

Journal Watch

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Dermal matrix remodelling after nonablative laser therapy

Orringer JS, Voorhees JJ, Hamilton T, Hammerberg C, Kang S, Johnson TM, et al.
J Am Acad Dermatol 2005;53:775-82.

This study, approved by the institution review board, investigated the dermal molecular changes after nonablative laser therapy for skin rejuvenation. Thirty-four patients (22 men, 12 women) aged 47 to 78, with moderate to severe photodamaged skin involving the forearms were recruited. The forearms of 13 patients were treated with a 585 nm pulsed dye laser and the other 21 patients were treated with a 1320 nm Nd-YAG laser. After one treatment session, serial punch 3 mm biopsies were obtained from the treatment areas at baseline and three different time points up to 11 days post-treatment. Tissues samples were analysed for levels of primary cytokines, matrix metalloproteinases (MMP)-1, 3, 9, type I and III procollagens, IL-1 β , and tumour necrosis factor- α (TNF- α).

After pulsed dye laser therapy to the photodamaged skin, a statistically significant increase of TNF- α levels was observed at day five and seven (60% and 77% respectively, $p < 0.05$). With Nd-YAG laser treatment, levels of cytokines peaked more rapidly and levels of TNF- α mRNA levels were elevated by 107% ($p < 0.05$) on the first day post-treatment. Such increase was also significant on day two and day three post-treatment. Increase in levels of various MMP were noted but not statistically significant after pulsed dye laser therapy, whereas the increase in MMP-9 were significantly elevated to 25.4 times baseline ($p < 0.05$) after treatment with Nd-YAG.

As clinical improvements in the appearance of wrinkles and atrophic scars might result from enhanced collagen biosynthesis as reflected by these molecular changes, the data suggested that the treatment may be efficacious in inducing collagen biosynthesis for some patients.

Nonsteroidal anti-inflammatory drugs and the risk of actinic keratoses and squamous cell cancers of the skin

Butler GJ, Neale R, Green AC, Pandeya N, Whiteman DC.
J Am Acad Dermatol 2005;53:966-72.

This was a case-control study conducted in Australia to investigate the possible beneficial effects of regular nonsteroidal anti-inflammatory drugs (NSAIDs) consumption against cutaneous squamous cell carcinoma (SCC) and actinic keratoses (AKs).

Eighty-seven patients with SCC and 187 age- and sex-matched controls were interviewed and examined. Actinic keratoses were counted on faces, ears, right hands and right forearms of all participants. The past and current exposure to NSAIDs among these subjects was assessed. Subjects with regular use of NSAID at least two times a week for a year were defined as low frequency regular users and eight or more times a week for a year as high frequency regular users. It was shown that patients with SCC were less likely to be regular high frequency users of NSAIDs, who were also associated with lower incidence of SCC. Regular low frequency use of NSAIDs was not

shown to reduce the risk of SCC. Moreover, the risk of SCC was lower with longer durations of regular NSAIDs use. It was also found that control subjects who were regular users of NSAIDs in the past year had significantly lower AK count than "never users". In addition, subjects with SCC had significantly higher AKs counts than controls.

This study provided new evidence that regular use of NSAIDs in full dose may confer protective benefit against cutaneous SCC and AKs.

Lipomas treated with subcutaneous deoxycholate injections

Rotunda AM, Ablon G, Kolodney MS.
J Am Acad Dermatol 2005;53:973-8.

Treatment of lipomas or cosmetically undesirable adipose tissue using subcutaneous injection of a mixture containing phosphatidylcholine and the bile salt sodium deoxycholate, labelled colloquially as "mesotherapy", are becoming increasingly popular. This study reported the authors' experience in the treatment of lipomas using subcutaneous injection of deoxycholate alone.

Six patients with 12 clinically lipomas were injected with a solution containing sodium deoxycholate (1%, 2.5% or 5%). The size, consistency, location, and shape of the lipomas were assessed before treatment. Intervals between injections were at least two weeks and treatment was continued until the patient was satisfied with the response. Most patients treated with 2.5% and 5% deoxycholate reported moderate to severe burning, dysesthesia and mild sustained localised swelling for up to six weeks. In contrast, injections with 1% deoxycholate were associated with less adverse reactions. Owing to these side effects, most patients were given lower concentrations in subsequent injections. All lipomas reduced in size, with a mean reduction of 75%, after a mean of 2.2 treatment sessions. The reduction in surface area ranged

from 37% to 100% and was similar for 1%, 2.5% and 5% deoxycholate administered. Two of the lipomas were assessed by ultrasonography and correlated closely with their measurements on physical examination. Lipomas that were firm to palpation before injection became softer after the first injection and two lesions fragmented after treatment.

The result supported the authors' postulation that deoxycholate alone rather than phosphatidylcholine, is the active ingredient in subcutaneously injected formulas used to treat adipose tissue.

British Association of Dermatologists guidelines for use of biological interventions in psoriasis 2005

Smith CH, Anstey AV, Barker JNWN, Burden AD, Chalmers RJG, Chandler D, et al.
Br J Dermatol 2005;153:486-97.

These guidelines have been developed to ensure safe and proper use of the new biological agents (infliximab, etanercept and efalizumab) in treating psoriasis in adult patients. The recommendations are evidence-based and developed after a systematic review of existing literatures.

Literature review was done by searching the EMBASE and Medline databases between 1965 and November 2004 for clinical trials involving efalizumab, etanercept and efalizumab.

Biologic therapies are recommended for patients with severe psoriasis who are intolerant or fail response to existing standard systemic therapies. Severe disease is defined as 10 or greater of the Psoriasis Severity and Area Index score or involving at least 10% of the body surface area. Consultant dermatologists experienced in managing difficult psoriasis are the best persons to initiate and monitor biologic therapy. The dosing, treatment duration, side effects and monitoring were discussed according to the data available.

Dermatologists should be familiar with these before starting the treatment.

It is recommended that etanercept should be considered as the drug of choice for patients with concurrent significant refractory psoriatic arthritis. Etanercept should be used in preference to infliximab in stable psoriasis. However, infliximab is indicated in situations when rapid control is desired such as unstable erythrodermic or pustular psoriasis. Efalizumab will be most suitable for patients at risk of latent tuberculosis or with evidence of demyelinating disease.

The potential of pharmacogenetics in optimising the use of methotrexate for psoriasis

Warren RB, Griffiths CEM.

Br J Dermatol 2005;153:869-73.

This review article focused on the application of pharmacogenetics in dermatology. The folate metabolic pathways and genetic polymorphism were reviewed for the potential of optimising the use of methotrexate in treating psoriasis. Currently there is no consistent predictor of efficacy and toxicity in using methotrexate to treat psoriasis.

Methotrexate primarily inhibits dihydrofolate reductase and other enzymes such as thymidylate synthase (TYMS), glycinamide ribonucleotide transformylase. The overall effect is a depletion of the intracellular pool of folate, which affect the activity of the enzyme methylenetetrahydrofolate reductase (MTHFR). MTHFR further contributes to the conversion of homocysteine to methionine. The efficacy and toxicity of methotrexate correlate with the MTHFR or TYMS gene polymorphism.

More than 10 single nucleotide polymorphisms exist in MTHFR. In the treatment of rheumatoid arthritis, both C677T and A1298C polymorphisms, homozygous or heterozygous, were associated with an increased risk of methotrexate toxicity due

to a raised level of homocysteine. On the other hand, more patients who were homozygous for the triplet repeat allele of the TYMS gene required a higher dose of methotrexate in treating rheumatoid arthritis than the double repeat allele.

However, it is difficult to evaluate the true significance of these polymorphisms when extrapolating from rheumatoid arthritis to psoriasis. The following factors have to be considered: the impact of polymorphisms in the presence of folate supplementation, observed increased susceptibility to hepatotoxicity among psoriasis patients and the possibility of multiple polymorphisms leading to a complex influence in the methotrexate metabolic pathway.

The advance in genetics makes rapid sequencing to detect single nucleotide polymorphisms possible. With more understanding of the pharmacogenetics, there is an increased chance of more accurate prediction in drug efficacy and toxicity.

Treatment of early-stage mycosis fungoides with twice-weekly applications of mechlorethamine and topical corticosteroids

de Quatrebarbes J, Estève E, Bagot M, Bernard P, Beylot-Barry M, Delaunay M, et al for the French Study Group of Cutaneous Lymphomas.

Arch Dermatol 2005;141:1117-20.

This multi-centre, prospective study was performed to determine whether twice weekly applications of 0.02% mechlorethamine (10 mg per 50 mL of water) and betamethasone dipropionate cream were effective in early-stage (stage IA, IB, IIA) mycosis fungoides (MF). Topical mechlorethamine was applied to the total skin surface except on the head, twice weekly, on two nonconsecutive days, and then up to 15 g of betamethasone cream was applied 10 minutes after. Treatment was continued for six months.

Sixty-four patients (mean age 63 years, range 7-82 years) were studied. There were 43 males and 21 females (male: female ratio 2:1). A complete response (CR) was defined as disappearance of all clinical MF lesions. A total of 37 (58%) cases achieved CR after a mean of 3.6 ± 2.5 months. A complete response was seen in 20 of 33 stage IA cases (61%), stage IB: 15/26 (58%), stage IIA: 2/5, (40%) after an average of 3.3, 3.8 and 3.0 months respectively.

Due to worsening of lesions, treatment was stopped in 10 (16%) patients. Three patients with mild cutaneous reaction were able to continue treatment. Severe cutaneous reactions were seen in 18 (28%) cases (burning sensation, pruritus, erythema: 11 patients; eczematous reaction: 7 patients) were seen after a mean of 3.4 ± 2.7 months. Patients with a severe cutaneous reaction had a lower CR (6/18, 33%) than those with mild reaction (2/3, 67%). No reactions were seen with topical steroids. Twenty (54%) of the 37 patients with CR were still in remission after a mean of 13.5 ± 8.4 months from starting treatment. Seventeen (46%) cases relapsed at mean time of 7.7 ± 6.5 months after CR.

The authors concluded that twice weekly applications of mechlorethamine and topical corticosteroids were effective and better tolerated in early stage MF. However, the outcome after a longer follow-up period needs to be determined.

Incidence of cancer among patients with atopic dermatitis

Hagströmer L, Ye W, Nyrén O, Emtestam L.
Arch Dermatol 2005;141:1123-7.

In this retrospective, cohort study done in Sweden, 15666 patients discharged with a diagnosis of atopic dermatitis between 1 January 1965 and 31 December 1999 were identified. Follow-up until the occurrence of malignancy, death, emigration or end of the study period, whichever

occurred sooner, was done by record linkage to the relevant registries. The first year of follow-up was excluded to reduce selection-bias. Relative risk of cancer was expressed as standard incidence ratios (SIR).

The overall incidence of malignancy was increased by 13% (95% confidence interval CI: 1-25%) as compared with the general population. There were a total of 331 cases of malignancy after exclusion of one squamous cell carcinoma in the first year (141 males, 190 females). The average age of diagnosis of cancer was 54.9 years in men and 53 years in women.

There was a non-significant increase in risk of non-melanoma skin cancer (SIR: 1.5; 95% CI: 0.8-2.6, 12 patients). This was confined to men in the first 10 years. A decreased risk was seen for melanoma (SIR: 0.6; 95% CI: 0.3-1.2, 10 patients). Increased risks were detected for oesophageal cancer (SIR: 3.5; 95% CI: 1.3-7.7, 6 patients), lung cancer (SIR: 2.0; 95% CI: 1.3-2.8, 31 patients), brain cancer (SIR: 1.6; 95% CI: 1.1-2.4, 27 patients), and lymphoma (SIR: 2.0; 95% CI: 1.4-2.9, 29 patients). A borderline increase was seen in pancreatic cancer (SIR: 1.9; 95% CI: 1.0-3.4, 11 patients).

As confounding factors such as smoking may be present, it was concluded that these findings should be interpreted with caution. Also, multiple significance testing and the small number of cancer cases detected could have led to chance findings.

A survey of traditional Chinese medicine use in children with atopic dermatitis attending a paediatric dermatology clinic

Hon KLE, Ma KC, Wong Y, Leung TF, Fok TF.
J Dermatol Treat 2005;16:154-7.

This study was conducted at the paediatric

dermatology clinic of a teaching hospital in Hong Kong, to investigate the attitude to traditional Chinese medicine (TCM) use in children with atopic dermatitis (AD). A survey questionnaire of about 14 items was used and was answered by the caretakers of children with AD. The severity of AD was assessed by the Chinese version of the Nottingham Eczema Severity Score (NESS). Two hundred and twenty-seven children (58% male) and their caretakers participated in this study. Seventy-two percent of the informants were the mother. Sixty-seven (30%) admitted that their children had received TCM in the past one year. Among which, 22 (33%) were taking TCM currently and 17 (25%) had taken TCM for more than six months. TCM was prescribed by a Chinese medicine practitioner in 94% (n=63) of those children. Herbal tea or soup was the commonest form. Ninety-four percent had not been informed of any possible adverse effects of TCM. Sixty percent believed TCM helped to improve their children's AD. Seventy-five percent learnt about the TCM from family members or friends. TCM use was associated significantly with 'more severe AD' (OR 3.24, 95% CI 1.67-6.31; p=0.0003) but was not associated with age of parents or 'grandparents as caregiver'.

The authors concluded that TCM use is popular among children with AD and the awareness of possible side effects of TCM in parents is low. They suggested doctors should routinely inquire about TCM use and watch out for any associated potential adverse effects.

An open study to determine the efficacy of blue light in the treatment of mild to moderate acne

Morton CA, Scholefield RD, Whitehurst C, Birch J. *J Dermatol Treat* 2005;16:219-23.

This is an open study to determine the effect of

narrowband blue light in the management of mild to moderate acne and to evaluate patient tolerance of the therapy. Thirty patients (53% male) of mean age 18 (range 16 to 52 years old) with mild to moderate facial acne as defined by the Global Acne Grading system were recruited in the study. The inclusion criteria are no topical or system treatment for two weeks and no oral retinoid for six months. They were randomised to receive 10- or 20-minute light treatment using a blue LED light source of 409-419 nm at 40 Mw/cm². They received eight treatments in total (twice weekly for four weeks). One subject withdrew due to personal reason. The response was measured by facial erythema and lesion counts (comedones, papules and pustules). They were assessed at one, four and eight weeks post treatment course. The authors demonstrated a significant reduction in inflammatory lesion counts at week 8 which continued to week 12. The onset of effect was noted at week 4 post treatment (28% of patients, 76% clearance). The maximal effect occurred between week 8 (55% of patients, 71% clearance) and week 12 (17% of patients, 73% clearance) after treatment. There was no effect on non-inflammatory lesions. Only minor adverse effects were reported including redness after treatment (n=16, 53%), dryness of skin (n=4, 13%) and mild pruritus (n=5, 16%).

They concluded that narrowband LED blue light therapy reduces inflamed acne lesions significantly. It appears to be an effective and safe treatment for mild to moderate acne. The proposed mechanism of blue light treatment in acne is photoexcitation of the bacterial porphyrins in *Propionibacterium acnes* after irradiation with blue light leading to singlet oxygen production and endogenous photodynamic destruction of *Propionibacterium acnes*. The bacterial porphyrins are coproporphyrin III and protoporphyrin IX which mainly absorb blue visible light. Secondly, inhibition of proliferation of *P. acnes* seems to have a significant role as well.

Prospective, double-blind, randomised, parallel-group, dose-ranging study of botulinum toxin type A in men with glabellar rhytids

Carruthers A, Carruthers J.

Dermatol Surg 2005;31:1297-1303.

This study was conducted to determine the optimal dose of botulinum toxin A in treating glabellar rhytids in men. Eighty men were randomised to receive a total dose of 20, 40, 60 or 80 units of botulinum toxin A injection in the glabellar area. The glabellar lines were assessed at rest and at maximum frown before injection and at two, four weeks and then monthly after the injection. The following outcomes were measured: the maximum attempted muscle contraction of the glabellar using the Facial Wrinkle Scale, duration of response, peak response rate and self-evaluation.

The study showed that 40, 60 and 80 unit dose of botulinum toxin type A were more effective than the 20 unit dose in all aspects. A dose-response relationship was found. The maximum effect on glabellar lines using the Facial Wrinkle Scale was severe to mild or none in 65% of participants given 20 units, in contrast to 90% in 40 unit group, 95% in the 60 unit group and 100% in the 80 unit group. The mean time to relapse was 17.6 weeks for the 20 unit dose, 21.7 weeks for the 40 unit dose, 22.8 weeks for the 60 unit dose and 24.2 weeks for the 80 unit dose. No difference was found in the adverse effects across the treatment groups.

It was concluded that male patients with glabellar rhytids should be treated at a dose of at least 40 unit of botulinum toxin type A.

High incidence of balanitis xerotica obliterans in boys with phimosis: prospective 10-year study

Kiss A, Király L, Kutasy B, Merksz M.

Paediatr Dermatol 2005;22:305-8.

The incidence of balanitis xerotica obliterans (BXO) was studied in boys undergoing circumcision for phimosis over a 10-year period. Balanitis xerotica obliterans was graded histologically as early, intermediate and late forms. Patients were reviewed at one, six and 12 months after circumcision and then annually.

Out of a total of 1178 boys (mean age 6.8 years, range 2 to 16 years) undergoing circumcision for phimosis, 471 (40%) cases of BXO were detected. The highest incidence of BXO was found in those between age 9 and 11 years (143 cases, 76%). The mean age of BXO cases was 8.7 years. Secondary phimosis was found in 438 (93%) BXO cases compared to 236 (32%) of those without BXO. Ninety-one (19%) BXO cases were in the early stage, 280 (60%) were in the intermediate stage and 100 (21%) in the late stage. There was no association between clinical appearance and histological stage. Circumcision was done in 464 (98%) cases for BXO on the prepuce and/or glans penis. In the remaining patients, meatotomy was required in six patients and meatoplasty in one case. White discoloration of the glans penis was seen in 231 (9%) cases. No voiding difficulties were reported and the glanular lesions resolved in 229 cases at six months. In the remaining two cases, BXO disappeared by two years after surgery.

It was concluded that BXO is more common than previously reported. It was therefore recommended that circumcision samples should be sent for histological examination and that BXO cases should be follow-up on a long-term basis.

Chlamydial and gonococcal infection in men without polymorphonuclear leukocytes on Gram stain: implications for diagnostic approach and management

Geisler WM, Yu S, Hook EW.
Sex Transm Dis 2005;32:630-4.

This was a retrospective study in a sexually transmitted disease clinic from February 1998 to October 2002 to determine the proportion of men with chlamydia or gonorrhoea confirmed by culture or nucleic acid amplification testing (NAAT) whose Gram stain smear showed no evidence of inflammation. Men who had both a urethral Gram stain, chlamydia and gonococcal NAAT performed were included. Those who reported their partners having trichomonas and those who had received antibiotics in the past one month were excluded. Urethral swab or first void urine specimen were used in NAAT. Gram stain result was reported as the following: none; 1 to 4, or ≥ 5 polymorphonuclear leukocytes (PMNs)/oil immersion field (oif).

A total of 2266 out of 2629 men were recruited. Forty-four were excluded because of antibiotic use and 319 reported their partners had trichomonas. There were 462 (20%) patients tested positive for N gonorrhoeae, 353 (16%) positive for C trachomatis and 175 (8%) were co-infected with both organisms. Out of these 990 infected men, 178 (18%) were asymptomatic and without urethral discharge on examination and 261 (26%) were asymptomatic. Out of 462 men with gonorrhoea, Gram stain revealed 35 PMNs/oif in 433 (94%), 1 to 4 in six (1%), and none in 23 (5%). In chlamydial infection, Gram stain showed ≥ 5 PMNs/oif in 291 (82%), 1 to 4 in 20 (6%) and none in 42 (12%). In gonorrhoea infection, Gram stain showed 35 PMN in 433 (94%), 1 to 4 in six (1%) and none in 23 (5%). In co-infection, Gram stain showed 35 PMN in 169 (97%), 1 to 4 in two (1%) and none in 4 (2%). Chlamydial infection are significantly more likely than gonorrhoea

infection to have < 5 PMN/oif or no PMN on Gram stain ($p < 0.001$). Urethral symptoms, urethral discharge and/or 5 PMN/oif were absent in 22 (5%) and 47 (13%) of gonorrhoea and chlamydial infection respectively. Only four of these 22 men with gonorrhoea received therapy in the initial examination and the other 65 did not.

The authors commented that patients infected with gonorrhoea or chlamydia with no gram stain evidence of inflammation went untreated on initial examination. Thereby, the partners of these cases were placed at risk of infection, the patients and their partners were at risk of complications. They concluded that NAAT can be a better screening tool than culture for asymptomatic infection when Gram stain does not show any evidence of urethral inflammation. NAAT is more sensitive than culture.

Giant annular dermatomyofibroma

Ku LP, Chong LY, Yau KC.
Int J Dermatol 2005;44:1039-41.

Dermatomyofibroma (DMF) is a benign, acquired, plaque-like proliferation of spindle cells that show features of both smooth muscle and fibroblasts (i.e. myofibroblasts). The authors report a dermatomyofibroma that affected a 74-year-old lady and presented as a painful giant abdominal plaque on the abdomen. Examination revealed a tender well-demarcated tender annular erythematous keloid-like plaque measuring about 13 x 15 cm surrounding the cholecystectomy scar and thought to develop from it.

The differential diagnosis in this case included keloid, dermatomyofibroma, extraabdominal fibromatosis and dermatofibrosarcoma protuberans (DFSP). A deep incisional biopsy of the plaque showed proliferation of spindle-shaped cells arranged in well defined elongated intersecting fascicles parallel to the skin surface.

Only a vague storiform pattern was seen at the edges of the lesion. The cells had uniform elongated nuclei and mitosis was absent. Smooth muscle actin was positive but desmin and CD34 were negative. These features confirm a dermatomyofibroma.

Histopathological distinction between DMF and DFSP is important but usually without problem. In DFSP, the lesion is more cellular and with a characteristic storiform pattern. There is almost invariable infiltration into the subcutis. In dermatofibroma, it is more nodular and cells are arranged in short intersecting fascicles in a haphazard array with epidermal hyperplasia and

basal hyperpigmentation. These features found in dermatofibroma serve to distinguish from DMF and DFSP. In piloleiomyoma, the cells show definite smooth muscle phenotype and are arranged in bundles growing in different directions. Again, they grow in nodules instead of plaques.

The definitive treatment for DMF is surgical excision. To the authors' best knowledge, it is the largest dermatomyofibroma reported so far up to the time this report was written. While this should be differentiated from other more aggressive conditions like DFSP, DMF remains benign despite that it can reach a giant size.