Hong Kong J. Dermatol. Venereol. (2018) **26**, 202-206

Journal Watch

Reviewed by CW Chow 周志榮, CC Koh 許招財, CK Kwan 關志強, AWH Leung 梁衛紅

Association of bullous pemphigoid with dipeptidyl-peptidase 4 inhibitors in patients with diabetes estimating the risk of the new agents and characterizing the patients

Kridin K, Bergman R.
JAMA Dermatol 2018;154:1152-8.

The objectives of this retrospective case-control study were to estimate the association between DPP-4 inhibitor exposure and the development of BP, and to characterise the clinical features and history of patients with DPP-4 inhibitor-associated BP. Overall 82 patients with diabetes and BP were compared with 328 age-, sex-, and ethnicity-matched controls with diabetes but without BP. Patients with diabetes and BP and exposure to DPP-4 inhibitors were followed up for a median of two years and compared with other patients with diabetes and BP who were not exposed to DPP-4 inhibitors.

The mean age at presentation was 79.1 (SD 9.1) years of which 44 patients were female (53.7%). Thirty-six (44%) case patients with BP were treated with DPP-4 inhibitor at the onset of BP and the use of DPP-4 was associated with the development of BP in multivariate logistic regression analysis (adjusted OR, 3.16; 95% CI, 1.86-5.37). For vildagliptin and linagliptin, the adjusted ORs were 10.67 (95% CI, 5.09-22.36) and 6.65 (95% CI, 2.24-19.72) respectively. The strongest association was observed in patients younger than 70 years (OR, 5.59; 95% CI, 1.73-18.01). There was a stronger association in male (OR, 4.46; 95% CI, 2.11-9.40) compared to female patients (OR, 1.88; 95% CI, 0.92-3.86).

There was a higher rate of mucosal involvement in patients exposed to DPP-4 inhibitor (22.2% vs 6.5%; P=0.04). Patients with BP who were not exposed to DPP-4 inhibitor had significantly higher mean (SD) circulating eosinophil counts (1117.6 [1847.6] vs 399.8 [508.0] cells/μL; P=0.01) and greater prevalence of peripheral eosinophilia (55.6% vs 22.2%; P=0.002). The median latency between the initiation of DPP-4 inhibitor use and the onset of BP was 10.4 months (range, 1.0-26.5 months). Withdrawal of DPP-4 inhibitor treatment led to clinical improvement.

The authors concluded that DPP-4 inhibitors increased the risk of BP significantly and that withdrawal of DPP-4 inhibitors in patients with diabetes should be considered if BP is diagnosed.

Risk factors for dupilumab-associated conjunctivitis in patients with atopic dermatitis

Treister AD, Kraff-Cooper C, Lio PA.
JAMA Dermatol 2018;154:1208-11.

This case series studied the characteristics of atopic dermatitis patients who developed conjunctivitis secondary to dupilumab treatment. Twelve cases of conjunctivitis were diagnosed in a cohort of 142 patients with atopic dermatitis treated with a 600-mg loading dose followed by bi-weekly 300-mg injections of dupilumab during a one-year study period. Primary outcome measures were severity of atopic dermatitis by the Investigator Global Assessment (IGA) score, (as a 5-point scale: 0 (clear) to 4 (severe)), at the time of dupilumab initiation and at conjunctivitis onset.

There were 12 patients of which 7 were male. The mean age of patients was 30 (SD 8.1) years at the time of development of conjunctivitis. Of 12 patients in whom conjunctivitis developed during dupilumab treatment, 9 had severe atopic dermatitis at baseline (IGA score, 4) and three had moderate atopic dermatitis (IGA score: 3). The mean time from treatment initiation to the development of conjunctivitis was 15.8 weeks (SD 9.4). There was an improvement of atopic dermatitis in all cases by the time of onset of conjunctivitis, (mean 1.9 (SD 0.8) point decrease in IGA score and 47.8% (11.2%) decrease in affected body surface area.

In this series, one patient temporarily discontinued and two patients permanently discontinued dupilumab therapy due to severe conjunctivitis. All three patients had severe baseline atopic dermatitis and at least one atopic condition in addition to atopic dermatitis.

The authors concluded the development of conjunctivitis may require the cessation of dupilumab. Cases of severe atopic dermatitis and atopy responding to duplimab were at higher risk of developing severe conjunctivitis. When stratifying the risk for conjunctivitis development due to dupilumab, baseline atopic dermatitis severity and history of atopic conditions should be considered.

Characteristics associated with lack of HIV testing during pregnancy and delivery in 36 U.S. states, 2004-2013

Koumans EH, Harrison A, House LD, Burley K, Ruffo N, Smith R, et al.
Int J STD AIDS 2018;29:1225-33.

Although HIV transmission in the U.S. remains a public health concern, HIV transmission from mother to child during pregnancy, delivery or postpartum is rare now because of the early detection and advancement of the combined anti-retroviral therapy (cART). The aim of this study was to use Pregnancy Risk Assessment Monitoring System (PRAMS) data from 36 U.S states and New York City from 2004 to 2013. There were 387,424 pregnancies during the study period and the response rate was 86%.

Seventy five point two percent (95% CI 75.0-75.5) of women with a recent live birth reported receiving HIV test during pregnancy or at delivery. The prevalence of HIV testing varied from 42.6% (95% CI 41.7-43.5) in Utah to 91.8% (95% CI 91.0-92.6) in New York City (NY). The national prevalence of HIV testing by year ranged from 71.9% (95% CI 71.2-72.7) in 2013 to 77.5% (95% CI 76.8-87.1) in 2015. Women who were either married, non-Hispanic, non-smoking during pregnancy, white, multiparous, or did not have Medicaid or Special Supplemental Nutritional Programme for Women, Infants and Children were less likely to have had HIV testing during pregnancy or at delivery. The following characteristics were associated with a lower rate of HIV testing: married, white, non-Hispanic and multiparous and these were 23% less like to have HIV test during pregnancy or at delivery. The authors concluded that the overall HIV testing rate was less than 80% and that HIV testing during pregnancy or at delivery can be enhanced, especially for certain groups.

Molecular screening for *Neisseria gonorrhoeae* antimicrobial resistance markers in Nigerian men who have sex with men and transgender women

Hardick J, Crowell TA, Lombardi K, Akintunde A, Odeyemi S, Ivo A, et al.
Int J STD AIDS 2018;29:1273-81.

Neisseria gonorrhoeae (NG) is a common bacterial sexually transmitted infection (STI) of which antimicrobial resistance (AMR) is now a global public health threat. Traditionally, AMR of NG is determined by using the agar plate dilution method to identify the minimal inhibitory concentration (MIC) of certain antibiotics. However, this method requires viable organisms, special NG culture medium, expertise and is expensive. Nowadays, nucleic acid amplification test (NAAT) is becoming more popular not only for identifying the organism but also for identifying the mutation gene makers associated with AMR. The aim of this study was to determine the prevalence AMR markers for penicillinase producing NG (PPNG), quinolone (Gyr A and Par C mutations) and extended spectrum of cephalosporins (ESC) (Pen A mosaic, Pon A, mtrR, PorB mutations).

There were 243 NG samples of urine, oral and rectal swabs collected from of Nigerian men who have sex with men and transgender women. Overall, 75% (183/243) were positive for NG DNA of which 93% (171/183) were positive for at least one of these resistance mutation markers. 46.2% (79/171) had dual resistance to penicillin and quinolones and 6% (10/171) of samples had the marker for ESC. The authors concluded that there was a need for continuous and consistent monitoring for NG AMR and molecular methods. Although these methods are not phenotypic, they provide a rapid, practical, accurate and affordable means of monitoring NG AMR.

Intravenous immunoglobulin is an effective treatment for refractory cutaneous dermatomyositis

Galimberti F, Kooistra L, Li Y, Chatterjee S, Fernandez AP.
Clin Exp Dermatol 2018;43:906-12.

Cutaneous dermatomyositis (DM) is a disease that is known to be refractory to multiple systemic agents. Previous studies have focused on the role of intravenous immunoglobulin (IVIG) on muscle rather than cutaneous manifestations. This study was a retrospective review of 42 patients in a United States tertiary care centre treated with IVIG for the condition. IVIG was given at a dose of 2 g/kg monthly. There were 15 patients with refractory cutaneous DM and 27 patients with refractory cutaneous and muscle/lung disease who had received various combination regimens of systemic therapies prior to IVIG. Methotrexate used alone or in combination had failed to control the disease in 64.3% of cases. Improvement in cutaneous DM was observed after a mean of 1.82+/- 1.38 IVIG cycles in 35/42 patients (83%) (in 13/15 patients (87%) with cutaneous disease only; in 22/27 (81%) with skin disease and/or refractory myositis and/or interstitial lung disease).

None of the factors studied was found to be statistically significant clinical predictors of response. These included age, sex, smoking status, DM subtype, reason for IVIG treatment, duration from DM diagnosis to IVIG treatment, specific cutaneous DM manifestations, medications prior to IVIG treatment, or serological manifestations. IVIG enabled a reduction in dose systemic steroid with or without a decrease in immunosuppressive medication in 80% of patients studied.

It was concluded that IVIG therapy is effective in patients with cutaneous dermatomyositis, regardless of DM subtype.

Oral ulcers as a presentation of secondary syphilis

Thakrar P, Aclimandos W, Goldmeier D, Setterfield JF.
Clin Exp Dermatol 2018;43:868-75.

There has been a recent increase in the number of syphilis cases reported in the Western population, in particular in relation to infections in men who have sex with men (MSM). The British Association for Sexual Health and HIV classifies primary, secondary and early latent phases of syphilis as early-stage syphilis; and late latent or tertiary syphilis as late-stage syphilis.

The article describes two cases of syphilis whereby oral ulceration presented as the primary symptom, and who were later diagnosed as secondary syphilis. Case 1 was a middle-aged man who presented with a two-month history of persistent oral, genital and facial skin lesions. His VDRL was negative and later RPR titre was found to be raised at 1:64 and TPHA positive, thereby confirming syphilis infection. The second case was a middle-aged man with a 3-month history of persistent sore throat despite oral antibiotics and antifungal. A raised RPR of 1:128 and positive TPPA confirmed syphilis infection.

Oral manifestations include ulceration or pseudomembranous lesions including mucous patches, keratosis, plaques or less commonly gummata. The differential diagnoses of oral mucosal lesions in suspected syphilis include atypical aphthae, bacterial infection, fungal infection, granulomatous inflammation, autoimmune bullous diseases, squamous cell carcinoma, traumatic ulceration, drug-related manifestations and bullous or ulcerative lichen planus.

Other ocular signs associated with syphilis could also be looked for e.g. Optic neuropathy, interstitial keratitis and retinal involvement. In 1-2% of secondary syphilis patients, there may also be neurological symptoms such as acute meningitis and cranial nerve palsies.

It was concluded that it is important to include secondary syphilis as a differential diagnosis of oral ulcers. A full sexual history and examination for other clinical signs will aid in the diagnosis.

Safety of tildrakizumab for moderate-to-severe plaque psoriasis: pooled analysis of three randomized controlled trials

Blauvelt A, Reich K, Papp KA, Kimball AB, Gooderham M, Tyring SK, et al.
Br J Dermatol 2018;179:615-22.

Psoriasis may have a significant impact on patient's quality of life. Tildrakizumab is a humanised IgG1 monoclonal antibody directed against the interleukin-23 pathway of psoriasis. This study investigated the safety and tolerability of tildrakizumab in treatment of moderate-to-severe plaque psoriasis (≥10% body surface area involved) over 64 weeks.

Placebo-controlled trial for treatment of moderate-to-severe plaque psoriasis between tildrakizumab 100 mg, tildrakizumab 200 mg, placebo and etanercept (ETN) were done. Treatment-emergent adverse events (TEAEs) for tildrakizumab 100 mg, tildrakizumab 200 mg, placebo and ETN were 48.2%, 47.9%, 53.8%, and 54% respectively. The most common TEAE in all treatment groups was nasopharyngitis. Candida skin infection was uncommon. No new or worsening events of inflammatory bowel disease or suicide were associated with tildrakizumab treatment. The frequencies of TEAEs (47.9-54%), serious TEAEs (1.4-2.3%), discontinuations due to adverse events (0.6-1.9%), major adverse cardiovascular events (MACEs; 0-0.1%) and severe infections (0-0.3%) were all lower than or comparable with placebo rates. In conclusion, tildrakizumab is safe and showed a showed a comparable safety profile with ETN.

Phase III randomized study of the proposed adalimumab biosimilar GP2017 in psoriasis: impact of multiple switches

Blauvelt A, Lacour JP, Fowler JF, Weinberg JM, Gospodinov D, Schuck E, et al.
Br J Dermatol 2018;179:623-31.

Adalimumab (ref-ADMB) was used in treatment of moderate-to-severe plaque psoriasis and GP2017 is a proposed adalimumab biosimilar. This was a randomized double blinded multicenter study to compare the efficacy, safety and immunogenicity between GP2017 or ref-ADMB in treatment of adult chronic plaque psoriasis over 51 weeks. Subcutaneous 80 mg GP2017 or ref-ADMB at week 0 followed by 40 mg biweekly from week 1 to week 15 was given to treat chronic plaque psoriasis. Patients were re-randomised to switch treatment (n=126) or continue treatment (n=253) at week 17.

A similar efficacy was found between GP2017 (66.8%) or ref-ADMB (65%) group with respect to Psoriasis Area and Severity Index (PASI 75) at week 16. Similar PASI improvement over time was found between GP2017 (-60.7%) or ref-ADMB (-61.5%) group for the switched or continued groups from weeks 17 to 51. Serious adverse events reported included skin eruption, pneumonia, cellulitis, hypersensitivity, and pulmonary tuberculosis. Other side effects included nasopharyngitis, upper respiratory tract infection, and gastrointestinal disorder. However, there was no significant difference in the proportion of reported adverse events and serious adverse events between GP2017 or ref-ADMB group. The proportions of patients developing anti-drug antibody was also similar between GP2017 or ref-ADMB group.

It was concluded that as GP2017 or ref-ADMB were biosimilar, switching between these two did lead to any adverse effect in terms of immunogenicity, efficacy, and safety.