

Journal Watch

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Quadrivalent vaccine against human papillomavirus to prevent high-grade cervical lesions

FUTURE II Study Group.

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Human papillomavirus types 16 (HPV-16) and 18 (HPV-18) cause approximately 70% of cervical cancers worldwide. A randomized, double-blind phase 3 trial was conducted to evaluate a quadrivalent vaccine against HPV types 6, 11, 16, and 18 (HPV-6/11/16/18) for the prevention of high-grade cervical lesions associated with HPV-16 and HPV-18.

The authors assigned 12,167 women between the ages of 15 and 26 years to receive three doses of either HPV-6/11/16/18 vaccine or placebo, administered at day 1, month 2, and month 6. The primary analysis was performed for a per-protocol susceptible population that included 5305 women in the vaccine group and 5260 in the placebo group who had no virologic evidence of infection with HPV-16 or HPV-18 through 1 month after the third dose (month 7). The primary composite end point was cervical intraepithelial neoplasia grade 2 or 3, adenocarcinoma in situ, or cervical cancer related to HPV-16 or HPV-18. The subjects were followed for an average of 3 years after receiving the first dose of vaccine or placebo.

Vaccine efficacy for the prevention of the primary composite end point was 98% (95.89% confidence interval [CI]=86 to 100) in the per-protocol susceptible population and 44% (95% CI=26 to 58) in an intention-to-treat population of all women who had undergone randomization (those

with or without previous infection). The estimated vaccine efficacy against all high-grade cervical lesions, regardless of causal HPV type, in this intention-to-treat population was 17% (95% CI=1 to 31).

It was concluded that in young women who had not been previously infected with HPV-16 or HPV-18, those in the vaccine group had a significantly lower occurrence of high-grade cervical intraepithelial neoplasia related to HPV-16 or HPV-18 than did those in the placebo group.

Quadrivalent vaccine against human papillomavirus to prevent anogenital diseases

Garland SM, Hernandez-Avila M, Wheeler CM, Perez G, Harper DM, Leodolter S, et al; Females United to Unilaterally Reduce Endo/Ectocervical Disease (FUTURE) I Investigators.

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A randomized, placebo-controlled, double-blind, phase 3 trial was conducted to evaluate the efficacy of a prophylactic quadrivalent vaccine in preventing anogenital diseases associated with human papillomavirus (HPV) types 6, 11, 16, and 18.

This trial involved 5455 women between the ages of 16 and 24 years of which 2723 women received vaccine and 2732 received placebo at day 1, month 2, and month 6. The coprimary composite end points were the incidence of genital warts, vulvar or vaginal intraepithelial neoplasia, or cancer and the incidence of cervical intraepithelial

neoplasia, adenocarcinoma in situ, or cancer associated with HPV type 6, 11, 16, or 18. Data for the primary analysis were collected for a per-protocol susceptible population of women who had no virologic evidence of HPV type 6, 11, 16, or 18 through 1 month after administration of the third dose. The women were followed for an average of 3 years after administration of the first dose. In the per-protocol population, those followed for vulvar, vaginal, or perianal disease included 2261 women (83%) in the vaccine group and 2279 (83%) in the placebo group. Those followed for cervical disease included 2241 women (82%) in the vaccine group and 2258 (83%) in the placebo group.

Vaccine efficacy was 100% for each of the coprimary end points in the per-protocol susceptible population. In an intention-to-treat analysis, including those with prevalent infection or disease caused by vaccine-type and non-vaccine-type HPV, vaccination reduced the rate of any vulvar or vaginal perianal lesions regardless of the causal HPV type by 34% (95% CI=15 to 49), and the rate of cervical lesions regardless of the causal HPV type by 20% (95% CI=8 to 31).

The authors concluded that the quadrivalent vaccine significantly reduced the incidence of HPV-associated anogenital diseases in young women.

The impact of total body photography on biopsy rate in patients from a pigmented lesion clinic

Risser J, Pressley Z, Veledar E, Washington C, Chen SC.

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Total body cutaneous photography is increasingly being used by dermatologists to monitor patients at risk for the development of melanoma, but limited evidence exists regarding the impact of such photography on melanoma and melanoma-related outcomes. The authors sought to compare

biopsy number in patients with multiple atypical nevi in their first year of care at their pigmented lesion clinic (PLC) between those who received total body skin examination alone and those who received total body skin examination and total body digital photography (TBDP). They sought to identify predictors of biopsy number and number of dysplastic nevi diagnosed in patients with multiple atypical nevi.

A chart review was performed for patients attending the PLC during the years 1998 to 2003 to identify the number of biopsies performed in the first year of care. Patient demographics, melanoma risk factors, and melanoma outcome events were also abstracted from the charts.

The mean number of biopsies performed in patients in their first year of care at the PLC in those who did not receive TBDP was equal to the mean number of biopsies performed in patients who did receive TBDP (0.82 and 0.8, respectively). Linear regression analysis revealed that the interaction term between a lack of both personal history of melanoma and severe dysplastic nevi (-0.930; $p=0.005$) has a significant protective effect on the number of biopsies. Similar regression analysis also showed that the interaction term between a lack of both personal history of melanoma and of severe dysplastic nevi (-1.209; $p<0.0001$), increasing provider experience (-0.047; $p=0.029$), and increased number of biopsies before the initial PLC (-0.028; $p=0.050$) have a statistically significant protective effect on the number of dysplastic nevi diagnosed in the first year of PLC. TBDP did not have an effect on the number of biopsies or on the number of dysplastic nevi diagnosed in the first year of care at the PLC.

Given these results, the authors concluded that this small retrospective study does not provide evidence that would suggest that TBDP changes provider behavior in caring for patients at high risk for melanoma. Rather, it supports the fact that a patient's positive history of melanoma and a

history of severe dysplastic nevi have the most significant impact on provider biopsy behavior, resulting in a lower threshold to biopsy suggestive lesions. However, this study is limited by being retrospective in nature, having a small sample size, and having a short follow-up period.

Skin tag as a cutaneous marker for impaired carbohydrate metabolism: a case-control study

Rasi A, Soltani-Arabshahi R, Shahbazi N.
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Skin tags are common benign skin tumour that may be associated with systemic disorders such as diabetes mellitus (DM). However, clinical studies have demonstrated with conflicting results. The authors evaluated the prevalence of diabetes and impaired glucose tolerance (IGT) by a case-control study in patients with skin tags.

The subjects were over 15-year old and examined by a trained dermatologist. For those with diseases associated with (1) secondary diabetes such as disorders of the exocrine pancreas, (2) endocrinopathies (Cushing's syndrome, acromegaly, phaeocromocytoma, glucagonoma, hyperthyroidism), (3) consumption of drugs which might induce DM (nicotinic acid, glucocorticoids, thyroid hormone, α and β -adrenergic agonists, thiazides, phenytoin, interferon- α), (4) conditions of acute infective, traumatic, circulatory or other stress that might cause reactive hyperglycaemia were all excluded. Total 198 patients completed the study. The cases (104 patients) and controls (94 patients) were matched for age, sex and body mass index (BMI).

The mean total number of skin tag was 24.75 (range 3-65). The mean age at the onset of skin tag was 41.58 (range 13-65 years). In case group, 13.2% patients had low number of skin tags (<10), 59.3% patients had moderate number (10-29) and 27.5% patients had high number of skin

tags (>30). The most common site was neck followed by axillae. DM and IGT were diagnosed according to WHO criteria after oral glucose tolerance test. While 24 patients (23.07%) in the case group had DM, only 8 patients (8.51%) in control group had DM. The difference was statistically significant ($p=0.005$). However, the difference was not significant in IGT analysis ($p=0.543$) in which 14 patients (13.46%) in case and 10 patients (10.63%) in control group had IGT. When both DM and IGT were considered together (defined as impaired carbohydrate tolerance), the difference was statistically significant ($p=0.007$). Patients with DM or IGT had greater number of skin tags compared to normoglycaemic one ($p=0.005$). In addition, patients with higher number of skin tags (>30) had significantly higher incidence of impaired carbohydrate metabolism than those who had less skin tags ($p=0.014$). There was no positive correlation between number of skin tags and BMI ($p=0.413$). The correlation between number of skin tags in obesity (BMI>30), overweight (BMI>25) and normal weight were not significant ($p=0.184$). There was no correlation between the anatomical location of skin tags and the presence of abnormal carbohydrate metabolism except those skin tags under the breast in women ($p=0.036$).

In summary, the results showed that patients with skin tag have a higher risk of DM or impaired carbohydrate metabolism, there was no correlation between DM and BMI or location of skin tag.

Treatment of port-wine stains with the 595-nm pulsed dye laser: a pilot study in Chinese patients

Liu H, Dang Y, Chai X, Wang Z, Ma L, Ren Q.
Clin Exp Dermatol 2007;32:646-9.

Port wine stain (PWS) is benign vascular malformations consisting of ectatic vessels situated mainly in the upper dermis. The 595-nm pulsed

dye laser (PDL) delivers a longer wavelength and higher fluence which enables deeper dermis vessels being targeted. The aim of this study was to investigate the effectiveness of the treatment of PWS in Chinese patients using 595-nm PDL.

A total of 184 patients were recruited (128 female and 56 male, mean age 18.3 ± 10.1 years). None of the patients received any treatment before. All belonged to Fitzpatrick skin types III and IV. The PWS occurred on the face in 125 patients (67.9%), on the neck in 35 (19%) and on the trunk and limbs in 24 (13.1%). A testing area within the lesion was treated to estimate the optimal parameters – pulse width, beam diameter and fluence. The treatment aim was to achieve maximum fading of PWS while avoiding adverse effects. This was achieved by using largest beam diameter with minimum overlapping spots. The most frequently selected parameters were 3-ms pulse with the fluence 8 to 12 J/cm². Most patients were treated at least 4-6 times with a 4-week interval. One hundred fifteen patients (62.5%) had an excellent results (>75% improvement), 38 cases (20.7%) had good results (50-75% improvement) whereas 31 cases (16.8%) showed moderate (25-50% improvement) and poor (<25% improvement) results. Excellent improvement was observed in 76% of facial PWS, 43% of neck PWS and only 20% of trunk or limbs PWS. The mean number of treatments per patient was 6 (range 3-12). However, for the subgroup with excellent results, significant improvement usually happened relatively earlier with the mean of 4 treatment sessions (range 3-6). Apart from the sites, the colour of PWS was also related to treatment response. The purplish PWS was the poor response group in which the patients received 8 treatments but was still difficult to have a good outcome.

Minor adverse effects including pain, local erythema and oedema were common. These adverse effects however resolved completely after a few hours. Three patients (1.6%) developed focal

textural skin changes consisting of slight skin depression. Hypertrophic scarring occurred in one child as a result of scratching. Eleven patients (6.0%) in the poor improvement group had hyperpigmentation which faded within 6 months. Four patients (2 in poor improvement group and 2 in moderate improvement group) had hypopigmentation.

This result showed that treatment of PWS in Chinese patients with the 595-nm PDL produced good clinical improvement in selected cases. The efficacy depended on the anatomical location and type of PWS.

Clinical characteristics of generalized idiopathic pruritus in patients from a tertiary referral center in Singapore

Goon ATJ, Yosipovitch G, Chan YH, Goh CL.

Int J Dermatol 2007;46:1023-6.

Generalized idiopathic pruritus (GIP) is a condition in which patient complains of widespread pruritus without any clinical evidence of primary skin or underlying diseases. The authors aimed to evaluate the characteristics of these patients by questionnaire.

Seventy-five patients were recruited. The study excluded subjects with clinical skin signs, psychogenic pruritus and systemic causes of generalized pruritus such as renal failure, cholestasis, thyroid abnormalities, HIV infection and ingestion of drugs. Sixty-nine (92%) found pruritus everyday, 61% of patients had pruritus in the evening and 56% at night. Only 21% and 20% experienced pruritus in the morning and at noon respectively. The duration of itching was 22.5 ± 61.7 months. The most frequently involved areas were the legs (79%), arms (76%) and back (68%). Sixty (80%) patients used sedative antihistamines while only two (3%) experienced long-term relief (>24 hours). Most (42 patients, 56%) reported

short-term relief (<24 hours) and sixteen patients (21%) claimed no effect. Thirty-four (45%) patients had been prescribed emollients and 71% reported short-term relief. Thirty-two (43%) patients used topical steroid and 28 (88%) reported to have short-term relief and one had long-term relief. The intensity of itchiness was assessed by Visual Analogue Scale (VAS). The worst VAS scores were significantly higher in patients who reported agitation ($p=0.006$), difficulty in concentration ($p=0.010$) and anxiety ($p=0.033$). Fifty-one (68%) patients reported a history of being woken up by itchiness. Fifty-two (69%) patients had difficulty in falling asleep. Heat (68%), sweat (57%) and dryness (53%) were the three commonest reported aggravating factors.

In summary GIP affected the quality of life and might be associated with psychological stress. Sedative antihistamine and topical steroid had only limited efficacy whereas emollients might be effective.

Long-term psychometric outcomes of facial lipoatrophy therapy: forty-eight-week observational, nonrandomized study

Orlando G, Guaraldi G, De Fazio D, Rottino A, Grisotti A, Blini M, et al.
AIDS Patient Care STDS 2007;21:833-41.

Facial lipoatrophy is the most evident and stigmatizing manifestation of HIV-related lipoatrophy. The aim of this observational, prospective, nonrandomized study was to assess long-term psychometric outcomes of surgical treatment of HIV-related facial lipoatrophy.

Two hundred ninety-nine participants (70.8% male) consecutively attending two metabolic clinics in Italy from November 2005 to July 2006, undergoing surgical interventions for HIV-related

facial lipoatrophy were enrolled. Fifty-four (18.1%) underwent facial lipofilling, harvesting the fat graft from the subcutaneous abdominal adipose tissue. Twenty-four (8%), after an initial lipofilling needed poly-lactic acid injections to correct cheek asymmetry. Ninety-one (30.4%) received only poly-lactic acid infiltrations, and 130 (43.5%) received only polyacrylamide infiltrations. Subjective outcome measures were face aesthetic satisfaction, body image perception, depression evaluated by a visual analogue scale (VAS) and the Assessment of Body Change and Distress questionnaire (ABCD) and by the Beck Depression Inventory questionnaire. Objective measure was cheek thickness evaluated by a 7.5-MHz frequency ultrasound probe perpendicular to the skin surface at the nasolabial fold, the corner of the mouth, the zygomatic arch and centrally between these points in the buccal fat pad area. Both subjective and objective variables were evaluated at baseline and 48 weeks after end of surgical treatment.

All 299 participants had significant improvement of the aesthetic satisfaction for the face (VAS mean \pm SD from 2.9 \pm 2.1 to 6.2 \pm 2.1, $p<0.0001$), of body image satisfaction (ABCD question 7 mean score \pm SD from 3.8 \pm 1 to 3.1 \pm 1, $p<0.0001$; ABCD question 8 mean score \pm SD from 70.7 \pm 16.7 to 77.2 \pm 17.2, $p<0.0001$), of depression score (Beck score mean \pm SD from 11.4 \pm 8.3 to 9.4 \pm 7.8, $P=0.001$). Participants also experienced a significant augmentation of both cheeks' thickness (right cheek mean thickness \pm SD from 4.3 \pm 1.9 mm to 9.5 \pm 3 mm, $p<0.0001$, left cheek mean thickness \pm SD from 4.4 \pm 2 mm to 9.6 \pm 3.1 mm, $p<0.0001$).

The authors concluded that facial surgery is an important option in the treatment of HIV-related lipoatrophy as an integral part of the management of HIV infection, because of the important and lasting psychological benefits.

A randomized, multicenter, open-label study of poly-L-lactic acid for HIV-1 facial lipoatrophy

Carey DL, Baker D, Rogers GD, Petoumenos K, Chuah J, Easey N, et al; Facial LipoAtrophy Study in HIV Investigators. *J Acquir Immune Defic Syndr* 2007;46:581-9.

Facial lipoatrophy can be disfiguring and socially stigmatizing. It may lead to reduced antiretroviral adherence. Poly-L-lactic (PLA) injections seem safe and effective, but no randomized study has included objective endpoints. The authors undertook a randomized, multicenter, open-label, 24-week study with a 96-week total follow-up comparing immediate versus deferred deep subcutaneous injections of PLA in adults with antiretroviral-induced facial lipoatrophy.

One hundred and one participants, recruited from 18 clinical sites in Australia, were randomized to 4 open-label PLA treatments administered every 2 weeks from week 0 (immediate group, n=51) or after week 24 (deferred group, n=50). The primary endpoint was mean change in facial soft tissue volume (FSTV), as assessed by spiral computed tomography (CT). Analyses were by intention to treat.

At week 24, mean changes in FSTV were 0 cm³ in the intermediate group and -10 cm³ in the deferred group (between-group difference 10 cm³; 95% CI: -7 to 28 cm³; p=0.24). The immediate group had a greater mean change in soft tissue depth at the maxilla (2.2 mm; 95% CI: 1.6 to 2.9 mm; p<0.0001) and base of the nasal septum level (1.0 mm; 95% CI: 0.3 to 1.6 mm; p=0.003). PLA did not have an impact on peripheral fat mass, viral load, or antiretroviral adherence. Patient-assessed and physician-assessed facial lipoatrophy severity, 2 of 8 Short Form-36 Health Survey and 2 of 5 Multidimensional Body-Self Relations Questionnaire-Appearance Scales scores improved significantly. The median duration of

treatment-related adverse events was 2 days (IQR: 1 to 3 days).

It was concluded that PLA did not increase FSTV, although tissue thickness in injection planes increased modestly, an improvement observed by patients. PLA was safe and well tolerated. Facial lipoatrophy severity and some quality-of-life domains improved.

A retrospective study of 2585 patients patch tested with the European standard series in Hong Kong (1995-99)

Lam WS, Chan LY, Ho SC, Chong LY, So WH, Wong TW. *Int J Dermatol* 2008;47:128-33.

Data on patch test findings in HK are scarce. The last survey was performed more than 10 years ago and was based on a single private dermatology practice. The aims of this study were to explore the demographic data associated with positive reactions and the profile of contact sensitizing allergens in HK. The investigators undertook a retrospective analysis of results from all patch tests performed on patients with suspected allergic contact dermatitis from Jan 1995 to Dec 1999 in the Social Hygiene Service.

Of 2585 patients who were patch tested, 99.1% were Chinese. Female-to-male ratio was 3:2. One or more positive responses were noted in 1415 patients (54.7%). The most common allergen was nickel sulfate (24.4%), followed by fragrance mix (13.7%), cobalt chloride (8.7%), p-phenylenediamine (6.0%), and balsam of Peru (5.7%). Nickel sensitivity was more common in female patients, and dichromate sensitivity was more common in male patients (p<0.01). Female gender, an age of 40 years or below, truncal and upper limb involvement, absence of lower limb

involvement, and a positive atopy history were significant risk factors for nickel sensitivity.

This study provides a profile of allergens responsible for allergic contact dermatitis in public dermatology service in Hong Kong. A prospective study, using a large panel of allergens, involving patients from both the private and public sectors, would provide a more comprehensive profile of contact allergens in HK and contribute to the establishment of a local standard series.

Association of androgenetic alopecia with smoking and its prevalence among Asian men

Su LH, Chen TH.

Arch Dermatol 2007;143:1401-6.

This study sought to evaluate the prevalence and types of androgenetic alopecia (AGA) in Taiwanese men. The authors also investigated the association between smoking and other potential risk factors of AGA.

The subjects were male Taiwanese residents older than 40 years old, living in Tainan County. Seven hundred forty subjects participated in the survey. The mean age was 65.2 years old (range 40-91). The diagnosis of AGA was based on the pattern of hair loss. The Norwood classification was used to classify the severity. Public health nurses trained by dermatologist were assigned to assess the study subjects. The authors divided the AGA into mild (Norwood types I-III) and severe (Norwood types IV-VII) to assess the association with smoking.

The age specific prevalence of AGA (Norwood type III-VII) increased with advancing age and was comparable with those of Korean men but was lower than men of white ethnicity. The age specific prevalence of severe hair loss was low. Smokers were found to have increased risk of moderate or severe AGA. Smoking of more than 20 cigarettes

per day, smoking intensity and dyslipidaemia were shown to have positive association with AGA. Earlier onset AGA was shown to have worse AGA grades. Risk of moderate to severe AGA were much increase in first degree relative with family history of AGA than second and third degree relative.

The authors concluded that the prevalence of AGA in Taiwan was much lower than white ethnicity and the severity was milder; positive association of smoking and AGA was demonstrated. Nevertheless, the study was limited by several aspects: the assessment of AGA by non-dermatologist, the representativeness of subjects as all were from the same county.

A comparison of oral methylprednisolone plus azathioprine or mycophenolate mofetil for the treatment of bullous pemphigoid

Beissert S, Werfel T, Frieling U, Bohm M, Sticherling M, Stadler R, et al.

Arch Dermatol 2007;143:1536-42.

The treatment of bullous pemphigoid (BP) is based on clinical experience than on randomized controlled trial. The best validated treatment modality is systemic corticosteroid but it is associated with considerable morbidity and mortality especially in elderly patients. The use of concomitant immunosuppressant had a steroid sparing effect but the efficacy and safety need further evaluation. This is a randomized trial which aims at comparing oral azathioprine or mycophenolate mofetil (MMF) in combination with oral corticosteroid for the treatment of BP.

It was a multicenter randomized non-blinded clinical trial conducted in Germany. Of 73 subjects with BP, 38 were assigned to azathioprine group and 35 were assigned to MMF group. Thirty-five

patients in azathioprine group had complete remission and all 35 patients in MMF group had complete remission. There was no significant difference in the cumulative dose of methylprednisolone in both treatment groups. The azathioprine group showed a significant raised liver parenchymal enzyme alanine aminotransferase compared to MMF group. However, the aspartate aminotransferase and gamma glutamyltransferase were not significantly raised.

The authors concluded that the efficacy of both adjuvant immunosuppressants was similar. The cumulative corticosteroid dosage in both treatment groups was comparable. Azathioprine however was shown to cause significantly more liver toxicity than MMF.

Thalidomide: an experience in therapeutic outcome and adverse reactions

Sharma NL, Sharma VC, Mahajan VK, Shanker V, Ranjan N, Gupta M.

J Dermatol Treat 2007;18:335-40.

Thalidomide is well known to dermatologists with its use in many inflammatory dermatoses where patients are unresponsive to usual treatments. The US FDA had approved the use of thalidomide in treatment of chronic recurrent or severe erythema nodosum leprosum (ENL). The authors conducted a prospective study to investigate the beneficial and adverse effects of thalidomide in 25 patients with different

inflammatory dermatosis that were poorly controlled with conventional therapy.

There were 16 male patients. The mean age was 38.8 years (range 25 to 56 years). Six (55%) out of the 11 patients suffering from chronic recurrent ENL showed excellent response to thalidomide with early subsidence of cutaneous lesion and reduction of steroid dose. All three patients with Bechet's disease showed excellent response to thalidomide. Three out of four patients who had disseminated discoid lupus erythematosus (DLE) and two patients with hypertrophic DLE showed excellent response with thalidomide. Other patients with DLE-lichen planus overlap, erosive lichen planus, recurrent aphthous stomatitis and prurigo nodularis respectively showed excellent response to thalidomide.

The most common side effect observed was deep vein thrombosis, occurred in 5 (20%) patients. Other common side effects observed were sedation in six patients and constipation in 2 patients. Peripheral neuropathy in form of acral paresthesia without sensory loss was observed in one patient, much lower incidence than other reports.

The authors concluded that thalidomide is highly promising in treating inflammatory dermatosis such as ENL and DLE who failed conventional treatment. However thrombotic complication must be closely monitored during treatment. The study was limited by the small number of patients enrolled; the efficacy and side effect profile may not reflect the actual situation when large number of patients was involved.