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Journal Watch

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Safety and efficacy of anakinra in severe hidradenitis suppurativa. A randomized clinical trial

Tzanetakou V, Kanni T, Giatrakou S, Katoulis A, Papadavid E, Netea MG, et al.
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Hidradenitis suppurativa (HS) is hypothesised to be an autoinflammatory condition due to specific deficiencies of the immune system. Prospective studies have demonstrated positive therapeutic effects after administration of tumour necrosis factor (TNF) antagonists. Anakinra is a recombinant interleukin 1 (IL-1) receptor antagonist which competitively inhibits the binding of both IL-1α and IL-1β to the IL-1 type 1 receptor. Interleukin 1 is a major mediator of the inflammatory response. This study investigated whether anakinra would be a novel safe and efficacious approach in the management of HS.

This study was a double-blind, randomised, placebo-controlled prospective clinical trial consisting of an initial 12-week treatment phase and a 12-week follow-up phase. Patients were randomised to receive either placebo or anakinra subcutaneously once daily for 12 weeks. After treatment, the patients were followed up from week 13 to week 24. Peripheral blood mononuclear cells (PBMCs) were isolated and stimulated for the production of TNF, IL-1β, IL-6, IL-10, IL-17, IL-22, and interferon-γ (IFN-γ). The primary end point was the safety and efficacy of anakinra based on decreased disease activity scores from the baseline visit to the end of treatment. The secondary end points were the effects of anakinra on the time to a new exacerbation of HS and the difference in cytokine production by PBMCs between the two study arms over the course of the study visits.

A total of 20 participants were recruited – 10 patients were randomised to the placebo arm and 10 patients were randomised to the anakinra arm. The disease activity score was decreased at the end of treatment in 20% of the placebo arm compared with 67% of the anakinra arm ($p=0.04$). HS clinical response at 12 weeks was achieved in 30% of the placebo arm and in 78% of the anakinra arm ($p=0.04$). The production of interferon-γ in the anakinra arm was decreased, and the production of interleukin 22 was increased. The time to a new HS exacerbation was prolonged compared to placebo in the anakinra arm (log rank, 6.137; $p=0.01$). There were no reported serious adverse events.

The present study is the first double-blind, randomised trial assessing the safety and efficacy of anakinra in HS. It was found that anakinra had the potential to be an effective and well-tolerated treatment for HS. However, whether patients who showed an insufficient response to anti-TNF treatment would benefit from anakinra therapy is unknown.

Laboratory monitoring during isotretinoin therapy for acne. A systematic review and meta-analysis

Lee YH, Scharnitz TP, Muscat J, Chen A, Gupta-Elera G, Kirby JS
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Isotretinoin is associated with several adverse effects including teratogenicity, hyperlipidaemia and associated pancreatitis, leucopenia, thrombocytopaenia and transaminitis. Previous studies have investigated the usefulness of laboratory monitoring during isotretinoin therapy.

However, the evidence to guide laboratory monitoring during isotretinoin therapy is limited by differences in the tests ordered, testing frequency, and small sample size in some studies. The aim of this systematic review and meta-analysis was to combine data across multiple published studies to develop estimates of laboratory changes during isotretinoin therapy for acne.

The inclusion criteria included studies of acne vulgaris, use of oral isotretinoin, dose regimens of 40 mg or more daily (or ≥0.5 mg/kg), duration of treatment for at least four weeks and treatment of children and adults (aged 9-35 years). The study had to report the values for the laboratory tests: complete blood cell count, aspartate aminotransferase (AST), alanine aminotransferase (ALT), alkaline phosphatase (ALP), triglycerides (TG), total cholesterol, low-density lipoprotein cholesterol (LDL-C) and high-density lipoprotein cholesterol (HDL-C).

This meta-analysis of changes in laboratory values included 22 randomised clinical trials and four retrospective studies with a total of 1574 participants. The mean (99% CI) values during treatment for TG was 119.98 mg/dL (98.58-141.39 mg/dL); for white blood cell count, 6890/μL (5700/μL-8030/μL), for total cholesterol, 184.74 mg/dL (178.17-191.31 mg/dL); for LDL-C, 109.23 mg/dL (103.68-114.79 mg/dL); for HDL-C, 42.80 mg/dL (39.84-45.76 mg/dL); for AST, 22.67 U/L (19.94-25.41 U/L); for ALP, 88.35 U/L (58.94-117.76 U/L); and for ALT, 21.77 U/L (18.96-24.59 U/L).

It was found that there was a statistically significant change in the mean value of several laboratory parameters (white blood cell count and hepatic and lipid panels) with isotretinoin treatment. However, the mean changes across a patient group did not reach criteria for high-risk values and the proportion of patients with these abnormalities was low. The authors suggested that less frequent laboratory monitoring may be safe, with few missed high-risk laboratory changes for many patients with acne who are receiving typical doses of isotretinoin. Clinical judgment should be used to determine monitoring frequency for each patient based on baseline laboratory findings and concomitant conditions, such as pre-existing liver disease, concomitant use of hepatotoxic medications, or metabolic syndrome, which may increase the risk of laboratory abnormalities.

Epidemiology and risk factors of childhood acne in Korea: a cross-sectional community based study

Park SY, Kwon HH, Min S, Yoon JY, Suh DH.
Clin Exp Dermatol 2015;40:844-50.

Acne is a common skin problem and often has an onset during the adolescent ages. Recently, childhood-onset acne at pre-adolescent period has been recognised as a variant of acne. The overall epidemiology of acne has evolved and the age of onset appears to be shifting earlier to the childhood. The present study aimed to investigate the prevalence and clinical features of acne vulgaris among paediatric patients studying in elementary school. The correlation between the severity of acne and the body mass index (BMI), dietary pattern, lifestyle habits and the treatment-seeking behaviour were analysed. A cross-sectional study was performed which included children studying in the elementary school between the age of 7 and 12 years. Structured questionnaires were used to obtained data on the clinical characteristics of acne and their lifestyle factors. The studied patients were also assessed clinically by two board-certified dermatologists. In the study, a total of 693 school children in Seoul were included, of which 36.2% of patients were diagnosed to have acne vulgaris. The prevalence rates had an overall rising trend with age and the highest was noted at age 11 (19.2%). The clinical severity, disease duration and the distribution of acne were significantly different between the lower (aged 7-9 years) and the higher (aged 10-12 years) age groups. For the disease severity according to the Leeds revised acnes grading, the higher age group had significant more severe disease than the lower group (1.0+/- 0.59 vs 0.9 +/- 0.27; p=0.03). The total number of both inflammatory and non-inflammatory acne lesions were also significant greater in the higher group. For lesional distribution, the higher group had more forehead and nose lesions while the lower group had more cheek lesions. There was also a significant difference in patients' disease recognition between the higher and lower groups (49% vs 17%). Overweight and obesity with a BMI more than 25 kg/m^2 at

18 years of age (OR=2.7; 95% CI, 1.81-3.92) and consumption of chocolates/sweets (OR=1.6; 95%CI, 1.24-2.39) were significant risk factors for the development of acnes. The authors concluded that there were an overall high prevalence of childhood acne and that there were phenotypical differences in clinical presentation between the older and younger school children.

Drug reaction with eosinophilia and systemic symptoms/drug-induced hypersensitivity syndrome: clinical features of 27 patients

Avancini J, Maragno L, Santi CG, Criado PR.
Clin Exp Dermatol 2015;40:851-9.

Drug reaction with eosinophilia and systemic symptoms (DRESS), one of the Severe Cutaneous Adverse Reactions (SCAR), which carries significant morbidity and mortality and risk of long term autoimmune complications. However, DRESS is well-known to be heterogeneous in clinical presentation and is associated with a variety of biochemical abnormalities. The present study aimed to investigate the clinical heterogeneity of DRESS in Latin America. This was a retrospective study which included 60 patients with suspected DRESS, who were managed in a tertiary academic hospital in Brazil. The criteria defined by the European Registry of Severe Cutaneous Adverse Reactions (RegiSCAR) was used to validate the cases. In the study, 27 patients (17 males; 10 females) who fulfilled the criteria for DRESS were investigated. For the clinical and laboratory characteristics, fever (96.2%), maculopapular exanthema (85.1%) and hepatic involvement (85. 1%) were the top three presentations. Erythroderma was noted in 15% of patients. Palpable lymphadenopathy was observed in 63% of the patients. Anti-convulsants were the commonest culprit agents, accounting for a majority (78%) of the cases. Other important agents included dapsone, allopurinol and nevirapine. All patients were managed with systemic prednisone, with a starting dose at 1 mg/kg/day. The overall mortality rate was observed to be 4%. A positive correlation was identified between the presence of atypical lymphocytes and higher serological levels of alanine aminotransferase (ALT) (Pearson correlation coefficient $r=0.62$; $p<0.001$). This may serve as a clue to the attending clinicians of the need of close monitoring for potentially fatal DRESS related hepatic involvement.

Efficacy of standard therapies against Ureaplasma species and persistence among men with non-gonococcal urethritis enrolled in a randomised controlled trial

Khosropour CM, Manhart LE, Gillespie CW, Lowens MS, Golden MR, Jensen NL, et al.
Sex Transm Infect 2015;91:308-13.

Ureaplasma urealyticum biovar 2 (UU) but not *Ureaplasma parvum* (UP) is associated with non-gonococcal urethritis (NGU) which is defined as visible urethral discharge or ≥5 polymorphonuclear leucocytes (PMNs) per high-power field (HPF). The aims of this study were (1) to compare the efficacy of azithromycin versus doxycycline in persistently positive men with UU and (2) to determine whether persistence of UU was associated with persisting clinical signs and symptoms of NGU. Eligible participants were men suffering from NGU and ≥16 years of age without use of antibiotics one month before the study. They were randomised 1:1 to receive either one of the following pre-packaged medications: (A) doxycycline 100 mg twice a day orally for seven days with a single oral dose of placebo azithromycin which looked identical to active 1 g azithromycin or (B) a single oral dose of 1 g azithromycin with placebo doxycycline given orally twice a day for seven days which looked identical to the active doxycycline capsules. Re-testing was done three weeks after the first treatment. If the urethral smear persistently positive, "reverse therapy" would be given to patients. Then, re-testing was performed three weeks after the "reverse therapy". If the urethral smear still positive, moxifloxacin 400 mg daily for seven days would be given.

A total of 490 men with NGU were included during the four-year study period. Of these, 22% were infected with UU. After the first treatment, a similar rate of persistent infection was detected in both the azithromycin and doxycycline groups (25.0% vs. 30.9% respectively $p=0.53$) and in over one-half of cases, UU was still detected after the "reverse therapy" and were treated with moxifloxacin.

Among these cases, 36% again had positive detection after moxifloxacin. Although 36% remained persistently positive for UU, all experienced resolution in signs and symptoms of NGU. The high failure rates were not due to antimicrobial resistance because all tested isolates demonstrated relatively low MICs to the three therapies and there was no association between persistence of UU and persistence of signs/symptoms of NGU. The authors postulated that infection with UU might not necessarily lead to urethritis or if UU did cause urethritis, the clinical syndrome might resolve over several weeks with or without effective treatment.

In conclusion, azithromycin and doxycycline had similar efficacy in treating UU related NGU and there was no benefit from prolonged antimicrobial therapy in asymptomatic NGU cases after initial treatment.

Imiquimod 5% cream for five consecutive days a week in an HIV-infected observational cohort up to 32 weeks in the treatment of high-grade squamous intraepithelial lesions

van der Snoek EM, den Hollander JC, van der Ende ME.
Sex Transm Infect 2015;91:245-7.

The incidence of human papillomavirus (HPV) induced anal cancer has increased in HIV-positive men having sex with men (MSM). Off label use of 5% imiquimod cream has been published in the precancerous anal high-grade squamous intraepithelial lesions (HSIL). The aim of this study was to establish the efficacy of 5% imiquimod cream used for five consecutive days a week in both perianal and intra-anal HSIL as well as the adverse effects.

During the three-year study period, 44 HIV-positive MSM who had HSIL were included. Of these, seven had perianal HSIL and 37 had intra-anal HSIL. High-resolution anoscopy (HRA) was used to screen the HSIL and diagnostic biopsies were taken from suspicious lesions, which were defined as perianal acetowhitening, hyper or hypopigmentated lesions, flat verrucous lesions or intra-anal punctation, mosaicism, flat leukoplakia and atypical vessels. The histology was read by the same pathologist and complete response (CR) was defined as reduction of moderate or severe dysplasia to complete absence of dysplasia and partial response (PR) was defined as reduction of HSIL to mild dysplasia (LSIL). A total of 9 (20%) out of 44 developed CR and 11 (25%) had PR. For the remaining patients, 20 patients received an additional 16 weeks of imiquimod treatment. Three cases reached CR and six had PR after additional treatment. However, three out of 29 patients who responded had recurrence of HSIL. Ninety-five point five percent of patients reported adverse effects including pain during defaecation (77.3%), anal burning sensation (56.8%), mood swings (9.1%) and fatigue (11.4%).

Although this study did not directly compare the regimens of five times weekly versus thrice weekly with imiquimod, the authors commented that 5% imiquimod cream is useful in HSIL but 5-weekly regimen did not seem to be more effective than thrice weekly therapy and the adverse effects were similar when comparing the experience of other studies.

Can pretreatment serum calcium level predict the efficacy of methotrexate in the treatment of severe plaque psoriasis

Zhai Z, Chen L , Yang H, Yan J , Wang C, Yang J, et al.
J Am Acad Dermatol 2015;73:991-7.

Methotrexate had been used for the treatment of psoriasis for a long time. However, its efficacy varied. This study evaluated whether pretreatment tests would help predict the efficacy of methotrexate.

The retrospective study was done in Southwest Hospital and Daping Hospital, Third Military Medical University in China between July 2012 and June 2014. Patients with severe plaque-type psoriasis, who had been treated with methotrexate (MTX) for 2 weeks (at 0.3 mg/kg/week) were included. Those already on systemic treatments, topical steroids or vitamin D analogues or phototherapy prior to study, patients who had diseases, or on medications, or on special diet which affect calcium metabolism, underlying parathyroid problem and pregnant or lactating patients were excluded. Pretreatment tests

including complete blood count, liver and renal function, biochemical and lipid profile and urinalysis were performed. Marked response to MTX was defined as 60% improvement. The effectiveness of pretreatment tests in predicting MTX efficacy was examined using receiver operating characteristic (ROC) analysis. Moreover, synergistic effect of MTX and calcium on keratinocyte growth and epidermal proliferation were tested using keratinocyte growth assay and a mouse-model.

A total of 77 patients were included. Pretreatment total calcium (tCa) level was shown to have the closest association with MTX efficacy and the relative psoriasis improvement with tCa was 61.07%. In-vitro study showed that calcium could significantly enhance the inhibitory effect on keratinocyte growth and mouse model also showed similar result in inhibition of epidermal proliferation in high calcium intake mice.

Calcium was shown in previous studies to be a regulator of keratinocyte differentiation. It was also shown that psoriatic patients tended to have more hypocalcaemia. Moreover, calcium can also influence MTX accumulation in hepatocytes. In this study, the authors demonstrated the synergistic effect of MTX with calcium in inhibiting keratinocyte proliferation and epidermal thickening by in-vitro and in-vivo tests.

The authors concluded that a higher pretreatment calcium level correlated with MTX efficacy and it might be used as a predictor in treatment response. However, this study was limited by the small sample size and its retrospective nature.

Rosacea is associated with chronic systemic diseases in skin severity-dependent manner: results of a case-control study

BM Rainer, AH Fischer, Luz Felipe da Silva D, Kang S, Chien AL.
J Am Acad Dermatol 2015;73:604-8.

Rosacea is a chronic inflammatory disease of the skin. However, few case reports and case series observed an association between rosacea with other systemic comorbidities. Systematic studies on these aspects were lacking.

In this single-centre case-control study, 65 patients with rosacea, aged 18 years or above, were recruited with the same number of age-, gender- and race-matched controls in the Johns Hopkins University Hospital between November 2012 and August 2013. Subjects were assessed by a dermatologist to confirm a diagnosis of rosacea and to evaluate its severity. Information on other medical conditions was collected using self-reported questionnaire and confirmed by medication use with medical records, if possible.

It was found that patients with rosacea were more likely to have allergies, respiratory diseases, gastro-oesphageal reflux disease (GERD), other gastrointestinal diseases, hypertension, metabolic disease, urogenital diseases and female hormone imbalance. Moreover, rosacea severity was also found to be correlated with a higher risk of hyperlipidaemia, hypertension, metabolic disease, cardiovascular disease and GERD.

This study provided some evidence in supporting the association between rosacea and systemic comorbidities in a skin severity-dependent manner and the authors recommended that physicians should be aware of these associations and provide comprehensive care for moderate to severe rosacea patients. However, the exact mechanism or pathophysiology remains unclear. This study was also limited by the possible recall bias in the self-reported questionnaires, the lack of control of possible confounders that might also be cardiovascular risk factors and the relative small sample size to assess the low-prevalence disease. The cross-sectional nature of the study also precluded the detection of the causal relationship.

Prenatal air pollutant exposure and occurrence of atopic dermatitis

Huang CC, Wen HJ, Chen PC, Chiang TL, Lin SJ, Guo YL.
Br J Dermatol 2015;173:981-8.

The presence of atopic dermatitis (AD) in early childhood was known to be due to environmental and genetic factors. However, the importance of prenatal and early postnatal exposure to air pollutants had not been fully explored.

The aim of this study was to evaluate the association between prenatal air pollutant exposure and the occurrence of AD. In the year of 2005, 24 200 infant-mother pairs were recruited to take part in the Taiwan Birth Cohort Study using multistage stratified sampling. Questionnaires were used to collect information on the medical history of infants six months of age. The monthly averages of five air pollutants, e.g. NO2, CO, O3, SO2 and PM10 were collected from 66 air-quality-monitoring stations. Exposure data during each of the three gestational trimesters and three months after birth were calculated for each recruit. The odds ratios (ORs) of AD occurrence were calculated by logistic regression.

In this study, a total of 16 686 mother-infant pairs were qualified for and included in the analysis. Among the qualified recruits, 1206 infants (7.2%) had been diagnosed as having AD before the age of six months. The prevalence of AD was higher in boys (8.3%) than in girls (6.1%). The association with CO exposure and occurrence of AD was statistically significant during the entire gestational period [adjusted OR (aOR) 1.37, 95% confidence interval (CI) 1.06-1.78] and the first trimester (aOR 1.51, 95% CI 1.16-1.97). The author did not find any significant association among the other air pollutants during the entire gestational period, three months after birth or any period of the three trimesters.

In summary, this study found an association between AD occurrence and gestational exposure to CO. The exposure to CO during the first trimester appeared to be the most significant.

Hidradenitis suppurativa and metabolic syndrome: a comparative cross-sectional study of 3207 patients

Shalom G, Freud T, Harman-Boehm I, Polishchuk I, Cohen AD.
Br J Dermatol 2015;173:464-70.

Hidradenitis suppurativa (HS) is an inflammatory skin disease characterised by nodules and abscesses in the apocrine-gland rich areas.

The aim of this study was to look at the association between HS and metabolic syndrome and its comorbidities in a large, community-based cohort of patients with HS. The authors used the database of Clalit Health Services which was the largest public healthcare provider in Israel.

This was a cross-sectional study done in Israel. In the study, metabolic syndrome was defined as the occurrence of at least three of the following conditions: hypertension, diabetes mellitus, hyperlipidaemia and obesity. The association between HS and metabolic syndrome was evaluated by a multivariate logistic regression model, correcting for age, sex, diabetes, obesity, hypertension, smoking status and hyperlipidaemia.

The study population consisted of 3207 patients with HS diagnosed by dermatologists in primary-care centres and 6412 age- and sex-matched control patients without HS. The author found that HS was significantly associated with metabolic syndrome [odds ratio (OR) 1.61, 95% confidence interval (CI) 1.36-1.89], diabetes (OR 1.41, 95% CI 1.19-1.66), obesity (OR 1.71, 95% CI 1.53-1.91), hypertension (OR 1.19, 95% CI 1.03-1.38) and hyperlipidaemia (OR 1.14, 95% CI 1.02-1.28).

The authors concluded that an association between HS and diabetes, hyperlipidaemia, obesity, hypertension and metabolic syndrome among a large community-based cohort of patients with HS was present. Doctors should be aware that patients with HS may have other undiagnosed components of metabolic syndrome and screening should be done accordingly.

Omalizumab in patients with chronic spontaneous urticaria: a systematic review and GRADE assessment

Urgert MC, van den Elzen MT, Knulst AC, Fedorowicz Z and van Zuuren EJ.
Br J Dermatol 2015;173:404-15.

Chronic spontaneous urticaria (CSU) is defined as wheals, and/or angio-oedema for longer than six weeks. Sometimes CSU cannot be controlled satisfactorily by H1 antihistamines.

The author assessed the quality of the evidence for the effects of omalizumab in patients with CSU. The PubMed, the Cochrane Database of

Systematic Reviews and the Cochrane Central Register of Controlled Trials up till 7 August 2014 were searched. There were three authors independently performing the study selection, risk of bias assessment and data extraction and two authors were responsible for data analysis. Five randomised controlled trials (RCTs), which included 1116 participants, all of which were determined to be of low risk of bias, were studied. After treatment with omalizumab, there was a statistically significant improvement in the disease activity and quality of life when compared with placebo [mean difference (MD) -11.58, 95% confidence interval (CI) -13.39 to -9.77 and MD -13.12, 95% CI-16.30 to -9.95, respectively]. Complete response and partial response were more common after treatment with omalizumab [risk ratio (RR) 6.44, 95% CI 3.95-10.49 and RR 4.08, 95% CI 2.98-5.60, respectively]. No significant difference in the proportion of participants reporting adverse events between the omalizumab and placebo treatment groups (RR 1.05, 95% CI 0.96-1.16) was found.

The authors concluded that there was high-quality evidence to support the efficacy and safety of omalizumab 300 mg monthly for six months for the treatment of CSU.