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Journal Watch

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Long-term management of chronic spontaneous urticaria with omalizumab

Pinto Gouveia M, Gameiro A, Pinho A, Goncalo M. Clin Exp Dermatol 2017;42:735-42.

Chronic urticaria is a common disease with a prevalence of 1%. Non-sedating antihistamines (H1 antihistamines) remain the first-line treatment, followed by escalation of doses up to four times the licensed limit. Cyclosporin, montelukast, or omalizumab have all been used in refractory cases.

Omalizumab has been shown to be a safe and efficacious treatment of recalcitrant chronic spontaneous urticaria at doses of 150 mg to 300 mg every 4 weeks. Long-term management strategies and efficacy are however, lacking. This study aims at identifying predictive factors which may better guide the optimum dosage regimens.

A total of 13 patients aged above 18 years, with severe chronic spontaneous urticaria defined as weekly urticaria activity score (UAS7) >28 not responding to second-generation H1-antihistamines at up to four times the licensed dose were recruited. The initial omalizumab dose was 150 mg every four weeks, and the dose was adjusted according to clinical response. Four patients showed complete response, two of which were controlled at 150 mg every four weeks, and another two tolerated a lengthened regimen at five weeks. One patient remained disease-free after stopping treatment. In eight patients a partial response was demonstrated, with dosages varying from 150 mg every four weeks, to 300 mg every three, four, or five weeks. Only one patient did not respond.

No significant differences in age, sex, previous therapies, disease severity, C-reactive protein level, pretreatment IgE level, histopathological findings and serological evidence of autoimmunity were identified.

The authors concluded that the difference in dosage and intervals required could be attributed to the natural exacerbations of the disease, which may on occasion require a higher dose of treatment These findings suggest that dosage and administration interval should be individualised to improve treatment responses.

Therapeutic efficacy and safety of oral tranexamic acid and that of tranexamic acid local infiltration with microinjections in patients with melasma: a comparative study

Sharma R, Mahajan VK, Mehta KS, Chauhan PS, Rawat R, Shiny TN.
Clin Exp Dermatol 2017;42:728-34.

Melasma is a common acquired disorder of hypermelanosis affecting sun-exposed skin on the face and neck. It causes considerable cosmetic disfigurement and psychosocial stress. Tranexamic acid is a plasmin inhibitor and anti-fibrinolytic agent that is used to treat melasma. It has been used via different routes including orally, intravenously, topically, and intradermally (by microinjection or microneedling) to treat melasma.

This study assessed the efficacy of tranexamic acid and evaluated the comparative efficacy of different routes of administration. One hundred patients were recruited; half were randomly assigned to receiving oral tranexamic acid 250 mg twice daily and half intradermal microinjections of tranexamic acid 4 mg/mL every four weeks. Percentage reduction in Melasma Area and Severity Index (MASI) was used as the primary outcome.

Both groups demonstrated marked reduction in percentage MASI. A very good response was seen in 25 of 39 patients and 32 of 41 patients in groups A and B, respectively with an average MASI decrease of 77.96±9.39 in group A and 79.00± 9.64 in group B at week 12. There was no statistically significant difference between the two groups. Adverse effects included mild epigastric discomfort, hypomenorrhoea, headache and injection site pain.

This study showed that both routes of administration of tranexamic acid in melasma were effective; and that the effect appeared to be independent of its route of administration.

Evaluating Comorbidities, Natural History, and Predictors of Early Resolution in a Cohort of Children With Chronic Urticaria

Netchiporouk E, Sasseville D, Moreau L, Habel Y, Rahme E, Ben-Shoshan M.
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In adult, 30% to 50% chronic urticaria resolve spontaneously within five years but the natural history and predictors in children are not known. The aim of this prospective study was to assess the clinical characteristics, natural history and associated comorbidities in chronic urticaria children, in addition to identify factors associated with resolution.

A total of 139 children under 18 years of were recruited from the urticaria and dermatology clinics at a children's hospital from December 2013 to December 2015. The most common type of chronic urticaria was chronic spontaneous urticaria (CSU) (108 [78.0%]). Thirty-one patients had inducible urticaria in which cold-induced urticaria was the most common subtype. Almost all patients (132[95%]) required second-generation antihistamines either alone, or in resistant cases, in combination with ketotifen and/or anti-leukotriene antagonists and/or omalizumab for symptom control. The most common associated comorbidity was atopy (39 patients). Six patients were diagnosed as having a comorbid autoimmune disease (two with type 1 diabetes, three with autoimmune hypothyroidism, one with systemic lupus erythematosus).

Regarding laboratory parameters, thyroid peroxidase antibodies were positive in four patients. Of those, three were diagnosed as having Hashimoto thyroiditis. Fifty-nine patients of this cohort had a positive basophil activation test (BAT), suggesting autoimmune urticaria

There were 43 cases of resolution over 419 patient-years of follow up since disease onset. The resolution rate was 10.3 per 100 patient-years. Patients with a positive BAT result (CD63 level >1.8%) were twice as likely to resolve after one year compared to those with negative BAT results (hazard ratio [HR], 2.33; 95% CI, 1.08-5.05). likelihood of resolution was decreased if basophils were presence (HR, 0.40; 95% CI, 0.20-0.99).

The study revealed a low rate of resolution of chronic urticaria in children. Patients with positive BAT results and absence of basophils were associated with earlier disease resolution.

Screening Guidelines for Thyroid Function in Children With Alopecia Areata

Patel D, Li P, Bauer AJ, Castelo-Soccio L.
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There is no common consensus on thyroid function screening in children with alopecia areata. This study investigated thyroid function in patients with alopecia areata in order to establish guidelines for screening.

Two hundred and ninety-eight patients seen at the Children's Hospital of Philadelphia between January 2008 and January 2016 were studied. They received clinical diagnosis of alopecia areata and had thyroid function screening. Patterns of alopecia areata were as follows: patchy (201 [68%]), ophiasis (39[13%]), totalis (28[9%]), and universalis (30[10%]). The severity of alopecia areata was graded according to percentage of hair loss on the scalp and were as follows: mild (30.2%), moderate (32.9%), and severe (36.9%).

There were 59 patients with abnormalities of thyroid function of which 29 patients had hypothyroidism, with Hashimoto thyroiditis being the most common cause. The other abnormalities were hyperthyroidism secondary to Grave's disease and subclinical thyroid dysfunction.

Age at diagnosis, duration of disease, pattern of alopecia, and diagnosis of autoimmune diseases had no significant association with abnormal thyroid findings. A personal medical history of Down's syndrome (P=0.004), atopy (P=0.009), and family medical history of thyroid disease (P=0.001) were significantly associated with thyroid abnormalities.

The authors suggested that thyroid function screening should be restricted to alopecia areata patients with a personal history of Down's syndrome, personal history of atopy, a family medical history of thyroid disease, or clinical findings suggestive of potential thyroid dysfunction in the individual patient.

Efficacy and safety of ustekinumab in Japanese patients with severe atopic dermatitis: a randomized, double-blind, placebo-controlled, phase II study

Saeki H, Kabashima K, Tokura Y, Murata Y, Shiraishi A, Tamamura R, et al.
Br J Dermatol 2017;177:419-27.

The pathogenesis of atopic dermatitis (AD) involves T helper (Th1/Th2/Th17) cell-mediated immune response and interleukin (IL) 12/23. Interleukin 12 stimulates differentiation of Th1 cells and IL 23 stimulates proliferation and survival of Th17 cells which produce various inflammatory cytokines. Ustekinumab is a human monoclonal antibody against interleukin 12, 23. It may be used for treatment of AD. This study was a randomised, double blind placebo-controlled study for 95 Japanese patients (age 20-65 years) with severe or very severe AD. Patients with AD received treatment of ustekinumab 45 mg, 90 mg or placebo subcutaneous injections at weeks 0 and 4. Patients were followed up for 24 weeks.

Mean change from baseline Eczema Area & Severity Index (EASI) score at week 12 for ustekinumab group (45 mg), ustekinumab group (90 mg), placebo group were -38.2% (P<0.94) and -39.8% (P<0.81) and -37.5% respectively. However, the differences were not statistically significant. Mean percentage improvement from baseline in EASI for ustekinumab 90 mg group and placebo group were 46% and 36% respectively at week 24 but result was not statistically significant. Improvement of other secondary endpoints (Investigator's Global Assessment score, change from baseline Atopic Dermatitis Itch Scale, Dermatology Life Quality Index and proportion of patients achieving EASI 50/75) in both ustekinumab groups over placebo group were not statistically significant. Adverse effects of ustekinumab included nasopharyngitis (commonest), mild erysipelas, worsened AD. There was no report of injection site reactions nor severe side effects (e.g. new malignancy, tuberculosis and deaths). In conclusion, ustekinumab (45 mg or 90 mg) is safe but did not show therapeutic benefits over placebo among Japanese patients with severe AD.

Open-label study of etanercept treatment in patients with moderate-to-severe plaque psoriasis who lost a satisfactory response to adalimumab

Bagel J, Tyring S, Rice KC, Collier DH, Kricorian G, Chung J, et al.
Br J Dermatol 2017;177:411-8.

Tumour necrosis factor (TNF) inhibitor (adalimumab and etanercept) are commonly used in the treatment of moderate to severe plaque psoriasis. However, anti-adalimumab antibodies (ADAs) may develop and response to adalimumab treatment lost with time. This study investigated the treatment response to another TNF inhibitor (etanercept) for patients with moderate to severe plaque psoriasis after secondary failure to adalimumab treatment. Etanercept 50 mg was given twice weekly for 12 weeks, followed by 50 mg weekly for 12 weeks to patients with psoriasis who developed secondary failure of adalimumab. Of the 64 patients recruited, ADAs were found in 67%. There was an improvement in static Physician's Global Assessment (sPGA) of clear/almost clear (39.7% at week 12), rate of Psoriasis Area and Severity Index (PASI) 75 response (47.5% for ADAs positive group, 50% for ADAs negative group) and patient-reported outcomes of itch, pain, flaking. Efficacy was maintained for 24 weeks and was not affected by the presence of ADAs. Adverse effects of etanercept include cough, vitamin D deficiency, ischaemic colitis and diverticulitis. No new safety concerns were found. In conclusion, etanercept treatment had a satisfactory clinical response for patients with moderate to severe plaque psoriasis after secondary failure to adalimumab therapy.

Meta-analysis of the efficacy of moxifloxacin in treating *Mycoplasma genitalium* infection

Li Y, Le WJ, Li S, Cao YP, Su XH.
Int J STD AIDS 2017;28:1106-14.

The prevalence of *Mycoplasma genitalium* (MG) in non-gonococcal urethritis (NGU) was ranges from 6% to 50%, and varies between different areas. It is an important pathogen that is transmitted through sexual contact. Doxycycline 100 mg twice daily for seven days or azithromycin 500 mg stat then 250 mg for next four days are the first line regimens for MG treatment. However, there have increasing reports of treatment failure with doxycycline or azithromycin in MG. Therefore this meta-analysis aimed to estimate the treatment efficacy of moxifloxacin, the second-line treatment for MG in NGU.

The electronic databases including PubMed, Embase, Medline, Cochrane Central Register for Controlled Trials and Google Scholar were

searched. The articles included were published between 1980 and 2016 with confirmed microbiological cure within 12 months after treatment. Those with inconsistent data, case reports or reviews were excluded.

A total of 17 articles including 252 participants were included. The microbial cure rate was 96% (95% confident interval [CI], 90%-99%). There was no difference between 7-day therapy and 10-day therapy and also no difference was identified in whether moxifloxacin was used as first line treatment or used after failure of doxycycline or azithromycin. Analysis found the microbial cure was 100% if the study collected the sample prior 2010. However, there was a significant decrease with the microbial cure was dropping to only 89% in the studies in 2010 or later. The authors concluded that this decline in microbial cure rate is cause for concern as it implies the development of resistance.

Self-collected glans/meatal 'dry' swab specimen and NAAT technology detects *Chlamydia trachomatis* and *Neisseria gonorrhoeae* - implications for public policy changes

Ferrero DV, Meyers HN, Ferrero GM, Schultz DE.
Int J STD AIDS; 2017;28:985-90.

Chlamydia trachomatis (CT) and *Neisseria gonorrhoeae* (NG) NAAT technology is commonly used in the diagnosis of sexually transmitted infections (STI). First-catch urine (FCU) or clinician-collected swabs (CCS) are the traditional ways for specimen taking. This study was a head-to head comparison of the effectiveness of non-invasive self-collected glans/meatal dry swab (SCS) specimens in detecting CT and NG as compared to traditional CCS and FCU specimens.

Enrolled patients were instructed to first collect a glans/meatal specimen and then a FCU. Finally, the patients were seen by clinicians for assessment and a urethral swab was collected as the CCS. Those had been treated with antibiotics for whatever reason within 21 days or those who had urinated within one hour before specimen collection were excluded. The sensitivity and specificity were based on an infected patient status of any two or more results being considered true results where at least one or both of the two FDA-cleared specimen types (FCU and CCS) had the same result as the SCS.

A total of 284 male patients were enrolled and 5.63% (16/284) were asymptomatic. The overall CT prevalence was 11.97% (34/284) and 5.98% (17/284) for NG. The sensitivity of the SCS for CT was 91.1% and the specificity was 99.2%. The sensitivity of the SCS for NG was 99.6% and the specificity was 99.6%. The overall agreement of SCS with CCS specimens was 97.7% and 90.4% with FCU specimens.

The authors concluded that dry glans/meatal swab specimens were easy to collect, non-invasive and viable specimen choice in diagnosis of CT and NG STI.

Efficacy and safety of ixekizumab for the treatment of moderate-to-severe plaque psoriasis: Results through 108 weeks of a randomized, controlled phase 3 clinical trial (UNCOVER-3)

Blauvelt A, Gooderham M, Iversen L, Ball S, Zhang L, Agada NO, et al.
J Am Acad Dermatol 2017;77:855-62.

Psoriasis is a chronic immune-mediated dermatological condition and there has been accumulating evidence for the key role of IL-17A in its pathogenesis. Ixekizumab, a highly-selected monoclonal antibody targeted IL-17A, had been shown in previous randomised controlled studies (RCT) to be effective in moderate-to-severe psoriasis. However, its long-term efficacy and safety are still uncertain. In this RCT, the authors aimed at evaluating its efficacy through 108 weeks treatment.

Patients with moderated-to-severe psoriasis were randomised to receiving subcutaneous ixekizumab injection 80 mg every two or four weeks following an initial dose of ixekizumab 160 mg; etanercept 50 mg twice weekly or placebo during a 12-week induction period at a ratio of 2:2:2:1. Afterwards, all patients switched to ixekizumab 80 mg every four weeks during a long-term extension (LTE) phase, and a dose of ixekizumab 160 mg was given to the placebo group at week 12. At 60 weeks, patients were allowed to increase dosage to 80 mg every two weeks. Efficacy was determined by the percentage of patients achieving 75%, 90%, or 100% improvement from baseline in the Psoriasis Area and Severity Index (PASI 75/90/100). Also, scalp, nail and palmoplantar involvement were also evaluated using Psoriasis Scalp Severity Index (PSSI), the Nail Psoriasis Severity Index (NAPSI) and Palmoplantar Psoriasis Area and Severity Index (PPASI) and percentage of complete clearance or score 0 were assessed. Efficacy data were summarised in three ways:as-observed, multiple imputation (MI, missing data were imputed to estimate what observations would have been if the patient had not discontinued) and modified MI(mMI, where missing data due to discontinuation secondary to side effects or efficacy were regarded as non-responder).

A total of 1346 patients were randomised and 79.3% completed the 108-week assessment. Around 385 cases received ixekizumab 80 mg bi-weekly injection. The respective as-observed, MI, and mMI response rates at week 108 were 93.4%, 88.3%, and 83.6% for PASI-75, 79.7%, 73.7% and 70.3% for PASI-90 and around 50% of these three categories achieved PASI-100. Moreover, clearance in nail, scalp and palmoplantar involvement were also observed in 60-80% patients receiving ixekizumab. Only 4% of patients required dosage escalation at week 60. Around 85% of patients complained some form of adverse events during the LTE, and most of them were mild or moderate including nasopharyngitis, upper respiratory tract infection and injection site reaction and 6.4% discontinued treatment due to side effects. Particular side effects related to IL-17A such as candida, inflammatory bowel disease, cardiovascular disease and tumorigenesis were infrequent.

It was concluded that ixekizumab is an effective and well-tolerated agent against moderate to severe psoriasis. However, due to the open nature at week 12, head-to-head comparison between different agents and placebo could not be evaluated.

Risk of malignancy with systemic psoriasis treatment in the Psoriasis Longitudinal Assessment Registry

Fiorentino D, Ho V, Lebwohl MG, Leite L, Hopkins L, Galindo C, et al.
J Am Acad Dermatol 2017;77:845-54.

Psoriasis is a chronic inflammatory dermatological condition. Previous observational studies showed an increased incidence of malignancies and non-melanoma skin cancer (NMSC) among psoriatic patients. However, conflicting results were seen in clinical trials of biologics and long-term results from rheumatoid arthritis and inflammatory bowel disease. In this large-scale, disease-based Psoriasis Longitudinal Assessment and Registry (PSOLAR), the authors aimed at evaluating the impact of conventional treatment and biologics on cancer risk among psoriatic patients.

This was a nested case-control study. Patients with newly diagnosed malignancies other than NMSC were identified and four randomly chosen controls were matched with each case by age, sex, geographic region and date of enrolment. Exposure was defined as one or more doses of study drugs received within one year of malignancy being identified and they were stratified according to the duration of treatment received (i.e. under three months, three months to one year, and over one year). Exposures to multiple agents were allowed.

Among 12,090 patients in the PSOLAR, 252 new malignancies were found. Breast, prostate, lung, melanoma and lymphomas were the top five malignancies. Treatment with methotrexate and ustekinumab were not associated with increased malignancies for all treatment durations. On the other hand, TNF-α inhibitors, in particular etanercept and adalimumab, for more than 12 months were shown to statistically increase malignancy risk (OR, 1.54; 95% CI, 1.10-2.15; p=0.01). However, on further sensitivity analysis to adjust for the effect of multiple exposures, the results were conflicting. Further studies with a larger number of malignancy cases, longer follow-up and mutually exclusive groups are needed to better delineate the malignancy risk of individual agents.

In conclusion, the use of methotrexate and ustekinumab did not show to increase malignancy risk in psoriatic patients. However, long-term use of TNF-α inhibitors may pose a danger. However, there were several limitations. The exposure was not randomised which may have allowed bias, multiple exposures were allowed, making it difficult to determine the effect of individual agents and information for various known risk factors of malignancy were not recorded in this registry which may be possible confounders.