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Journal Watch

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Dupilumab treatment improves quality of life in adult patients with moderate-to-severe atopic dermatitis: results from a randomized, placebo-controlled clinical trial

Tsianakas A, Luger TA, Radin A.
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The pathogenesis of atopic dermatitis involves type 2 T-helper cell (Th2) cytokines, interleukin (IL)-4 and IL-13 of Th2 immune system. Dupilumab is a human monoclonal antibody which inhibits IL-4 and IL-13 immune pathway. It showed efficacy and tolerability in previous phase II and III clinical trials and is the first biological therapy approved by the U.S. Food and Drug Administration for treatment of adult moderate-to-severe atopic dermatitis.

This was a 12 weeks double blind, randomised, placebo-controlled study for outcome of patients with atopic dermatitis treated by dupilumab. Sixty-four adult patients (age >18) with moderate-to-severe atopic dermatitis were randomised to either subcutaneous injections of dupilumab 300 mg or placebo once weekly for 12 weeks. The mean Quality of Life Index of Atopic Dermatitis (QoLIAD) score at baseline ± standard error (SE) was 11.3±1.09 in dupilumab group and 13.3±1.34 in placebo group at week 12 ($p<0.001$). Mean percentage improvement from baseline in QoLIAD score ± SE was significantly higher in dupilumab group (-64±6.91) than placebo group (-11.1±9.31). Reduction from baseline in Eczema Area and Severity Index (EASI) score was more in dupilumab group (20.6±1.97) than placebo group (6.3±2.04). Other clinical outcomes also improved significantly (all $p<0.05$) in dupilumab group when compared with placebo group: including percentage of body surface area (BSA) affected with atopic dermatitis, 5-dimensional pruritus, pruritus numerical rating scale (NRS) score, SCORAD visual analogue scale (VAS) scores for sleep and pruritus. Dupilumab also showed a favourable safety profile. Side effects included nasopharyngitis, headache, fatigue, and most were mild or moderate and transient. In conclusion, dupilumab is efficient and safe and improves the quality of life for adult patients with moderate-to-severe atopic dermatitis.

Safety and efficacy of guselkumab in Japanese patients with moderate-to-severe plaque psoriasis: a randomized, placebo-controlled, ascending-dose study

Nemoto O, Hirose K, Shibata S, Li K, Kubo H.
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The interleukin (IL)-23/IL-17 axis is involved in the pathogenesis of psoriasis. Guselkumab (human monoclonal antibody) is a new biological agent that specifically targets IL-23. It inhibits the IL-23/T-helper (Th) 17 axis and reduces the inflammatory process of psoriasis.

This study was a double blind, placebo-controlled, single ascending-dose study done in Japan. It investigated the safety and efficacy of single subcutaneous injection of guselkumab in management of moderate psoriasis (≥10% Body

Surface Area with Psoriasis Area and Severity Index (PASI) score ≥12). Twenty-four patients were recruited and randomised into four active groups (guselkumab 10 mg (n=5), 30 mg (n=5), 100 mg (n=5) and 300 mg(n=5)) and one placebo group (n=4). PASI 75 response of guselkumab-treated patients at 24 week achieved in 40% (10 mg), 80% (30 mg), 60% (100 mg) and 80% (300mg) of patients respectively. PASI 90 response of guselkumab-treated patients at 24 week achieved in 0% (10 mg), 60% (30 mg), 40% (100 mg) and 60% (300 mg) of patients respectively. The median percentage improvement of PASI score from baseline in placebo, 10 mg, 30 mg, 100 mg and 300 mg dose groups was 5%, 63%, 91%, 87% and 91% respectively at week 16. The most common side effect was pruritus. Other side effects were folliculitis, infection, nasopharyngitis, injection-site erythema, heat rash, eczema, and urticaria. No deaths or serious side effect was reported in both the placebo and guselkumab group. In conclusion, guselkumab is safe and effective for the treatment of moderate-to-severe plaque psoriasis.

Association of nodal metastasis and mortality with vermilion vs cutaneous lip location in cutaneous squamous cell carcinoma of the lip

Wang DM, Kraft S, Rohani P, Murphy GF, Besaw RJ, Karia PS, et al.
JAMA Dermatol 2018;154:701-7.

Squamous cell carcinoma of the lip most frequently begins as a premalignant ulcerative lesion and is associated with chronic sun exposure, alcohol use and tobacco exposure.

The aim of this retrospective cohort study was to compare differences in risks of recurrence, metastasis, and death from cutaneous squamous cell carcinoma (cSCC) on the vermilion vs. cutaneous lip.

In this study, there were 303 patients (153 men; 150 women) who were diagnosed with cSCC of the lip between 1 January 2000 and 31 December 2015 at two academic tertiary care centres of which the median age at diagnosis was 68 years (range 27-93 years). Of the 310 cSCCs of the lip, 138 were located on the cutaneous lip whereas 172 were located on vermilion. Most tumours were less than 2cm in diameter (267[86.1%]), well differentiated tumour (239[77.1%]), confined to the dermis (284[91.6%]), and free of perineural invasion (289[93.2%]). Regarding the primary treatment, Mohs Surgery and standard excision were performed in 199 (64.2%) and 69 (22.3%) patients respectively. Local recurrence occurred in 15 (4.8%) tumours, nodal metastasis occurred in 15 (4.8%) tumours, disease-specific death occurred in 10 (3.2%) tumours.

When the two lip zones were compared, cSCC on the vermilion lip had a greater risk than cSCC of the cutaneous lip of developing local recurrence (6.4% (11 of 172) in vermilion vs 2.9% (4 of 138) in cutaneous location); nodal metastasis (7.6% (13 of 172) in vermilion vs 1.5% (2 of 138) in cutaneous location) and disease-specific death (3.5% (6 of 172) in vermilion vs 2.9% (4 of 138) in cutaneous location). Besides, cutaneous SCCs on the vermilion lip had more aggressive histological characteristics (moderate or poor differentiation) than cutaneous lip (28.5% (49 of 172) vs 15.9% (22 of 138); P=0.01).

On multivariable analysis, elevated risk of nodal metastasis in cSCC of the lip was associated with location on the vermilion lip (vs cutaneous lip; subhazard ratio [SHR], 5.0; 95% CI, 1.1-23.8) and depth of invasion beyond subcutaneous fat (SHR, 4.4; 95% CI, 1.3-14.9).

The authors concluded the risk of nodal metastasis is five-fold greater for cSCCs on the vermilion lip compared with those on the cutaneous lip. Radiological nodal staging may be indicated in vermilion lip involvement.

Endocrine therapy-induced alopecia in patients with breast cancer

Freites-Martinez A, Shapiro J, Chan D, Fornier M, Modi S, Gajria D, et al.
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Endocrine therapy in breast cancer includes: (i) tamoxifen, which is a competitive inhibitor of oestrogen binding to endocrine receptors, and (ii) aromatase inhibitors (e.g. anastrozole, letrozole, and exemestane), which suppress plasma oestrogen levels.

The aim of this retrospective cohort study was to characterise endocrine therapy-induced alopecia (EIA) in patients with breast cancer and response to dermatological therapy.

In this study, 112 female patients who had received endocrine therapy for breast cancer with a diagnosis of alopecia attributed to their current therapy were included. In 75 (67%) patients alopecia was attributed to aromatase inhibitors and attributed to tamoxifen in 37 (33%) patients. The mean time to development of alopecia from endocrine therapy initiation was 16.8 months. Of 104 patients, 79 with basic type alopecia presented with recession of frontal and parietal hairlines, mimicking an androgenetic pattern of alopecia. The severity of alopecia using Common Terminology Criteria for Adverse Events, version 4.0 was grade 1 in 96 of 104 patients. Intermediate- and thick-density terminal hairs and vellus hairs were the most common trichoscopic features at baseline.

Alopecia-related quality of life was analysed in 52 of 112 patients with the Hairdex Questionnaire which consists of five domains: emotions, functioning, symptoms, stigmatisation, and self-confidence. A higher negative impact on emotion was found when compared with other domains (mean 41.8; SD 21.3; P<.001). In addition, 37 of 46 patients demonstrated a moderate to significant improvement in alopecia after treatment with topical minoxidil.

The authors concluded that patients with breast cancer receiving endocrine therapy are associated with an androgenetic pattern of alopecia. Although most cases of alopecia were mild, there was a negative impact on emotion. Topical minoxidil may be efficacious in these cases.

The impact of *Chlamydia trachomatis* infection on sperm parameters and male fertility: a comprehensive study

Moazenchi M, Totonchi M, Yazdi RS, Hratian K, Mohseni Meybodi AM, Ahmadi Panah M, et al.
Int J STD AIDS;2018;29:466-73.

Clamydia trachomatis (CT) is a common sexually transmitted infection (STI) leading to urethritis, epididymo-orchitis, prostatitis, cervicitis, pelvic inflammatory diseases (PID), ectopic pregnancy and sub/infertility. However, its relationship in male infertility is not clear. This study was to determine the prevalence of CT in semen samples of the male partners of infertility couples and to investigate whether CT could be associated with poor semen quality and sperm DNA damage.

Semen samples from 1080 subfertile couples were tested for CT by ELISA. The subjects were then divided into three groups:

i. Control group – normal spermogram and negative for CT infection;
ii. Asymptomatic group – CT positive with abnormal spermogram;
iii. Symptomatic group – CT positive with abnormal spermogram, high wbc count, low sperm count, reduced sperm normal morphology and low sperm motility. Patients with a history of any antibiotic use in the last two months, positive for HIV, HBsAb and anti-HCV, varicocele and azoospermia and history of epididymitis or epididymo-orchitis were excluded.

The mean age was 36.1+7.1 years. A total of 14.3% (155/1080) were CT positive either by serology or molecular methods. Among these,

11% (89) were in the symptomatic group and 26% (66) were from the asymptomatic group. The symptomatic group had significantly ($p<0.05$) lower sperm concentrations, high leukocytes in semen and a lower percentage of motile sperm cells.

The authors concluded that the poor quality of sperm may be the cause of infertility and due to the high frequency of asymptomatic CT infection among subjects with poor sperm quality, screening for occult CT infection is essential.

Association between eye diagnosis and positive syphilis test results in a large urban sexually transmitted infection/primary care clinic population

Lobo AM, Gao Y, Rusie L, Houlberg M, Mehta SD.
Int J STD AIDS;2018;29:357-61.

Ocular syphilis often presents with blurred vision and uveitis during the second or tertiary stage of syphilis and the incidence has been increasing particularly in MSM and HIV-infected patients. This study was aimed to analyze whether patient with eye disease had a higher chance of having syphilis.

During the 5-year study, the medical records of cases who were tested for syphilis in a large STI and primary care clinic were retrieved and the prevalence of eye diseases according to the code of International Classification of Diseases, 9 Revision (ICD-9) was studied.

There were 71,299 syphilis tests were performed on 30,422 patients. The prevalence of eye disease was 0.25% (77/30,422). Among these patients, 50 (65%) had conjunctivitis; 14(18%) redness; 5(6.5%) iridocyclitis; 5(6.5%) chorioretinitis and 3(4%) keratitis. Patients with eye diseases were more likely to have positive syphilis tests (32.5%) compared to those without eye disease (7.5%) ($p<0.01$). Subgroup analysis showed that patients with eye disease were more likely to be HIV-infected, MSM, 40 years or older and have private insurance compared to those without eye disease ($p<0.01$). After multi-variable logistic regression analysis, there was 5.97 higher odds of a positive syphilis test result in the eye disease group ($p<0.01$). When adjusted for other risk factors such as HIV, age race, sex and insurance, this association was slightly less but still significant ($OR=2.00$ $p=0.01$). When the analysis was restricted to MSM, the odds for a positive syphilis test was 4.61 ($p<0.01$) and 1.97 ($p=0.02$) in unadjusted and adjusted model respectively for eye disease group compared to those without eye disease.

The authors concluded that patients who present with an eye diagnosis to STI clinic have a higher probability of positive syphilis tests. Therefore, high risk patients with eye symptoms should have STI screening and a full ophthalmological examination.

Efficacy and safety of oxymetazoline cream 1.0% for treatment of persistent facial erythema associated with rosacea: Findings from the 52-week open label REVEAL trial

Draelos ZD, Gold MH, Weiss RA, Baumann L, Grekin SK, Robinson DM, et al.
J Am Acad Dermatol 2018;78:1156-63.

Rosacea is a chronic dermatological disease characterised by persistent facial erythema, flushing, telangiectasia and inflammatory papules. Most topical agents approved for rosacea target the inflammatory papules, but have no effect on the dysregulation of cutaneous vasomotor response and facial erythema. Brimonidine is an $\alpha 2$ adrenergic agonist and is the first FDA-approved agent that targets facial erythema. As $\alpha 2$-adrenoceptors expressed pre and/or post-synaptically on vascular smooth muscle cells of

blood vessels, vasocontriction occurs if postsynaptic α2 receptors are activated and there will be vasodilatation when presynaptic or endothelial α2 receptors are activated. This explains why patients on brimonidine complain of worsening of erythema, flushing and rebound with the treatment. Oxymetazoline, a newer α1a-adrenoceptor agonist, has gained FDA approval for the treatment of erythema in rosacea. As α1a-adrenoceptors are only present in post-synaptic vascular smooth muscle, they should have better vasoconstrictive effect.

This study reported the findings of REVEAL trial at 52-weeks. This was a multi-centre, open-label trial to assess the long-term safety and efficacy of oxymetazoline on rosacea. Between 9 April 2014 and 19 August 2014, patients with rosacea were recruited. Those with other dermatological conditions affecting the face that affected erythema assessment, contraindication to a-agonists, and history of topical steroids, acne treatments and isotretinoin use were excluded. They were then given oxymetazoline 1% cream to be applied once daily on the entire face and were follow-up at weeks 4, 12, 26, 39, 52 and two weeks post-treatment. Patients were assessed for inflammatory lesions, erythema using the Clinician Erythema Assessment (CEA) and Subject Self-Assessment for rosacea facial redness (SSA) and telegiectasia using Clinician Telangiectasia Assessment (CTA) score. Patient tolerability and reported side effects were recorded.

A total of 440 patients were recruited and analysed. All of them had moderate-to-severe rosacea with grade 3 to 4 in CEA and SSA. Only 3.2% of subjects discontinued treatment due to side effects, which were mostly treatment-site reactions. The incidence of treatment-related adverse events was 8.2% and the most common reported side effects were application-site dermatitis, paresthesia, pain, and pruritus. Less than 1% complained of rebound after stopping treatment. Concerning the efficacy, 36.7%, and 43.4% of patients achieved a 2-grade or greater improvement in both CEA and SSA after application, 3 and 6 hours respectively. However, there were no statistically significant effect on inflammatory counts, telangiectasia and blanching.

The authors concluded that oxymetazoline cream is useful in patients with moderate-to-severe rosacea and this long-term study proved its safety, tolerability and minimal rebound after withdrawal. This safety profile seems more favourable than the previous studies on brimonidine. However, further head-to-head comparison is required to draw such conclusion.

Postdiagnosis aspirin use and overall survival in patients with melanoma

Rachidi S, Wallace K, Li H, Lautenschlaeger T, Li Z.
J Am Acad Dermatol 2018;78:949-56.

Prostaglandins and platelet have been shown to promote melanoma growth and affect melanoma immunotherapy in mouse models. Aspirin, by inhibiting platelets and tumour-derived prostaglandin production, should theoretically improve melanoma outcome. It has been shown to improve survival and exert a protective effect on various solid tumours. Moreover, pre-diagnosis use of aspirin has been shown to lower the incidence of melanoma and is associated with melanoma with lower Breslow thickness. However, its protective effect on patients with melanoma is still uncertain.

In this retrospective study, the authors reviewed all records in one centre with the diagnosis of melanoma between 2000-2014. Those who had more than one primary melanoma, or without complete TNM staging, and cessation of aspirin use before the diagnosis of melanoma were excluded.

A total of 1522 patients were included for analysis. Aspirin users were significantly older, more likely to have cardiovascular risk factors and cardiovascular diseases and with earlier stage of melanoma than non-users. However, it was found that aspirin use significantly improved overall survival, even after adjusting for age, sex, cardiovascular risk, treatment and stage of disease (hazard ratio [HR], 0.58; 95% confidence interval [CI]: 0.45-0.75). This prolonged survival was observed irrespective of aspirin before or after diagnosis. Although, aspirin use was not associated with prolonged survival in stage I and in-situ disease, it did show a better survival in more advanced disease (stages II (HR, 0.45; 95% CI, 0.24-0.82) and III (HR, 0.57; 95% CI; 0.34-0.96))

The authors concluded that aspirin use after diagnosis can prolonged survival in melanoma patients. However, larger prospective clinical trials are required to further evaluate its effect and to eliminate possible bias and confounders associated with retrospective observational studies.

Invasive squamous cell carcinoma: comparison of differentiation grade and Tumour depth by anatomical site in 1666 tumours

Pyne JH, Barr E, Myint E, Clark SP, David M, Na R.
Clin Exp Dermatol 2018;43:3-10.

The increasing incidence of squamous cell carcinoma (SCC) is attributable to chronic ultraviolet light exposure, sequential SCC in individual patients and increasing incidence among organ transplant recipients. Adverse prognostic factors include increased tumour diameter and depth, poor differentiation, perineural invasion, immunosuppression, invasion into cranial bone and anatomic site of occurrence.

The article reviewed 1666 consecutive cases of SCC identified from 2009 to 2015 in a clinic in Sydney, Australia. These tumours were identified among 842 patients, about two-thirds (63.5%) were men and one-third women (36.5%). The median age of diagnosis of the first SCC was 71 years. There was a significant rise in median age from well-differentiated to moderately-differentiated to poorly-differentiated SCC. Among the tumours, 82.1% were well-differentiated, 13.3% moderately-differentiated and 4.6% poorly-differentiated. More than 60% of the well-differentiated SCCs were located at sites other than those in the head and neck region, while the respective rates for moderately differentiated was 45% and that of poorly-differentiated 30%.

The overall median thickness was 8 mm and the median tumour depth was found to be 1.2 mm. The median maximum diameter was found to be inversely proportional to differentiation grade, and the difference reached statistical significance. There was also an inverse correlation between tumour depth and differentiation, reaching statistical significance of $p<0.001$ as well.

On multinomial regression, elderly patients were more likely to develop moderately and poorly-differentiated SCC after adjustment. The shift towards poorly-differentiated SCC was significant for head and neck sites and for increasing tumour depth. Poorly-differentiated tumours were also found to have significantly larger diameters.

Poorly-differentiated SCC was most commonly found on the scalp in men (15.6%) and in women, the cheek or chin (9.1%). Tumours on the ear, forehead and chest were also found to have increased tumour depth and poor differentiation. These are important aspects to consider when treating patients with suspected SCC.

The clinicoaetiological, hormonal and histopathological characteristics of melasma in men

Handa S, De D, Khullar G, Radotra BD, Sachdeva N.
Clin Exp Dermatol 2018;43:36-41.

Melasma is a disease with female preponderance. Existing literature on the clinical pattern, triggering factors, endocrine profile and histopathological findings of melasma among male patients are lacking. This study reviewed the clinicoaetiological, hormonal and histopathological characteristics of melasma among men.

Fifty consecutive male patients with melasma and 20 age- and sex-matched controls were identified. Mean age of the patients was 27.6 years and mean disease duration 3.25 years. The commonest clinical pattern was malar, accounting for 52% of cases, followed by centrofacial (46%) and mandibular in 2%. Sixteen percent of patients reported a positive family history and sun exposure aggravated the disease in 34% of patients. Almost two-thirds (62%) used mustard oil for hair growth and/or emollient. As it is a photosensitiser, its use on the face and hair is possibly important in causing melasma in Indian men. Stress was identified as an aggravating factor in 28% of patients. The epidermal type of melasma was seen on Wood's lamp examination in 54% cases. Hormonal profile was not statistically different between the patients and their controls.

On histology, elastotic degeneration, epidermal melanin, mast cells and vascular proliferation were more prominent in lesional as compared with nonlesional skin. In lesional skin, there was absent to weak expression of stem cell factors and hormonal receptors.

It was concluded that ultraviolet light and mustard oil may play an important causative role in male melasma. Future studies with quantitative analysis of immunohistochemical markers will further our understanding of the pathogenesis of melasma.