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Journal Watch

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Long-term adalimumab efficacy in patients with moderate-to-severe hidradenitis suppurativa/acne inversa: 3-year results of a phase 3 open-label extension study

Zouboulis CC, Okun M, Prens EP, Gniadecki R, Foley PA, Lynde C, et al.
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A phase 3, open-label extension (OLE) trial was designed to assess the long-term tolerability of and response to Adalimumab (ADA) in patients with moderate-to-severe hidradenitis suppurativa (HS).

Patients with HS were randomised to receiving ADA 40 mg weekly or placebo for 12 weeks. At the end of this 12-week period, patients who were treated with ADA were then allocated to ADA or placebo for another 24 weeks. In the open-label extension of the trial (OLE), all patients received ADA 40 mg weekly for at lease 60 weeks.

Of the 316 patients who were treated with ADA, 50.6% (160 of 316) achieved a HiSCR clinical response (defined as 50% reduction in abscess and nodule count) at week 12, which was significantly higher than the rate for the placebo group (26.8%, 85 of 317 cases) ($P<0.001$). In the OLE trial, 52.3% cases achieved HiSCR at week 12 that was maintained at week 36. There was a decrease in draining fistula count, inflammatory nodule count, and total fistula count as well as an improvement in pain that was maintained through to study week 168.

The mean patient-years of exposure were 2.21 in the ADA weekly group. There were no adverse events of opportunistic infections except oral candidiasis. Moreover, there were no reports of non-melanoma skin cancer, malignancy, active tuberculosis, lymphoma, or demyelinating disorder or deaths. Frequently reported treatment related adverse events (>/=10%) included headache, hidradenitis, upper respiratory tract infection, arthralgia, urinary tract infection, sinusitis, bronchitis, dizziness.

It was concluded that Adalimumab (ADA) 40 mg weekly resulted in significantly higher clinical response rates in patients with moderate-to-severe HS.

Mycetoma: reviewing a neglected disease

P Verma, A Jha.
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Mycetoma is the chronic granulomatous infection of the skin and subcutaneous tissue. They can be caused by fungus in which case the mycetoma will be called eumycetoma or they can be caused by bacteria in which case the mycetoma will be called actino-mycetoma.

Examples of agents of the actinomycotic species include *Streptomyces somaliensis,* and *Nocardia asteroides, while Madurella mycetomatis,* and *Leptosphaeria senegalensis* are commonly seen causative eumycotic agents. These organisms are found in soil and gain a foothold through an area or trauma.

Mycetoma is regarded as a neglected disease as it commonly affects the poor living in remote areas

with poor access to health care, as well as its chronic disease course and poor clinical outcomes. It presents with the classical triad of firm indurated swelling with or without discharging sinuses and presence of grains. Advanced cases can invade muscle and bone resulting in morbidity. The commonest site of involvement is the foot. Grains are sometimes visible through the discharging sinuses.

Potassium hydroxide mount of grains may show fungal hyphae, while Gram stain is used to demonstrate filamentous bacteria. Radiographs may aid in diagnosing bone disease in which cavities may be found. Magnetic resonance imaging may demonstrate the "dot-in-circle" sign which are tiny hypo-intense foci within hyper-intense spherical lesions. Histopathology and culture are important to diagnose the disease and causative organisms. Newer technologies involve gene sequencing studies and pan-fungal PCR which are useful in culture-negative cases.

Eumycetoma is more difficult to treat than actinomycetoma. Surgery is indicated to remove smaller lesions and to reduce the organism load in bigger lesions. The former will require treatment by systemic antifungal from one to three years whereas the latter three months to one year.

Skin cancer and welding

Falcone LM, Zeidler-Erdely PC.
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Ultraviolet radiation (UVR) is a risk factor for skin cancers. UVR is classified as Group 1 carcinogen by the International Agency for Research in Cancer, and in particular, UVR from arc welding was classified in 2017. Full-time welders as well as workers in various occupations including construction, farming, shipbuilding and vehicle servicing may be exposed to UVR.

Welders are exposed to the whole spectrum of UVR including UVA, UVB and UVC and are known to be at higher risk of developing ocular melanoma. UVR from welding can lead to erythema of exposed skin and burns are also frequently encountered from radiation, hot metal and sparks generated during the welding process. Gas metal arc welding produces the most UV, in contrast to plasma arc welding which produces the least. Argon produces more UV than carbon dioxide or helium when used as a shielding gas. Some metals may also sensitise the skin to UVR.

The authors searched for publications describing the relationship between skin cancer and welding. Eight case reports and five case-control studies were found. The largest and most recent study recruited 4333 metal arc welders who were followed-up for 25 years. There was a significantly increased risk of basal cell carcinoma in the head and neck region of welders compared with controls [hazard ratio(HR)=2.49 (95% CI 1.03-5.99) for welders exposed for more than 20 years and HR=2.46 (95% CI 1.02-5.94) for welders exposed for more than 30 years. There was no clinical evidence that welding increases risk of skin cancer at other sites (HR 0.99; CI 0.94-1.04). The study is however limited by lack of evidence of other risk factors which may affect the risks of skin cancers among welders.

As yet, a definite association between welding and increased risk of skin cancer has not been established. The American Welding Society recommends the use of helmets, gloves and safety glasses to protect welders from UVR. Future studies may require more in-depth analysis of confounding factors.

Omalizumab in patients with chronic spontaneous urticaria nonresponsive to H1-antihistamine treatment: results of the phase IV open-label SUNRISE study

Berard F, Ferrier Le Bouedec MC, Bouillet L, Reguiai Z, Barbaud A, Cambazard F, et al.
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Omalizumab is a humanised anti-immunoglobulin E monoclonal antibody used as a third-line treatment (add-on to H1-antihistamines) for chronic spontaneous urticaria (CSU). The SUNRISE study was a prospective, non-randomised, multicentre, phase IV study to evaluate the therapeutic response of subcutaneous omalizumab (300 mg every 4 weeks for 12 weeks) in 136 moderate-to-severe (H1-antihistamine nonresponsive) CSU adult patients (mean age 44.4+/-12.7 years). This study also investigated the relationship between plasma D-dimer concentrations and CSU disease activity. Urticaria control test (UCT) and 7-day urticaria activity score (UAS7) were used to assess disease activity at week 0, 4, 8, 12 week. D-dimer concentration was also measured at week 0, 4 and 8.

Most patients improved significantly after 12 weeks of omalizumab (74.6% patients had UCT score ≥12 and 67.7% patients had UAS7 ≤6 at week 12). Eight (out of nine) patients were responders (UAS7 ≤6) to omalizumab at week 12 even with a very high baseline D-dimer concentration (>3000 ng mL^{-1}). In conclusion, omalizumab was an effective treatment to H1 antihistamine non-responsive CSU patients. Baseline D-dimer concentration was not useful for predicting the disease prognosis.

Assessment of a Bidirectional Association Between Major Depressive Disorder and Alopecia Areata

Vallerand IA, Lewinson RT, Parsons LM, Hardin J, Haber RM, Lowerison MW, et al.
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The aim of this population-based retrospective cohort study was to assess the bi-directional association between major depressive disorder (MDD) and alopecia areata (AA). It included patients 10 to 90 years of age registered with The Health Improvement Network in general practice in the United Kingdom between January 1, 1986 and May 16, 2012. The development of incident AA and development of incident MDD during follow-up were the main outcome measures.

In the analysis of the risk of AA, 622 cases in the MDD cohort (0.2%) developed AA (IR, 25.6 per 100,000 person-years) versus 6356 cases in the reference cohort (0.1%; IR, 13.1 per 100,000 person-years). After consideration of other variables, MDD was found to increase the risk of AA by 90% (HR, 1.90; 95% CI, 1.67-2.15; P<0.001) while antidepressants had a protective effect on AA (HR, 0.57; 95% CI, 0.53-0.62; P<0.001).

In the analysis of the risk of MDD, 6861 patients who developed AA and 6,137,342 patients who did not develop AA were followed up for 26 years. After adjusting for other variables, AA was found to increase the risk of subsequently developing MDD by 34% (hazard ratio, 1.34; 95% CI, 1.23-1.46; P<0.001)

It was concluded that AA may increase the risk of developing MDD and vice versa and that further studies are required to elucidate common underlying inflammatory and genetic susceptibilities between the brain and skin.

Safety and efficacy of methotrexate for Chinese adults with psoriasis with and without psoriatic arthritis

Yan K, Zhang Y, Ling Han L, Huang Q, Zhang Z, Fang X, et al.
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The objective of this prospective, single-arm, interventional study was to evaluate the effectiveness and safety of methotrexate in treating patients with psoriasis with and without psoriatic arthritis. A total of 235 patients with psoriasis, (107 without psoriatic arthritis; 128 with psoriatic arthritis) were treated with a 12-week course of low dosage oral methotrexate (7.5 mg-15 mg weekly). Change in disease severity, blood cell counts, liver and renal function and adverse events were the main outcomes studied.

The response rates were significantly higher in patients without psoriatic arthritis compared with those with psoriatic arthritis at week 8 (PASI90: 12 [11.2%] vs 4 [3.1%]; P=0.02) and week 12 (27 [25.2%] vs 19 [14.8%]; P=0.049).

Adverse events due to methotrexate were significantly higher in patients with psoriatic arthritis than that in patients without psoriatic arthritis: gastrointestinal symptoms (32 of 128 [25%] vs 13 of 107 [12.1%]; P=0.01), dizziness (12 of 128 [9.4%] vs 1 of 107 [0.9%]; P=0.007), and hepatotoxicity (34 of 128 [26.6%] vs 16 of 107 [15.0%]; P=0.04). Elevation of alanine aminotransferase levels due to methotrexate was associated with smoking [17 of 34 cases (50.0%) in cases with arthritis (P=0.02) and 9 of 16 (56.2%) in cases without arthritis (P=0.04)] and body mass index (mean body mass index 26; Standard deviation (SD): 4 in psoriatic arthritis cases compared to 26 SD: 4 in cases without arthritis P=0.005).

The authors concluded that methotrexate appeared to be more effective with fewer adverse effects in patients without psoriatic arthritis compared with those with psoriatic arthritis and is therefore a first-line treatment for psoriasis without arthritis.

Methotrexate for alopecia areata: a systematic review and meta-analysis

Phan K, Ramachandran V, Sebaratnam DF.
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Methotrexate has either been used as monotherapy or an adjuvant maintenance therapy with corticosteroids for alopecia areata (AA). This systematic review and meta-analysis aimed to determine the efficacy and risks of methotrexate (monotherapy and combination therapy) for AA and to compare the relative efficacy of methotrexate for AA in adult and paediatric cases.

Twenty-nine studies were included in this systemic review. A complete response (100% regrowth of hair) to methotrexate in AA was seen in 35.8% (95% confidence interval [CI] 25.0%-48.3%). The pooled complete response in adult studies was 44.7% (95% CI 32.9%-57.1%) as compared with 11.6% (95% CI 5.1%-24.5%) in the paediatric population (P=0.001).

There was a significantly higher odds of response (50-100% hair growth) with combination therapy compared with methotrexate monotherapy (odds ratio 2.73, 95% CI 1.19-6.27, I^2 = 0%, P=0.018). There was a pooled time delay to beginning diffuse hair regrowth of 3.125 (95% CI 2.3-4.0) months and a pooled time of 9.9 (95% CI 6.0-13.8) months was required for initial complete regrowth.

There was a pooled recurrence rate was 47.7% (95% CI 35.2%-60.5%), which was associated with significant heterogeneity (I^2 =61.09%, P=0.002). In the subgroup analysis, there was a higher pooled recurrence rate in adult cases [52.0% (95%

CI 37.5%-66.2%)] as compared to paediatric cases [31.7% (95% CI 16.3%-52.6%)].

A total pooled complication rate of 22.1% (95% CI 14.8%-31.7%) was found. In the subgroup analysis, the pooled complication rate was 24.2% (95% CI 15.2%-36.4%) in adults as compared to 14.5% (95% CI 6.6%-28.9%) in the paediatric population. There was no significant difference between the two groups (P=0.31)

In conclusion, methotrexate alone or combination with corticosteroids is effective for alopecia areata.

Prospective, randomized, double-blind assessment of topical bakuchiol and retinol for facial photoageing

Dhaliwal S, Rybak I, Ellis SR, Notay M, Trivedi M, Burney W, et al.
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Bakuchiol is a plant-derived phytochemical natural product which has retinoid-like effects. It is a purified meroterpene phenol found in the seeds of Indian plant *Psoralea corylifolia* which has anti-inflammatory, antiproliferative and antioxidant effects. A randomised, double-blind 12 week study with 50 patients was performed to evaluate the role of bakuchiol as an anti-ageing cosmetic agent. It compared the efficacy and side effects of topical 0.5% bakuchiol cream (twice daily) and topical 0.5% retinol cream (nocte) in the treatment of of facial ageing over 12 weeks. Facial Modeling and Analysis System (Brigh-Tex BioPhotonics, U.S.A.) with dermatologists (blinded to study groups and graded the scaling, pigmentation, erythema of face) was used to assess patient's face at 0,4,8 and 12 week. Patients were also asked to complete skin tolerability questionnaires (e.g. itching, burning, stinging etc.) at each follow-up visit. At week 12, both and retinol groups had statistically significantly decrease of 19% in wrinkle surface area in the Bakuchiol and 23.2% in the retinol group. For hyperpigmentation a 59% decrease was seen in the bakuchiol group and 44% in retinol group. Both treatments decreased the area of pigmentation and improved pigment intensity. Compared to retinol, bakuchiol group had less side effects of facial skin itching, burning and scaling. In conclusion, bakuchiol had comparable therapeutic efficacy with retinol to improve face photoageing and is better tolerated than retinol.