of utmost importance to appropriately screen all patients for latent TB infection prior to initiating any immunologic therapy. Delaying immunologic therapy until latent TB infection prophylaxis is completed is preferable. However, if the patient is adhering to his prophylactic regimen and is appropriately tolerating the regimen, therapy may be started after 1 to 2 months if the clinical condition requires.

### **Intermittent therapy for flare prevention and long-term disease control in stabilized atopic dermatitis: a randomized comparison of 3-times-weekly applications of tacrolimus ointment versus vehicle**

Breneman D, Fleischer AB Jr, Abramovits W, et al. *J Am Acad Dermatol* 2008;58:990-9.

Intermittent dosing of a topical calcineurin inhibitor for preventing atopic dermatitis (AD) disease relapse in patients with stabilized AD has not been evaluated. The authors sought to evaluate the long-term efficacy and safety of 3-times-weekly use of tacrolimus ointment in preventing AD disease relapse.

Adult and pediatric patients with moderate to severe AD who were clear of disease after up to 16 weeks of treatment with tacrolimus ointment were randomized in a double-blind fashion to 3-times-weekly treatment with either tacrolimus

ointment (0.03% or 0.1%) or vehicle for 40 weeks. The primary end point was the number of flare-free treatment days.

A total of 125 patients were randomized to tacrolimus and 72 patients to vehicle. The mean number of flare-free treatment days was 177 for tacrolimus and 134 for vehicle ( $P=0.003$ ). Median time to first relapse was 169 days for tacrolimus and 43 for vehicle ( $P=0.037$ ).

The authors concluded that maintenance therapy with tacrolimus ointment was associated with significantly more flare-free days compared with vehicle, and a significantly longer time until first disease relapse. However, generalizability to all patients seen in clinic may be limited because only patients who responded to tacrolimus ointment in the stabilization phase were randomized into the maintenance phase of the trial.

### **Bathing and generalized asteatotic eczema: a case-control study**

Li LF, Lan YZ.

Br J Dermatol 2008;159:243-5.

Asteatotic eczema is characterized by pruritic, dry, cracked and fissured skin with irregular scaling. Over-bathing is always assumed to be a cause and a brief shower lasting less than 10-15 min has been suggested in one study. However, this has not been proven. This study is aimed for studying the association of bathing habits and asteatotic eczema in Beijing.

A study group of 40 patients (male=13/female=27) with generalized asteatotic eczema (GAE) were recruited in a University hospital. Half of patients were aged between 21 and 40. Patients with generalized unclassified eczema (GUE) and atopic dermatitis (AD) were the controls. Bathing habits were investigated by questionnaire. Significant statistical difference between the study and control group was not found in the frequency of shower (GAE=3.4/week, GUE=2.9/week and AD=2.3/week), the length of showering time (GAE=28.3 min, GUE=24.1 min and AD=25.7

min), the preference for hot water (GAE=25%, GUE=23.8% and AD=26.7%) and the use of emollient after bath (GAE=30%, GUE=47.6% and AD=26.7%).

The median age of case group was 31 which was relative young so the decreased sebaceous and sweat gland activity as in elderly should not occur. Given the results, the authors suggested that other factors such as environment humidity, concurrent ichthyosis, atopic diathesis, skin barrier function disturbance and other endogenous factors should further be studied.

### **Prevention and treatment of glucocorticoid-induced osteoporosis in daily dermatologic practice**

Vermaat H, Kirtschig G.

Int J Dermatol 2008;47:737-42.

Systemic glucocorticoids (GCs) are often needed to treat dermatologic patients. However, the long-term use of GCs is associated with potentially severe side-effects. GC-induced osteoporosis (GIO) is one of the most serious complications, but the exact prevalence of GIO remains unknown. The aim of this article is to update the recent advances and to provide some practical advice for prevention and treatment of GIO in dermatologic practice by reviewing the literature, European and US guideline up to August 2007.

Although data regarding the prevention and treatment of GIO are limited and guidelines for the prevention of GIO are not fully consistent, the authors drew some recommendations that might improve the clinical practice in dermatological field: (1) The lowest possible dose and shortest duration of treatment should be adopted. (2) Weight-bearing exercise and adequate level of dietary calcium intake should be encouraged to all patients taking glucocorticoid. (3) Both vitamin D (400-800 IU/day) and calcium (500-1200 mg/day) should be given to patient on 5 mg or greater prednisolone equivalent dose for more than 3 months. (4) Bisphosphonate (alendronate 75 mg

once/week or risedronate 35 mg once/week) is indicated to all patients receiving >5 mg prednisolone daily for more than 3 months. Alternatively, bisphosphonate can be given to elderly patients (age >65) or younger patients who have risk factors for osteoporosis or low bone mineral density (BMD) score. (5) For those patients with contraindication or who intolerate to bisphosphonate, other treatments including hormonal replacement therapy (HRT), calcitonin and recombinant human parathyroid hormone (Teriparatide) could be considered after thorough discussion with endocrinologist.

### **Methotrexate for psoriasis in the era of biological therapy**

Warren RB, Chalmers RJG, Griffiths CEM, Menter A.  
Clin Exp Dermatol 2008;33;511-4.

The use of methotrexate in treating severe psoriasis was since 1971 after an incidental finding of rapid clearance of psoriasis by using a folate antagonist in treating the carcinoma patients. It is given once weekly starting with a test dose 5 mg-7.5 mg to maximum 30 mg. It is usually prescribed with folic acid to diminish potential side-effects although it remains controversial. An impediment to use methotrexate in psoriasis patients is its potential risk for causing liver fibrosis and the periodic liver biopsy recommended for monitoring. Recent advance finds that by monitoring the serum aminoterminal peptide fragment of type III procollagen can triage those at higher risk and hence reduce the overall frequency of liver biopsy. Deranged liver and renal function and haematological abnormality are also other adverse events of the methotrexate treatment. The CHAMPION study (Comparative Study of Humira vs. Methotrexate vs. Placebo In Psoriasis Patients) found that 79.6% of patients achieved a PASI 75 response after 16 weeks of adalimumab compared with 35.5% on methotrexate and more drop-out was in methotrexate group. However, the study period was short and the response rate

(end point: PASI 75) in the placebo group was high (19.8%) that made the result in the methotrexate group questionable. The authors comment that there is little question that most biologic have superior efficacy to traditional systemic agents such as methotrexate in the short term. However, the significant cost different and lack of long-term (>3 years) data for biologics mean that methotrexate is still likely to remain one of the first-line systemic psoriasis treatments in the foreseeable future.

### **Risk factors associated with human immunodeficiency (HIV) infection among attendees of public sexually transmitted infection clinics in Hong Kong: implications for HIV prevention**

Lee PM, Ho KM.  
Hong Kong Med J 2008;14:259-66.

The incidence of HIV infection in Hong Kong has entered a period of rapid growth over the last 3 years. Sexual contact remains the predominant mode of transmission, accounting for 81% of the cumulative total. The authors conducted a retrospective case-control study to examine the risk factors for HIV transmission among attendees of public sexually transmitted infection (STI) clinics in HK.

All public STI clinic attendees' records from Jan 1995 to Dec 2002 were reviewed. Of 139,336 STI clinic attendees, 196 HIV sero-positive cases were recruited to the study.

Multivariate analysis showed that HIV infection was associated with the following factors: non-Chinese ethnic groups (mainly South-East Asian) [odds ratio =9.32; 95% confidence interval 3.27-26.55], coexisting syphilis (other than primary) [ 5.67; 1.66-19.36], current non-gonococcal urethritis (2.10; 1.08-4.07), current genital warts (1.94; 1.10-3.43), history of prior sexually transmitted infection (2.19; 1.29-3.72), casual sex with friends (2.89; 1.07-7.80) and casual sex in Mainland China (1.91; 1.04-3.49).

This study identified certain factors that were positively associated with HIV infection among patients attending public STI clinics. To prevent and control HIV transmission, targeted intervention should be offered to individual with these high-risk factors.

### **Cutaneous pemphigus vulgaris with skin features similar to the classic mucocutaneous type: a case report and review of the literature**

Shinkuma S, Nishie W, Shibaki A, et al.  
Clin Exp Dermatol 2008;33:724-8.

Pemphigus vulgaris (PV) can be classified into two subtypes, namely mucosal type PV (mPV) and mucocutaneous type PV (mcPV). Recently, a cutaneous type PV (cPV), which is yet to be categorized, has been suggested. cPV does not clinically involve mucosal membrane, but is histopathologically characterized by the distinctive suprabasal acantholysis upon which the diagnosis is based. To date, seven cases of cPV have been reported in the literature. Variable skin eruptions of cPV have been described, but none of the cases had skin eruption similar to that of mcPV. The authors of this article reported the first case of cPV that showed skin lesions very similar to typical mcPV.

The case was a 50-year-old man presented with widespread tense or flaccid blisters, erosions and pruritic erythema over the trunk and limbs. Nikolsky's sign was positive. Nomucosal involvement was found in oral, pharyngeal, laryngeal or oesophageal membranes.

Clear-cut positive values of IgG antibodies to desmoglein (Dsg) 1 and Dsg 3 were demonstrated by ELISA test. Skin biopsy showed suprabasal and pricke cell layer bullae. Direct immunofluorescence (DIF) of skin showed *in vivo* IgG and C3 deposition on the keratinocyte cell surface in all layers of the epidermis.

The patient was treated with oral prednisolone at an initial dosage of 0.8 mg/kg/day which resulted

in a good clinical response. The prednisolone was subsequently reduced to 0.2 mg/kg/day.

The pathogenesis of cPV remains unclear. The authors postulated that anti-Dsg3 autoantibodies in concert with anti-Dsg1 autoantibodies in this case were sufficient to disrupt cell adhesion in the epidermis, but the quantities of these autoantibodies were insufficient to cause acantholysis in the oral and other mucous membrane.

### **Molecular epidemiology demonstrated three emerging clusters of human immunodeficiency virus (HIV) type 1 subtype B infection in Hong Kong**

Leung TWC, Mak D, Wong KH, et al.  
AIDS Res Hum Retroviruses 2008;24:903-10.

Molecular epidemiology is recognized as a powerful tool to study the origin of the HIV-1 pandemic and to track the course of global transmission patterns among different risk groups. The authors conducted a molecular epidemiological study on newly diagnosed HIV-1 infected patients in Hong Kong to identify the epidemiological linkage of HIV-1 infection in the locality.

Reverse transcription polymerase chain reaction (RT-PCR) for HIV-1 was performed on newly diagnosed HIV-1-positive sera collected from Jan 2002 to Dec 2006. PCR products correspond to the *env* C2V3V4 region and the *gag* p17/p24 junction were nucleotide sequenced.

Of 1,265 HIV-1-positive leftover sera studied, 1,202 (95%) samples had HIV-1 subtype successfully determined. During this period, CRF01\_AE (48.8%) was found to be the most common subtype, followed by subtype B (36.4%). Three emerging HIV-1 clusters (designed as Cluster I, II, III) were observed among the subtype B sequences. The *env* and *gag* evolutionary distances of these three clusters

were significantly different from the control (*env* gene comparison:  $p < 0.0001$ ; *gag* comparison:  $p < 0.0001$ ), suggesting the close relatedness of members within individual clusters. The evolutionary distance of the *gag* gene ( $2.43 \pm 2.28$ ) within Cluster 1 was found to be more diverse than its *env* gene.

All cluster members were adult male. Of the 42 members in Cluster I, two were first detected in 2003, 8 in 2004 and 12 in 2005. A significant increase was noted in 2006 with 20 additions. Thirty-three members (78.5%) of this cluster acquired the infection through homosexual or bisexual contact. For Cluster II ( $n = 12$ ), two members were first detected in 2004. Five more cluster members were detected in 2005 and another five in 2006. Cluster III, comprising 6 members, was detected in 2006. Again all members in Cluster III had acquired the infection through homosexual or bisexual contact.

In addition to the unique cluster-specific amino acid signature, the majority of sequences in Cluster I harbour a 6-amino acid insertion at the *gag* p17/p24 junction in a region that is thought to be closely associated with HIV-1 infectivity.

These results demonstrated the use of molecular analyses to elucidate the distribution of the HIV-1 subtype in Hong Kong. The rapid expansion of HIV-1 genetic cluster indicated the need to continue the molecular surveillance and to track the course of HIV-1 transmission in Hong Kong.

### **Prospective study of the cutaneous adverse effects of sorafenib, a novel multikinase inhibitor.**

Autier J, Escudier B, Wechsler J, Spatz A, Robert C. *Arch Dermatol* 2008;144(7): 886-92.

Sorafenib is a novel orally active anti-epidermal growth factor receptor agent. It is a small molecule multikinase inhibitor that inhibits several tyrosine kinase receptors involving in tumor angiogenesis and tumor progression. Sorafenib was recently approved for the treatment of advanced renal cell

carcinoma and hepatocellular carcinoma. Ongoing studies have included treatment of melanoma, non-small cell lung cancer as monotherapy or combination therapy. Cutaneous side effects of this group of anti-cancer drugs were frequently reported. This prospective study sought to describe and to evaluate the incidence and severity of cutaneous adverse reactions induced by sorafenib.

A total of 85 patients with renal cell carcinoma receiving treatment in a phase III clinical trial were recruited. The cutaneous reactions were classified as alopecia, skin eruption and desquamation and hand-foot skin reaction. More than 90% of patients treated with sorafenib had at least one cutaneous symptom.

Of 43 patients treated with sorafenib, 26 (60%) reported hand-foot skin reaction. This reaction occurred 2-3 weeks after start of treatment. The symptoms were paresthesia, burning or painful sensation. Physical signs included symmetric acral erythematous and edematous lesions with desquamation and fissures which were largely seen on palm and sole, hyperkeratosis with erythematous or edematous halo and bullous lesions. Histopathological features were parakeratosis, dyskeratosis, dense superficial perivascular lymphocytic infiltrate with some leucocytoclastic vasculitis.

Facial and scalp erythematous eruption appeared as classic seborrheic dermatitis. Lesions usually spared the periorbital area. Histopathological features were non-specific.

Scalp dysesthesia was frequently reported and occurred early between first and third week of treatment and spontaneously resolved within days to weeks. Subungual splinter hemorrhage was characterized by straight black or red lines under almost exclusively the finger nails. This commonly occurred in the first 2 months of treatment and resolved spontaneously.

Alopecia was developed generally between third and fifteenth weeks and spontaneously resolved

in some patients despite continued with treatment. Body hair loss and slowing of facial hair growth was also noted.

Other cutaneous signs included stomatitis, cheilitis, hyperkeratosis of nipple, diffuse xerosis, multiple facial cystic lesions including different forms epidermoid cyst, diffuse keratotic lesions and keratoacanthoma.

The authors concluded that skin reactions are very frequent in sorafenib treatment. Severe reactions such as hand-foot skin reaction might negatively affect quality of life and might even lead to discontinuation of treatment. Early recognition of symptoms and prompt treatment could result in significant improvement of hand-foot skin reaction and other cutaneous reactions of sorafenib.

### **Azithromycin pulses in the treatment of inflammatory and pustular acne: efficacy, tolerability and safety**

Antonio JR, Pegas JR, Cestari TF, Nascimento LV  
J Dermatol Treat 2008;19:210-5.

Oral antibiotics such as tetracycline and erythromycin were commonly used in treatment of acne. Apart from anti-inflammatory effect, these drugs suppress growth of *Propionibacterium acne* (*P. acne*). Azithromycin is an azalide with mode of action analogous to erythromycin. But it has a longer half-life that allows a single daily dose. Azithromycin is also more stable in acidic medium, thus enhances greater absorption and higher tissue penetration. This study evaluated the efficacy and safety of pulse azithromycin in the treatment of moderate severe acne.

A total of 57 patients with grade II inflammatory acne were recruited. Patients were given weekly pulses of azithromycin 500 mg for 3 consecutive days with interval of 7 days without medication. A significant reduction in number of lesions (55.5%) was noted at the end of third cycle of

treatment. Clinical insignificant laboratory changes in complete blood count, AST and ALT were noted. The main adverse events were gastrointestinal and central nervous system and were regarded as mild or moderate. Gastrointestinal effects such as epigastric pain, abdominal pain, diarrhea, soft stool and nausea were noted in nine patients (15.8%). CNS effects such as headache and drowsiness were noted in only three patients (5.3%). All the events resolved with suspension of the drug without any sequelae.

The authors concluded that the use of pulse azithromycin therapy in treatment of acne in teenagers and young adults would facilitate drug compliance. Moreover the antibiotic resistance of *P. acne* would thus be reduced. The pulse treatment is well tolerated. No clinical significant adverse effect occurred.

### **Comparison of the efficacy and tolerability of 3% diclofenac sodium gel and 5% imiquimod cream in the treatment of actinic keratosis**

Kose O, Koc E, Erbil H, Caliskan E, Kurumlu Z.  
J Dermatol Treat 2008;19:159-63.

Actinic keratosis is a common premalignant skin lesion in the photodamaged skin. An effective and well tolerated treatment is necessary especially for those patients with large number of lesions. Studies showed that both topical diclofenac and imiquimod treatments were effective in treating actinic keratosis. This study aimed at comparing the efficacy of topical diclofenac and imiquimod in the treatment of actinic keratosis.

A total of 49 patients were recruited. The mean age was 57.6 years in the diclofenac group and 56.5 years in the imiquimod group. The gender distribution in both treatment groups was similar. Most of the patients had a moderate to severe baseline severity index of actinic keratosis. The 3% diclofenac gel was applied once daily and the

5% imiquimod cream was applied three times per week for 12 weeks. Both study arms showed no significant difference in the Investigator and Patient Global Improvement Indices.

A greater improvement was noted in patients with a baseline severity index of mild or moderate compared to those with severe baseline index. Both treatments were found to be well tolerated with the most common side effects being erythema, pruritus, dry skin and scaling. Most of the side effects were mild or moderate. No discontinuation of drugs was needed. No clinical significant abnormality in laboratory parameters was noted.

Diclofenac is a potent cyclooxygenase inhibitor. It acts via an effect on metalloproteinases that

would have keratolytic action and degrade collagen and epidermal cytoskeletons. Imiquimod is an immune response modifier. It may facilitate immunologic recognition of disease and augment the immune response. It was shown to activate antigen presenting cells to produce interferon and other cytokines. This would in turn stimulate the innate immune response and direct the acquired immune response to the target the lesions.

The authors concluded that both topical 3% diclofenac and 5% imiquimod were equivalent in efficacy in the treatment of actinic keratosis. Both treatments were well tolerated with mild side effect profile. A long term follow-up study to evaluate safety and recurrence rate was recommended by the authors.