

Journal Watch

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Does hormone therapy improve age-related skin changes in postmenopausal women? A randomized, double-blind, double-dummy, placebo-controlled multicenter study assessing the effects of norethindrone acetate and ethinyl estradiol in the improvement of mild to moderate age-related skin changes in postmenopausal women

Phillips TJ, Symons J, Menon S, HT Study Group. *J Am Acad Dermatol* 2008;59:397-404.

In postmenopausal women, declining estrogen levels are associated with a variety of skin changes, many of which are reportedly improved by estrogen supplementation. A study was conducted to assess the effects of continuous combined norethindrone acetate (NA) and ethinyl estradiol (EE) in the control of mild to moderate age-related skin changes in postmenopausal women.

Four hundred eighty-five subjects were enrolled in this 48-week randomized, double-blind study. Subjects were randomized to one of three study arms: placebo group (165 subjects), 1 mg NA/5 microg EE group (162 subjects), or a 1 mg NA/10 mcg EE group (158 subjects). The primary efficacy parameters of the study were investigator global assessment of coarse and fine facial wrinkling at week 48 and subjective self-assessment of changes in wrinkling from baseline at week 48. Secondary parameters included investigator global assessment of skin laxity/sagging at week 48, investigator global assessment of skin texture/dryness at week 48, patient self-assessment of laxity/sagging, texture/dryness, and wrinkle depth determined by image analysis of skin replicas of the periorbital (crow's feet) and jowl areas, and skin elasticity determined by timed deformation and recoil.

The results showed that there were similar scores in investigator global assessment in wrinkling and sagging modules at baseline across all three treatment groups. There were slight decreases in all parameters for all treatment groups for the primary subject end points, but there were no statistically significant differences between the NA/EE groups and placebo. For subject self-assessment of overall severity of skin wrinkling, there were no significant changes at weeks 24 and 48 compared to baseline. These data were unaffected by smoking status or alcohol consumption.

The authors concluded that low-dose hormone therapy for 48 weeks in postmenopausal women did not significantly alter mild to moderate age-related facial skin changes. This study however, assessed the effects of 48 weeks of low-dose estrogen upon facial skin in women who were, on average, 5 years postmenopausal. The effects of higher estrogen doses, longer treatment duration, or effects upon perimenopausal women cannot be extrapolated from this study.

An aqueous gel fixed combination of clindamycin phosphate 1.2% and benzoyl peroxide 2.5% for the once-daily treatment of moderate to severe acne vulgaris: assessment of efficacy and safety in 2813 patients

Thiboutot D, Zaenglein A, Weiss J, Webster G, Calvarese B, Chen D. *J Am Acad Dermatol* 2008 ;59:792-800.

The authors sought to evaluate efficacy, safety, and tolerability of a combination of clindamycin phosphate 1.2% and benzoyl peroxide 2.5% (clindamycin-BPO 2.5%) aqueous gel in moderate to severe acne vulgaris.

A total of 2813 patients, aged 12 years or older were randomized to receive clindamycin-BPO 2.5%, individual active ingredients, or vehicle in two identical, double-blind, controlled 12-week, 4-arm studies evaluating safety and efficacy (inflammatory and noninflammatory lesion counts) using Evaluator Global Severity Score and subject self-assessment.

The results showed that clindamycin-BPO 2.5% demonstrated statistical superiority to individual active ingredients and vehicle in reducing both inflammatory and noninflammatory lesions and acne severity. Visibly greater improvement was observed by patients with clindamycin-BPO 2.5% as early as week 2. No substantive differences were seen in cutaneous tolerability among treatment groups and less than 1% of patients discontinued treatment because of adverse events.

The authors concluded that clindamycin-BPO 2.5% provides statistically significant greater efficacy than individual active ingredients and vehicle with a highly favorable safety and tolerability profile. One however must bear in mind that data from controlled studies may differ from clinical practice.

Placebo-controlled, double-blind, randomized pilot study of imiquimod 5% cream applied once per week for 6 months for the treatment of actinic keratoses

Zeichner JA, Stern DW, Uliasz A, Itenberg S, Lebwohl M.

J Am Acad Dermatol 2009;60:59-62.

Imiquimod 5% cream applied twice weekly for 16 weeks is effective for treating actinic keratoses (AK) but may be limited by local side effects. The authors sought to explore the efficacy and safety of a once weekly for 24 weeks dosing regimen using a left versus right side of head design.

Twenty patients were enrolled; 15 completed and 5 discontinued for reasons unrelated to

adverse events. Patient assessments were performed at each visit. Efficacy was evaluated using an investigator assessment scale (IAS), comparing changes with the baseline visit. This 7-point scale is as follows: e2=much worse; e1=slightly worse; 0=no change; 1=mild improvement; 2=moderate improvement; 3=marked improvement; and 4=cured. A total lesion number score, defined as the total number of lesions present in the target area, was determined for each side. As some patients had AKs too numerous to count, patients were categorized as follows for each side: 0 AKs (clear, score=0), 1 to 3 AKs (mild, score=1), 4 to 6 AKs (moderate, score=2), and greater than 6 AKs (severe, score=3).

At the post-treatment visit (week 28), 7 (46.7%) of 15 patients had marked improvement or better on the imiquimod side versus one (6.7%) of 15 on the placebo side. The average investigator assessment scale score change was +2.20 for imiquimod compared with -0.27 for placebo (P=0.0002, Wilcoxon signed rank test). Skin reactions were minimal or nonexistent in most patients.

The authors concluded that imiquimod 5% cream applied once weekly for 24 weeks was convenient for patients and resulted in improvement of actinic keratoses with minimal side effects. Limitations of the study include a small sample size and a lack of objective measure of local side effects. Further study involving larger sample size is warranted. Future studies must also be performed to evaluate cure rates with once-weekly application versus FDA approved twice weekly dosing.

Chronic urticaria: an internet survey of health behaviours, symptom patterns and treatment needs in European adult patients

Maurer M, Ortonne JP, Zuberbier T.

Br J Dermatol 2009;169:633-41.

Chronic Urticaria (CU) is a common skin disorder characterized by spontaneous outbreaks of itchy

wheals and / or angioedema over 6 weeks or longer and often last for years. The aetiology remains unknown. A survey was conducted in German and France to determine how patients with CU managed their condition, when and where their symptom outbreaks occurred and what their greatest unmet treatment needs were.

The inclusion criteria included the "yes" response to the question "Have you ever suffered from a spontaneous outbreak of hives that lasts for 6 weeks or longer?" and a response of one or more to the question of "approximately how many spontaneous outbreaks of hives lasting more than 6 weeks (chronic urticaria) within the past 12 months?" The exclusion criteria were the occupation of the respondent or any immediate family member in marketing, market research, advertising, healthcare products, pharmaceuticals or healthcare professions (doctor, nurse or pharmacist) and age under 18 or over 99 years.

Of 321 respondents, 43% felt that they were as healthy as other people and 76% were making efforts to avoid triggering factors. Seventy-eight percent of respondents were taking prescription or over the counter medication but among them, only 33% reported taking medication preventively and the majority started the medications when symptoms began. Legs, wrist/hands/palms, face and scalp were more often affected in women than men whereas armpits and ears were more often affected in men than women. Sixty-one percent of respondents had outbreaks increased in warmer months, 34% of respondents said that outbreaks were the worst in the evening, 69% of respondents found that itching remained an unresolved problem and 48% reported that sleep disturbances remained unresolved.

A better understanding of health behaviour, symptom patterns and unmet treatment needs of patients with CU will enable physicians and patients to manage this disabling condition more effectively.

Polymerase chain reaction compared to other laboratory findings and to clinical evaluation in the diagnosis of cutaneous tuberculosis and atypical mycobacteria skin infection

Abdalla CM, de Oliveira ZN, Sotto MN, Leite KR, Canavez FC, de Carvalho CM.
Int J Dermatol 2009;48:27-35.

Cutaneous tuberculosis and atypical mycobacteria skin infection have wide range of clinical manifestations including warty lesion, nodules, papulonecrotic lesions, ulceration and even abscess. It is difficult for the laboratory to confirm the diagnosis by using conventional techniques such as direct demonstration of acid fast bacilli (AFB) on smears, histopathological examination and culture. The objective of this study was to compare polymerase chain reaction (PCR) with other examination techniques in diagnosis of cutaneous TB and atypical mycobacteria skin infections.

Thirty-four skin biopsies were done in 32 patients with clinical suspicion of cutaneous TB or atypical mycobacteria skin infection. All these skin biopsy were evaluated by histopathological examination, AFB smear and culture, PCR test and immunohistochemistry test with polyclonal anti-BCG. Confirmation of cutaneous tuberculosis and atypical mycobacteria skin infection were based on the successful treatment with antituberculosis drugs. Fourteen of 16 skin biopsies performed showed positive PCR. All 14 were clinically confirmed with cutaneous TB or atypical mycobacterial skin infection. The sensitivity was 88%. Granulomatous tissue reaction was observed in 24 skin biopsies and only 11 compatible with cutaneous TB or atypical mycobacteria skin infection. Tuberculin test was positive in 9 patients and 8 had cutaneous TB or atypical mycobacteria skin infection. AFB smear was only found in one patient who have leprosy. Polyclonal anti-BCG was noted on 5 patients of whom 3 confirmed the mycobacterial infection, 1 had sarcoidosis, 1 had leishmaniasis. Of the 5 patients who had positive skin culture, 4 were *M. tuberculosis* and one was *M. peregrinum*.

The authors concluded that PCR was the best method in the diagnosis of cutaneous TB and atypical mycobacteria skin infection when compared with AFB smear and culture.

Biologic therapies for psoriasis: practical experience in a UK tertiary referral centre

Warren RB, Brown BC, Lavery D, Ashcroft DM, Griffiths CEM.

Br J Dermatol 2009;160:162-9.

Clinical trials provide clear evidence of the efficacy and short-term toxicity of biologic therapies for psoriasis. However, there has been no report of the practical use of these therapies outside trial setting in UK. This study was conducted to assess efficacy and safety of efalizumab, etanercept and infliximab in a UK cohort of patients with psoriasis.

One hundred and two patients with psoriasis treated by biologics at a specialty clinic were reviewed. All patients had chronic plaque psoriasis except one who had concomitant palmoplantar pustulosis. The mean duration of disease was 27 ± 13 years. They were all intolerant or failed to respond to at least three other traditional systemic treatments including methotrexate, cyclosporin, acitretin, fumaric acid ester, PUVA, narrow band UVB and mycophenolate mofetil.

Some patients used two or three biologic agents. At 3 months of treatment by efalizumab ($n=28$), etanercept ($n=70$) and infliximab ($n=20$) the PASI 75 (75% decrease from the baseline score) was 24%, 35% and 85% respectively. The mean PASI reduction at 3 months was 49% for efalizumab, 55% for etanercept and 95% for infliximab. The mean baseline Dermatology Life Quality Index (DLQI) was 21.7 ± 6.8 . At 3 months, the mean DLQI reduction was 6.5 ± 7 , 13.5 ± 7 and 21.7 ± 7 for efalizumab, etanercept and infliximab respectively. All three biologics were well tolerated. In efalizumab group, two patients experienced herpes zoster and plantar warts. One developed corneal ulceration and two had elevated liver enzymes but none of them needed to stop the drug. In etanercept group, three patients experienced cutaneous infections of cellulitis, herpes simplex and warts. Two patients with

asthma experienced worsening of symptoms and one more patient without history of asthma had newly developed wheezing. Two patients with rhinosinusitis had symptoms worsening and the other two had newly developed rhinosinusitis. Two patients noted to have transient eosinophilia and twelve patients found elevated liver enzymes. Three patients ceased etanercept because of liver function dysfunction, septicaemia and severe GI upset. In infliximab group, three had cutaneous infection of cellulitis, furunculosis and infected sebaceous cyst. One had a toxic erythema reaction at three months after influenza and one patient experienced scleritis. One had alopecia areata universalis. Four patients developed abnormal liver function. Four patients stopped the infliximab due to severe hypersensitivity reaction ($n=2$), lupus-like syndrome ($n=1$) and exacerbation of cardiac failure ($n=1$). Except for those stopped the biologics, other adverse effects were mild and easily managed. The authors did not encounter any reactivation of tuberculosis in this study.

In conclusion, the authors opined that biologic therapy was a significant step forward in expanding the therapeutic armamentarium for severe psoriasis.

Distribution of human papillomavirus types in anogenital warts of men

Chan PKS, Luk ACS, Luk TNM, Lee KF, Cheung JLK, Ho KM, et al.

J Clin Virol 2009;44:111-4.

A wide-spectrum of human papillomavirus (HPV) types can infect the male genitalia. An HPV vaccine covering HPV 6 and 11 is now available. Little is known on the distribution of these two types in anogenital warts in Hong Kong. This study examined the distribution of HPV types in anogenital warts of a cohort of Chinese men in Hong Kong so as to assess the potential benefits of HPV vaccines that contain HPV 6 and 11.

Anogenital warts specimens collected from 130 Chinese men were examined for HPV-type distribution by a method that covered a broad spectrum of high- and low-risk HPVs, and was able to reveal multiple types from a single specimen.

Forty-four (33.8%) of the 130 specimens had coinfection with multiple HPV types. In 26.2% of cases, only HPV 6 and /or HPV 11 were found. In 26.2% of cases, HPV 6 and /or HPV11 were found together with one or more other HPV types. In 10.8% of specimens, only non-6/11 HPV types were found. HPV 16 and /or 18 were found in 12 (9.2%) specimens, with majority (8/12, 66.7%) of which existed as coinfections with HPV 6/11. Other HPV types found included HPV 39, 51, 55, 59, 61, 61, 68, 58, 72, 81, 83, 84 and CP6108.

Therefore, a substantial proportion of HPV 6/11-positive male anogenital warts are coinfecting with other HPV types. The efficacy of HPV6/11 vaccine for preventing these lesions needs to be defined before the benefits of vaccinating men can be precisely assessed.

Trends in the incidence of cancers among HIV-infected persons and the impact of antiretroviral therapy: a 20-year cohort study

Crum-Cianflone N, Hullsiek KH, Marconi V, Veintrob A, Ganesan A, Barthel RV, et al. *AIDS* 2009;23:41-50.

There have been conflicting results regarding to the fatal non-AIDS defining cancers (NADCs) and fatal AIDS-defining cancers (ADCs) among HIV positive people. This study sought to describe trends in incidence rates of NADCs and ADCs during the HIV epidemic and to evaluate the predictors of cancer development.

The investigators retrospectively examined data collected from the Tri-Service AIDS Clinical Consortium HIV Natural History Study, a multicenter, observational study which enrolled 4566 HIV-positive persons from 1984 to 2006 at seven geographic locations in the United States.

Predictors evaluated included demographics, clinical data, time-updated CD4 cell counts, HIV viral loads and antiretroviral history. Time periods were classified as early pre (1984-1990), late pre (1991-1995), early post (1996-2000), and late post (2001-2006) HAART eras.

Ten percent of HIV-infected persons developed cancer. ADC rates increased between the early and late pre-HAART era (7.6 and 14.2 cases per 1000 person-years) and have since declined from 5.4 to 2.7 in the early and late HAART eras, respectively ($p < 0.0001$). Rates of NADCs have risen over the four periods (2.9, 2.8, 4.2, 6.7; $p = 0.0004$). During the late HAART era, 71% of cancers were NADCs. Predictors for ADCs included low CD4 cell count, noncancer AIDS diagnosis and lack of HAART. NADCs were associated with increasing age and white race (due to skin cancers).

Although the rate of ADCs continues to fall, the rate of NADCs is rising and now accounts for the majority of cancers in HIV-infected persons. The development of NADCs is associated with increasing age among HIV patients. It was concluded that HAART use was protective for ADCs, but did not significantly impact NADCs.

Male circumcision and *Neisseria gonorrhoeae*, *Chlamydia trachomatis* and *Trichomonas vaginalis*: observations after a randomised controlled trial for HIV prevention

Sobnwi-Tambekou J, Talijsaard D, Nieuwoudt M, Lissouba P, Puren A, Auvert B, et al. *Sex Transm Infect* 2009;85:116-120.

Recent evidence has show that male circumcision is a promising prevention strategy for sexually transmitted infections (STIs). However, there are conflicting results about the association between male circumcision and non-ulcerative STIs such as *Neisseria gonorrhoeae*, *Chlamydia trachomatis*, and *Trichomonas vaginalis* infections among men. This study sought to evaluate the association between these non-ulcerative STIs and male circumcision.

The investigators used data collected during the male circumcision trial conducted in South Africa among men aged 18-24 years. Altogether, 1767 urine samples collected during the final follow-up visit were analysed using PCR.

The prevalence of *N gonorrhoeae*, *C trachomatis* and *T vaginalis* among intervention and control

groups were 10.0% vs 10.3% (OR 0.97; $p=0.84$), 2.1% vs 3.6% (OR 0.58; $p=0.065$) and 1.7% vs 3.1% (OR 0.54; $p=0.062$) respectively. The association between *T vaginalis* and male circumcision remained borderline after controlling for age, ethnic group, number of lifetime partners, marital status, condom use and HIV status (adjusted OR 0.48; $p=0.069$).

This study demonstrated for the first time that male circumcision might reduce *T vaginalis* infection among men. This finding provides an explanation why women with circumcised partners are less at risk for *T vaginalis* infection than other women. The protective effect on *T vaginalis* is an additional argument to recommend male circumcision in Africa where it is acceptable.

Melanocytic nevus development in Colorado children born in 1998: a longitudinal study

Crane LA, Mokrohisky ST, Dellavalle RP, Asdigian NL, Aalborg J, Byers TE, et al.

Arch Dermatol 2009;145:148-56.

This is a prospective observational study that sought to describe the pattern of melanocytic nevi development in children of Colorado in the US.

The children recruited were examined annually from age 3 to 8 years for total number of nevi, nevi smaller than or larger than 2 mm diameter, nevi on frequent and intermittent sun exposed area. The phenotypic features such as skin color, hair color, eye color, degree of tanning, freckling, weight and height were recorded by trained health care providers using standard instruments and methods. Ethnicity was reported by parents. Congenital nevi were excluded from the study.

Most of the children recruited were non-Hispanic white (>80%) and the authors focused the analysis on this ethnic group as they have the highest incidence of melanoma. The non-Hispanic white children had a greater number of nevi compared with Hispanic white, Asian/Pacific Islander and Black. The difference became significant from five years of age. The non-Hispanic white children developed 4 to 6 new nevi per year between 3 to

8 years of age. There was significantly more nevi in boy than girl in whole body, chronically exposed area, nevi <2 mm size and posterior neck from six years of age. When comparing larger nevi of >2 mm size and nevi in intermittently exposed area, there was no significant sex difference.

There was no proven physiological explanation behind the phenomenon. The authors suggested that this may be due to difference in activities between boy and girl, parents' attitude towards sun protection in male and female children including clothing and use of sun screen. When comparing with studies in other countries, similar pattern of nevus development was observed in United Kingdom but different in Canada, Germany and Australia where they had a higher total number of nevus developed. Further studies on the seasonal trend of nevus development, mechanism of sex difference and a longer cohort to include the adolescent can help to understand relationship between nevus development and melanoma.

Estrogen receptor expression in cutaneous melanoma: a real-time reverse transcriptase-polymerase chain reaction and immunohistochemical study

de Giorgi V, Mavilia C, Massi D, Gozzini A, Aragona P, Tanini A, et al.

Arch Dermatol 2009;145:30-6.

The estrogen receptor α (ER α) and estrogen receptor β (ER β) had been found to play an important role in pathogenesis and progression in many cancers. Epidemiological studies suggested that women with metastatic melanoma had a better survival than men. This leads to the study of the role of estrogen receptor in melanoma and tumor progression. This study explored the estrogen receptor expression in melanocytic lesion and adjacent healthy skin.

A total of 14 patients in which 12 had melanoma and 2 had dysplastic nevi were studied. The Clark's level of invasion, Breslow thickness, the levels of ER α and ER β mRNA and ER β protein staining in melanocytic lesions and adjacent healthy skin were determined. The level of ER α and ER β mRNA was

found to be significantly higher in melanoma with lower (≤ 1.0 mm) Breslow thickness. A stronger ER β protein staining in immunohistochemical analysis in thin melanomas (≤ 1.0 mm) was also noted.

Therefore, a lower level of ER α and ER β mRNA and ER β protein staining is associated with melanoma invasiveness. The authors suggested there is a potential role for estrogen receptor in the metastasis of melanoma. The expression of estrogen receptor can serve as a prognostic indicator of melanoma. Further evaluation with larger study of the underlying mechanism and role of estrogen receptor in melanoma metastasis is warranted

Evaluation of the efficacy of acitretin therapy for nail psoriasis

Tosti A, Ricotti C, Romanelli P, Cameli N, Piraccini BM.

Arch Dermatol 2009;145:269-71.

This study aimed to determine the effect of low dose acitretin in the treatment of patients with nail psoriasis.

A total of 36 patients with moderate to severe psoriasis limited to nail were recruited in this

open label study. The diagnosis of nail disease was clinical. The severity of nail disease was assessed with Nail Psoriasis Severity Index (NAPSI) and modified NAPSI scores before start of treatment, every two months during treatment and six months after stopping therapy. The NAPSI is used to evaluate the overall disease severity in nail bed and nail matrix in all nails while the modified NAPSI is used to evaluate the target nail. Acitretin was given at dose 0.2 to 0.3 mg/kg/day for six months. Some studies showed that higher dose may actually worsen nail disease with paronychia and increase fragility.

A 46% reduction of NAPSI was noted at 20 weeks with low dose acitretin treatment which was comparable with the treatment by adalimumab and infliximab. Half of the patients showed complete or almost complete to moderate improvement in nail disease. One-third of patients showed mild improvement and the remaining six patients showed no improvement. All the patients tolerated well with the treatment. Only one patient developed cutaneous side effect of severe xerosis and paronychia and multiple pyogenic granulomas which subsided with reduction of acitretin dosage.

The authors concluded that low dose acitretin was a promising treatment for nail psoriasis.