

## Journal Watch

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### **The use of alternative medicine in pediatric patients with atopic dermatitis**

Hughes R, Ward D, Tobin AM, Keegan K, Kirby B. *Pediatr Dermatol* 2007;24:118-20.

A questionnaire-based study was performed on 80 paediatric patients with atopic dermatitis. The parameters studied included the duration of alternative medicine treatment, reason for using alternative therapy, effect of treatment and cost, the duration of childhood eczema and whether there were any hospital admissions for eczema.

The mean age was 3.9 years (range 2 months to 17 years). There were 49 (61.25%) boys. At least one form of alternative medicine had been used in 34 (42.5%) of which herbal remedies and homeopathic medicine were used in 41% and 23.5% cases respectively. Fifteen patients had used more than one form of alternative therapy. Most treatments had been used for one or more months. The reasons for using alternative therapy were fear of steroid side effects (26.4%), recommendation from others (47%), dissatisfaction with conventional treatments (17.6%) and others (5.8%).

No improvement was reported in 57.7% cases and deterioration was reported in almost 10% of cases. Some improvement was seen in 15 cases. An improvement in pruritus was the most commonly reported effect. The cost of treatment varied from nil to Euro 4000 (average Euro 321.8). Six of the 34 cases who had used alternative therapies had been hospitalised for eczema compared to four cases in those who had not used

alternative therapy. This suggested that severity of eczema in both groups was similar.

It was concluded that alternative therapies were ineffective and that routine enquiry about the use of alternative therapies was recommended.

### **Treatment of oral erosive lichen planus with 1% pimecrolimus cream: a double-blind, randomized, prospective trial with measurement of pimecrolimus levels in the blood**

Passeron T, Lacour JP, Fontas E, Ortonne JP. *Arch Dermatol* 2007;143: 472-6.

The efficacy of 1% topical pimecrolimus cream in treating oral lichen planus (OLP) was studied. Twelve patients with OLP were randomised to either placebo or 1% pimecrolimus cream twice daily for four weeks. The change in spontaneous and meal-triggered pain as well as the surface area of OLP were assessed, with a maximum score of four for each item.

The mean duration of OLP was 12 years (range 2-58 years). In the placebo group, the total score improved in three cases with a mean decrease from 4.67 on day 0 to 3.33 on day 28 ( $p=0.22$ ). Five cases improved in the pimecrolimus group with a mean total score of 6.83 on day 0 to 3.33 on day 28 ( $p=0.04$ ). The mean surface area score of OLP was 1.67 on day 0 versus 1.33 on day 28 in the placebo group and 2.17 on day 0 versus 0.83 on day 28 in the pimecrolimus group. The most notable improvement in pimecrolimus group

was reduced pain on eating. All but one patient reported improvement in symptoms within the first week. Only one patient reported improvement in the placebo group.

Burning sensations in the first few days of treatment were reported in two cases in the pimecrolimus group. Pimecrolimus was detectable in blood in the treatment group, with a mean concentration of 2.32 ng/ml and 2.84 ng/ml on day 14 and day 28 respectively. Blood pressure remained stable and no laboratory abnormalities were detected. However, all of the cases that improved with pimecrolimus relapsed within one month of stopping treatment.

The authors concluded that topical pimecrolimus was effective for the treatment of OLP but further studies into the effect of systemic absorption on long-term use of this treatment were required.

### **Randomized double-blind trial of treatment of vitiligo: efficacy of psoralen-UVA therapy vs narrowband UVB therapy**

Yones SS, Palmer RA, Baribaldinos TM, Hawk JLM. Arch Dermatol 2007;143:578-84.

The efficacy of oral psoralen-UVA (PUVA) in the treatment of vitiligo was compared with that of narrowband UVB (NB-UVB). Fifty patients with non-segmental vitiligo were treated with either PUVA (n=25) or NB-UVB (n=25) twice weekly. Patients were assessed after 48 sessions of therapy, at the end of therapy and at 12 months post treatment.

The median percentage body surface area with vitiligo (BSA-V) at baseline were 8.4% (range 3-64) and 6.9% (range 2-55) for PUVA and NB-UVB group respectively. The median number of treatments in PUVA group was 47 compared to 97 in NB-UVB group. After 48 sessions, there was a greater improvement in BSA-V in NB-UVB group (p=0.007). All 25 patients in NB-UVB group and

23 patients in PUVA group had areas of repigmentation. The match with the unaffected skin of the patient was excellent in all cases treated with NB-UVB but only 11 (44%) of cases treated with PUVA showed a similar improvement. The repigmented areas were obviously darker in the remaining PUVA cases. The Dermatology Life Quality Index and visual analog scale for subjective vitiligo grading were improved for both forms of phototherapy treatment.

Erythema was reported in 24 (96%) PUVA cases compared to 17 (68%) cases treated with NB-UVB ( $\chi^2=6.6$ , p=0.02). The median number of sessions given before the onset of erythema was 5 in PUVA cases and 21 in cases treated with NB-UVB. At 12 months follow-up, greater than 75% improvement in BSA-V was maintained in 6 (24%) cases treated with PUVA and in 9 (36%) NB-UVB treated cases. The colour match remained excellent in all NB-UVB cases compared to only 61% of PUVA cases ( $\chi^2=12$ ; p<0.001).

It was concluded that NB-UVB was more effective than PUVA in the treatment of vitiligo.

### **A randomized, open-label trial of continuous versus interrupted etanercept therapy in the treatment of psoriasis**

Moore A, Gordon KB, Kang S, Gottlieb A, Freundlich B, Xia HA, et al. J Am Acad Dermatol 2007;56:598-603.

This is a randomized, open-label study to evaluate the effectiveness and safety of continuous versus interrupted etanercept therapy in the treatment of psoriasis. There were altogether 2546 patients recruited into the study and all received continuous subcutaneous etanercept 50 mg twice weekly for 12 weeks. In the next 12 weeks, half of them (n=1272) received etanercept 50 mg once weekly (continuous group). For the interrupted group (n=1274), the treatment was stopped at week 12 if they responded well and etanercept was

restarted upon relapse. Nonresponders in interrupted group at week 12 received etanercept 50 mg once weekly till week 24. At baseline, both groups had similar demographic and disease severity. At week 12, the percentage of responders was similar for both arms (72%), but significantly higher for the continuous group at week 24 (71.0% versus 59.5%;  $p < 0.0001$ ). Most patients from the interrupted group regained response once treatment was resumed. The mean time of relapse after stopping etanercept was 39.6 days and that to regain response after treatment was 35.0 days. All adverse effects were comparable for both arms, including serious adverse effects like non-cardiac chest pain (3 continuous, 3 interrupted) and non-melanoma skin cancers (7 continuous, 9 interrupted). Three patients died during the study. Two deaths were related to thrombosis after thrombectomy and brain haemorrhage respectively. One patient died from pneumonia, immunosuppression and sepsis, which was considered to be possibly related to etanercept.

It was concluded that continuous therapy provided greater improvement but it could be interrupted if necessary and resumed with successful re-treatment. One major limitation of the study was its open-label design. The study was funded by Amgen Inc. and Wyeth Research.

### **Distribution of toenail dystrophy predicts histologic diagnosis of onychomycosis**

Walling HW, Sniezek PJ.

*J Am Acad Dermatol* 2007;56:945-8.

This study evaluated whether the distribution patterns of toenail dystrophy were associated with fungal infection of the nail. It reviewed retrospectively over a 5-year period, between 1999 and 2004, the results of toenail clippings submitted for periodic acid-Schiff (PAS) staining for the diagnosis of onychomycosis. Cases of non-dermatophyte fungus were excluded.

Demographic and clinical information was collected from electronic records of the clinics. There were 311 patients (130 male, 181 females) with a mean age of 48.3 years. There were 150 specimens (48.2%) histologically positive for onychomycosis, which was significantly more likely in men, in person older than the age of 64 and in the presence of tinea pedis. Interestingly, involvement of the third or fifth toenails of either foot was significantly correlated with onychomycosis. In about half (49.8%) of the cases of onychomycosis, the great toenail was involved and dystrophy of first and fifth nails on the same foot was predictive of onychomycosis ( $p < 0.01$ ). Unilateral involvement of two or more nails was also a strong correlation with onychomycosis ( $p < 0.001$ ). However, female gender was a negative predictor of onychomycosis ( $p < 0.001$ ). The presence of psoriasis vulgaris was not a risk factor for onychomycosis in this study.

It was concluded that patterns of nail dystrophy might help to clinically distinguish onychomycosis and guide laboratory testing. The lack of fungal smear and culture results to correlate with the histologic results was a limitation in this study.

### **From sporadic atypical nevi to familial melanoma: Risk analysis for melanoma in sporadic atypical nevus patients**

de Snoo FA, Kroon MW, Bergman W, ter Huurne JA, Houwing-Duistermaat JJ, van Mourik LV, et al. *J Am Acad Dermatol* 2007;56:748-52.

This was a Dutch study reviewing the development of melanoma in either the index case or their family members of 167 sporadic patients who had five or more clinical and/or histological atypical nevi. Clinically, atypical nevi were defined as flat lesions fulfilling three of the following five criteria: size of 5 mm or larger in diameter, variegated brown pigmentation, hazy border, irregular shape and red hue. Patients were excluded if he was a first-degree relative of a melanoma family, defined

by at least two first-degree relatives with invasive melanoma, or the subject was a melanoma patient with at least one first-degree relative with invasive melanoma. They were followed up yearly in the pigmented lesion clinic of the Leiden University Medical Centre. Germ line mutation analysis of CDKN2A and CDK4 gene was conducted.

The average age of the subjects was 28 years and 47% were men. The median follow-up time was 9.7 years (range: 2 months to 27 years). Sixteen patients were diagnosed to have invasive melanoma before commencement of the study and were excluded. It was found that 9 patients developed melanoma during follow-up. The relative risk of melanoma development in these 151 subjects was 46.1 (95% CI 21.0-87.5). The relative risks of melanoma development for male and female patients were 33.8 and 54.1 respectively. Six patients were found to have mutations in the CDKN2A gene. Four of these mutation carriers became a member of a melanoma family during follow-up and five of them developed melanoma themselves subsequently.

The author concluded the increased risk for melanoma in sporadic atypical nevi patients and the association of germ line mutation with melanoma.

### **Tacrolimus ointment is more effective than pimecrolimus cream in adult patients with moderate to very severe atopic dermatitis**

Fleischer Jr AB, Abramovits W, Breneman D, Jaracz E for the US/Canada tacrolimus ointment study group.

J Dermatol Treatment 2007;18:151-7.

This was a prospective, randomized, investigator-blinded multicentre study aiming to compare the efficacy and safety of tacrolimus ointment 0.1% and pimecrolimus cream 1% in adult patients with

moderate to very severe atopic dermatitis (AD). This was a subanalysis of a previous study on adult patients with mild to very severe AD. Patients of  $\geq 16$  years old with AD affecting  $\geq 5\%$  of body surface area (BSA) and of moderate to very severe degree according to the Investigator Global Atopic Dermatitis Assessment were recruited. A total of 281 patients entered into the study. They were randomized to receive either tacrolimus ointment 0.1% ( $n=141$ ) or pimecrolimus cream 1% ( $n=140$ ). The study medication was applied twice daily to affected areas for up to six weeks or until one week after the affected areas cleared completely. Only non-medicated topical agents were allowed in other non-treated areas during the study period. The primary end point was the percentage change in the Eczema Area Severity Index (EASI) score. The secondary outcome measures included success of therapy, percentage change in the BSA affected and patient's assessment of itch measured by visual analogue scale.

271 (112 tacrolimus; 105 pimecrolimus) completed the study. Withdrawal due to lack of efficacy was significantly more in pimecrolimus group than in tacrolimus group (10 versus 1,  $p=0.005$ ). Eight withdrew due to adverse effect (3 tacrolimus, 5 pimecrolimus). The improvement in the EASI score was significantly greater in tacrolimus group as compared with pimecrolimus group (57% versus 39%,  $p=0.0002$ ). Success with therapy (40% versus 22%,  $p=0.001$ ) and improvement in %BSA affected (reduction of 49% versus 34%,  $p=0.01$ ) were significantly higher in the tacrolimus group. There was no significant difference in the incidence of adverse effect (30% for tacrolimus versus 25% for pimecrolimus,  $p=0.823$ ). Amongst which, the most common adverse events were application site burning and application site pruritus.

These results were consistent with those from the full study analysis. The improvement in the symptoms and signs were observed in the first week and reached a significant difference in tacrolimus group as compared with pimecrolimus

group by week 3 till the study end. In the pimecrolimus group, the improvement from baseline seemed to have reached a plateau at week 3. The withdrawal rate due to lack of efficacy in the pimecrolimus group was comparable to other studies. The authors concluded that tacrolimus ointment 0.1% was more effective than pimecrolimus cream 1% in adults with moderate to very severe AD. This study was supported by Astella Pharma US, Inc.

### **Prevention of chronic furunculosis with low-dose azithromycin**

Aminzadeh A, Demircay Z, Ocak K, Soyletir G. *J Dermatol Treatment* 2007;18:105-8.

This is an open-labeled prospective study to evaluate the efficacy and safety of low-dose azithromycin in the long-term suppressive treatment of chronic furunculosis. Patients, aged 18 to 60, with a history of three or more episodes of furuncles caused by *Staphylococcus aureus* in the last 6 months were recruited. The exclusion criteria were pregnancy, breast-feeding, diabetes mellitus, renal dialysis, AIDS, atopic dermatitis, use of immunosuppressive drugs and allergy to azithromycin. The patients were treated with azithromycin 500 mg/day for 3 consecutive days for active furuncles followed by weekly dosage of 500 mg for 12 weeks as suppressive treatment. They were instructed to use daily antibacterial skin cleanser. The patients were evaluated at baseline, first, second, fourth and 12th week of treatment and at 24th and 48th week of post-treatment period. The primary efficacy parameter was the complete clearance of furuncles during the treatment period. The secondary efficacy parameter was the duration of remission among the responders for a further 3 months of follow up. Samples from the active furuncles and nasal and perianal areas were obtained for microbiological study and in vitro susceptibility test. Azithromycin susceptibility was detected by E-test®.

Twenty-four patients entered the study and 21

completed. Three dropped out during the suppressive therapy period. The mean disease duration was  $3.7 \pm 3.9$  (0.5-13) years. Nineteen of 24 (79%) responded to azithromycin at the end of 3 months treatment. Eighteen of the responders remained in remission during the 3 month follow up period. Fifteen of the responders were followed up for 12 months. At the end, 13 of 15 (86.7%) remained in remission. Eighteen patients' specimens were evaluated for antibiotics susceptibility. All were methicillin sensitive strains. Fifteen of 18 (83.3%) strains were sensitive to azithromycin. There was a statistically significant correlation between the in vitro susceptibility and clinical efficacy of azithromycin ( $r=0.88$ ). The most common side effect was mild diarrhea.

The authors commented that the prolonged therapeutic actions of low-dose azithromycin might be due to its antibacterial and anti-inflammatory effects. The long tissue half life allowed the schedule of consecutive three daily doses in the very first week during the treatment phase and weekly dosage regimen for the suppressive therapy. The single dose regimen improved patient compliance. They concluded that low-dose azithromycin was effective and safe in the suppression of chronic furunculosis caused by methicillin sensitive *Staphylococcus aureus*. The potential emergence of resistant strains to azithromycin limited its widespread use.

### **A multicentre, randomized, controlled study of the efficacy, safety and cost-effectiveness of a combination therapy with amorolfine nail lacquer and oral terbinafine compared with oral terbinafine alone for the treatment of onychomycosis with matrix involvement**

Baran R, Sigurgeirsson B, de Berker D, Kaufmann R, Lecha M, Faergemann J, et al. *Br J Dermatol* 2007;157:149-57.

This was a randomized, open-label, parallel group

study carried out in 20 centres in nine European countries between February 2002 and September 2004. This study aimed at showing the efficacy and cost-effectiveness of a combination of amorolfine nail lacquer and oral terbinafine in the treatment of onychomycosis. It included patients with dermatophytic onychomycosis with matrix involvement affecting at least one big toenail, which was confirmed by both direct microscopy and mycological culture.

Patients were randomized to receive either a combination of amorolfine hydrochloride 5% nail lacquer once weekly for 12 months plus terbinafine 250 mg once daily for three months (AT group) or terbinafine alone once daily for three months (T group). The study duration was 18 months including a 6-month treatment free phase following the 12-month active treatment phase for the AT group and a 15-month treatment-free phase following the 3-month active treatment phase for the T group. The primary efficacy criterion was overall response, using a dichotomous scale of success or failure; success being the combination of clinical cure and negative mycology at month 18. Secondary efficacy criterion included clinical cure, defined by disappearance of all lesions on nail or residual disease of less than 10% of the original disease surface area.

In total, 249 patients were included into the study: 120 in the AT group and 129 in the T group. At month 18, treatment with the amorolfine-terbinafine combination resulted in a significantly higher success rate (59.2%) compared with treatment with terbinafine alone (45.0%;  $p=0.03$ ). In terms of clinical response, patients in the AT group were significantly more likely to be clinically cured at month 18 than those treated with terbinafine (66.7% vs. 53.5%, respectively;  $p<0.04$ ). Both treatment groups showed reductions in the percentage of the total diseased surface on the target nail, with mean reductions of 85.1% for the AT group and 78.5% for the T group at month 18. Both treatment regimens were safe and were well tolerated.

Pharmacoeconomic evaluation showed that treatment cost per cured patient was lower for the combination therapy than for terbinafine alone in all participating countries. The cost per cured patient with the combination therapy was lower, depending on the country, by up to 15.47% compared with oral terbinafine monotherapy.

The authors thus concluded that amorolfine nail lacquer in combination with oral terbinafine enhanced clinical efficacy and was more cost-effective than terbinafine alone in the management of dermatophytic toenail onychomycosis with matrix involvement. The authors worked as consultants or employees for Galderma Laboratories and Galderma R&D.

### **Cutaneous melanoma: a population-based epidemiology report with 989 patients in Hong Kong**

Hui SK, Tang WYM, Wong TW, Lau KH, Lee S, Chong LY, et al.

Clin Exp Dermatol 2007;32:265-7.

This is a retrospective population-based epidemiological study of 20 years of data on cutaneous melanoma (CM) between 1983 and 2002 with data drawn from the Hong Kong Cancer Registry.

The local population in Hong Kong comprises 94.9% Chinese, 3.9% non-Chinese East Asians and 1.2% whites. Between 1983 and 2002, 989 new cases of CM and 378 deaths from CM were registered. These data were analyzed, focusing on the incidence rates, mortality rates and their relationship with age. Incidence and mortality were presented as actual rate (crude rate) and world age-standardized rate (WASR). In these 989 new cases of CM, 510 were male and 479 were female patients. There were 378 deaths from CM registered during this period, in which 217 were males and 161 were females.

There was a significant increase in melanoma incidence and mortality rates (both  $p < 0.001$ ) proportional to age in both sexes. The mean crude rate and mean WASR of the incidence of CM in Hong Kong within this period were 0.8 and 0.7 (new cases per year per 100000) respectively. The mean crude rate and mean WASR of the CM mortality in male within this period were 0.4 and 0.3 (deaths per year per 100000) respectively, whereas the mean crude rate and mean WASR of CM mortality in female in the same period were 0.3 and 0.2 (deaths per year per 100000) respectively. Both the mean crude rate and WASR for melanoma mortality were thus higher in males.

The incidence and mortality rates of CM in Hong Kong showed a positive relationship with advanced age for both genders. The author therefore concluded that advanced age was a definite risk factor for CM in the local population and the estimated incidence rates and mortality rates of CM in the future were likely to rise in an ageing population.

### **Redarkening of port-wine stains 10 years after pulsed-dye-laser treatment**

Huikeshoven M, Koster PH, de Borgie CA, Beek JF, van Gemert MJ, van der Horst CM. *N Engl J Med* 2007;356:1235-40.

This was a prospective study aiming at assessing the long term efficacy of pulsed-dye-laser therapy for the treatment of port-wine stains (PWS). Fifty-one patients with PWS were included in this study and they were followed up for a median time of 9.5 years.

PWS were treated with a Candela pulsed-dye-laser (model SPTL-1) with a wavelength of 585 nm, a radiant exposure level of 6 to 8 J/cm<sup>2</sup>/ pulse, a pulse duration of 45 ms and a spot size of 5 to 7 mm. PWS area was cooled by gauze dressings drenched in ice water during treatment.

The results at long-term follow-up were compared with colour measurements obtained before treatment and after completion of an average of five laser treatments of the complete PWS. Patients' satisfaction with the treatment and their perception of long-term changes in PWS were assessed by a questionnaire at the end of study period. Colour of the PWS, as compared with normal contralateral skin, was measured by using a Minolta chromometer (model CR-300). The difference in colour between PWS and the normal skin was denoted by (Delta) E. A small number for (Delta) E indicated a small color difference.

In this study, 51 patients underwent repeated colour measurements and completed the questionnaire. The median duration of the original five treatment regimen for the 51 patients was 1.9 years (interquartile range, 1.4 to 2.4). Forty-five of the 51 patients had a median additional laser sessions of 7 (interquartile range, 3 to 13; range 1 to 39) during the remaining follow-up period. The median time between the measurement obtained after the first five treatments and the follow-up measurement was 9.5 years (interquartile range, 9.2 to 10.1). Fifty-nine percent of patients were satisfied with the overall treatment result. Of the remaining patients, six percent of patients reported that the stain had become lighter since their last treatment, 59% claimed that it was unchanged and 35% reported that it had become darker.

The median (Delta) E increased significantly from 8.9 (interquartile range, 6.5 to 12.4) after the first five treatments to 12.4 (interquartile range, 8.7 to 14.8) at a median of 9.5 years of follow-up ( $p = 0.001$ ). However, the median (Delta) E was still significantly lower at follow-up (12.4; interquartile range, 8.7 to 14.8) than before laser treatment (15.2; interquartile range, 12.3 to 19.5;  $p < 0.001$ ), indicating a persistent effect of pulsed-dye laser treatment.

The author concluded that there was significant redarkening of PWS at long term follow-up after

pulsed-dye-laser therapy. Therefore, it was suggested that patients should be informed about the possibility of redarkening/relapse before beginning treatment.

### **A recalcitrant case of cicatricial pemphigoid**

Yu JHT, Chong LY, Lee KC.

Hong Kong Med J 2007;13:157-60.

This is a case report of a 57-year-old Chinese woman with cicatricial pemphigoid (CP), presenting with a one-year history of erosions on her oral mucous membranes, conjunctivitis and blisters on her hands and feet. A clinical diagnosis of CP was made and it was confirmed by skin biopsy. She also had subglottic mucosal inflammation. Despite she was jointly cared by dermatologist, ophthalmologist and otolaryngologist and treated intensively with the combination of prednisolone, cyclophosphamide and intravenous immunoglobulin (IVIg), the patient died from overwhelming sepsis and multi-organ failure in April 2006.

CP is a rare autoimmune blistering disorder that affects the mucous membranes and skin. Recent studies conducted in Europe estimated an incidence of 1.16 cases per million per year with a female-to-male ratio of 2:1 and a mean age of

64 years at diagnosis. There is no racial predilection.

Oral lesions are the most common presentation in CP and are associated with the best prognosis. The conjunctiva is the second most frequent site of involvement and can be the only site affected. Larynx may sometimes be involved; the earliest manifestation of laryngeal involvement is hoarseness. Once scarring of the larynx occurs, it is permanent and may result in life-threatening obstruction requiring tracheostomy. Two types of skin lesions have been described in CP. The first type consists of recurrent tense bullae, similar to those seen in bullous pemphigoid, which rupture and heal without significant scarring. The second type consists of flaccid blisters surrounded by patches of erythema in which significant scarring can occur and is known as the Brunsting-Perry type.

Immunosuppressive therapy forms the mainstay of treatment. This disease is extremely difficult to treat despite the use of aggressive combination immunosuppressive regimens. CP with multiple mucosal sites involvement has the worst prognosis due to its high resistance to medical therapy, resulting in loss of function through scarring. The therapies reported to be of value in the treatment of CP include prednisolone, dapsone, cyclophosphamide, IVIg, azathioprine, methotrexate, mycophenolate mofetil and plasmapheresis.