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Welcome to issue 33 of Psoriasis Research Review.

Hyperuricemia appears to be an independent risk factor for psoriatic arthritis according the first study reviewed in this issue. The Japanese study authors suggest that hyperuricemia may increase uric acid crystallisation in and around joints, leading to psoriatic arthritis. Following on, we discover that the incidence of hepatitis B virus reactivation in psoriatic patients is lower than in patients with other immune-mediated diseases receiving TNF inhibitors. Among the other studies included in this issue we cover the topics of adverse events and treatment discontinuation in plaque psoriasis, psoriasis in patients with schizophrenia, HLA-Cw6-positive patients with psoriasis, herpes zoster after tofacitinib, risk of malignancy in biologic-naive paediatric psoriasis and adalimumab versus methotrexate in children and adolescents.

We hope you find the latest issue of Psoriasis Research Review stimulating reading and look forward to any feedback.

Kind Regards,
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Hyperuricemia is an independent risk factor for psoriatic arthritis in psoriatic patients

Authors: Tsuruta N et al.

Summary: This single-centre study from Japan enrolled 331 patients with psoriasis vulgaris to determine which psoriatic patients had the highest risk of developing psoriatic arthritis (PsA). In total, 55 (17%) psoriasis vulgaris patients were diagnosed with PsA, and these patients had higher frequencies of nail lesions (62% vs 29%, p < 0.0001) and hyperuricemia (22% vs 9%, p = 0.01). Logistic regression analysis indicated that nail lesions (OR 5.05; p < 0.0001) and hyperuricemia (OR 4.18; p < 0.01) were independent risk factors for PsA. There was no relationship between PsA and age at onset, sex, BMI, and incidence of diabetes mellitus, dyslipidaemia or hypertension.

Comment: Clinically I have come across a number of patients who have been diagnosed with gout by General Practitioners. Usually these are isolated joint involvement of usually the big toe. Occasionally, also hand and finger lesions, namely dactylitis. Our standard psoriatic male is overweight and will invariably have hyperuricemia. Whether this is really indeed gout or not remains a difficult diagnosis. I consider the viewpoint that this is PsA. Occasionally I come across a patient who has been diagnosed and managed by a medical specialist, particularly a rheumatologist, as gouty arthritis. Trying to tease out what is indeed gout and what is PsA is almost impossible. This is a paper that looks at PsA in Japanese patients. In their cohort of 331 patients, of which 55 had PsA, nail lesions and hyperuricemia were independent risk factors for PsA.

They postulate that hyperuricemia may increase uric acid crystallisation in and around joints, leading to PsA.

Reference: J Dermatol. 2017;July 10 [Epub ahead of print]

Abstract

Hepatitis B reactivation in psoriasis patients treated with anti-TNF agents: prevention and management

Authors: Cannizzaro MV et al

Summary: This study assessed the incidence of hepatitis B virus (HBV) reactivation (HBVR) in chronic HBV carriers, and potential occult carriers, receiving biological therapy for psoriasis and PsA. Based on data from nine studies (HBV during adalimumab, etanercept, golimumab or infliximab), the incidence of HBVR in psoriatic patients was found to be lower than in patients with other immune-mediated diseases receiving TNF inhibitors.

Comment: Thankfully my patient group does not have a lot of HBV; however, you can’t tell which of your Australian born patients have dabbled in high-risk activities either at home or abroad. Equally with an increased number of immigrants from regions where HBV is far more frequent. This issue is something we will all need to be able to handle. This is a review of published manuscripts coming out of Rome that concluded that although anti-TNFs are considered moderate immunosuppressive drugs, the incidence of HBV in psoriatic patients is lower compared to patients affected by other immune-mediated diseases treated with TNF inhibitors. The authors suggest that HBV prophylaxis be reserved for patients who are anti-HB surface or anti-HB core positive with viral loads <2000 IU/mL and who have experienced changes in serum liver enzymes.


Abbreviations used in this issue:

BMI = body mass index; GP = general practitioner;
HBV = hepatitis B virus; HR = hazard ratio;
HZ = herpes zoster; IR = incidence rate;
NS = non-significant; OR = odds ratio;
PASI = Psoriasis Area and Severity Index;
PGA = Physician’s Global Assessment;
PsA = psoriatic arthritis;
TNF = tumour necrosis factor.

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Adverse events associated with discontinuation of the biologics/classic systemic treatments for moderate-to-severe plaque psoriasis: data from the Spanish Biologics Registry, Biobadaderm
Authors: Belinchón I et al.
Summary: This multicentre, prospective, observational, cohort study assessed adverse events associated with systemic therapy discontinuation using data from a registry including 1938 patients with moderate-to-severe plaque psoriasis. Over a total of 4216 treatment courses, 447 (11%) discontinuations occurred because of adverse events, giving an incidence rate of 13 events/100 patient-years (PY; 95% CI 12.1–13.9). The incidence rate for biological therapies was 9.3 events/100 PY (95% CI 8.4–10.3) while for classic systemic therapies it was 19.7 events/100 PY (95% CI 17.9–21.6; p < 0.001). Among 810 discontinuation-related adverse events, 117 (14%) were classified as serious. The highest IRs were for cyclosporine (49.2 events/100 PY; 95% CI 41.9–57.7) and infliximab (26.5 events/100 PY; 95% CI 21.0–33.5), while the lowest was for ustekinumab (2.6/100 PY; 95% CI 1.8–3.7).

Comment: This is a large study looking at 4216 courses of treatment given to 1938 patients. Of these 11% (447) were discontinued due to adverse events. The IR of adverse events associated with discontinuation of systemic therapies was 13 events/patient-years. 9.3 events/100 PY for biologics and 19.7 events/100 PY for classic systemic therapies; 14% of discontinuation-related adverse events were serious. The highest IRs were for cyclosporine and infliximab; ustekinumab presented the lowest rate. The conclusion was that biologic therapies are associated with a lower rate of discontinuation-related adverse events than are the classic systemic therapies in real clinical practice.


Risk of developing psoriasis in patients with schizophrenia: a nationwide retrospective cohort study
Authors: Yu S et al.
Summary: This Taiwanese retrospective cohort study, analysed data from 1 million people enrolled in the National Health Insurance Research Database to determine the risk of psoriasis in people diagnosed with schizophrenia between 1 January 1996 and 31 December 2010. The adjusted HR for schizophrenia-associated psoriasis was 2.32 (95% CI 1.81–2.90), with a 15-year cumulative incidence of psoriasis in schizophrenia patients of 2.82% versus 1.17% in a comparison population. Kaplan–Meier curves for cumulative incidence of psoriasis in schizophrenia patients of 2.82% looking at the clinical modified coding in their database. The HR of psoriasis associated with schizophrenia was 2.32 and the cumulative incidence of psoriasis in patients with schizophrenia was 2.82% versus 1.17% in a comparison population. In conclusion, patients with schizophrenia have a higher risk of psoriasis. This is considered possibly due to genetic susceptibilities and/or immunologic mechanisms in both diseases. T-helper 17 (Th17) signalling and pro-inflammatory cytokines may act as a link between these two diseases. Yet another comorbidity to tell our patients, that they can become schizophrenic.

Comment: This is a large study out of Taiwan. This is a nationwide retrospective cohort study in which 1 million enrollees from the Taiwan’s National Health Insurance Research Database were reviewed. Patients were assessed from the 1st January 1996 through to the 31st December 2010 looking at the clinical modified coding in their database. The HR for psoriasis associated with schizophrenia was 2.32 and the cumulative incidence of psoriasis in patients with schizophrenia was 2.82% versus 1.17% in a comparison population. In conclusion, patients with schizophrenia have a higher risk of psoriasis. This is considered possibly due to genetic susceptibilities and/or immunologic mechanisms in both diseases. T-helper 17 (Th17) signalling and pro-inflammatory cytokines may act as a link between these two diseases. Yet another comorbidity to tell our patients, that they can become schizophrenic.

Reference: J Eur Acad Dermatol Venereol. 2017;May 3 [Epub ahead of print]

HLA-Cw6-positive patients with psoriasis show improved response to methotrexate treatment
Authors: West J et al.
Summary: This Scottish, prospective, cohort study examined whether there was an association between the human leucocyte antigen (HLA)-Cw6 allele and the use of methotrexate as the first-line systemic treatment for psoriasis. Patients positive for HLA-Cw6 had an improved response to methotrexate (p = 0.03), and greater response was identified in a sub-cohort of HLA-Cw6 positive patients without concomitant PsA (p = 0.01). Patient’s positive for HLA-Cw6 also had fewer treatment-limiting adverse events.

Comment: This is a study out of Dundee. The genetics of psoriasis in HLA type genetics is poorly understood. HLA-Cw6 positivity is associated with increased severity and reduced age of onset of psoriasis. This is particularly the antigen found in young women. Not much is known about any differential response of this genetic subgroup to various treatments. A cohort of patients from Tayside in Scotland was recruited and HLA-Cw6 positive patients showed a notably improved response to methotrexate and a greater response in those without concomitant PsA.


Herpes zoster in psoriasis patients treated with tofacitinib
Authors: Winthrop KL et al.
Summary: Data from phase II, phase III and long-term extension trials of tofacitinib were used to assess the relationship between tofacitinib use and risk of herpes zoster (HZ) infection in patients with psoriasis. HZ developed in 130 (3.6%) tofacitinib recipients (IR 2.55 events per 100 patient-years), two etanercept recipients (IR 2.68 events per 100 patient-years) and no placebo recipients. Of these, nine (7%) patients were hospitalised and eight (6%) experienced multi-dermatomal HZ, but no encephalitis, visceral involvement or deaths occurred. Risk factors included Asian descent (HR 2.92), receiving tofacitinib 10 mg twice daily versus 5 mg twice daily (HR 1.72), prior biological therapy (HR 1.72) and older age (HR 1.30).

Comment: Tofacitinib is an oral Janus kinase (JAK) inhibitor. They reviewed phases II and III as well as long-term extension data from the tofacitinib development program in psoriasis. Tofacitinib was associated with increased HZ risk relative to placebo. Asian race, increasing age, higher dose, and prior biologic exposure were associated with heightened risk. No comment regarding the potential ability to vaccinate patients against HZ was made. Potentially this is a therapeutic question we will need to answer.


The risk of malignancy among biologic-naive pediatric psoriasis patients: A retrospective cohort study in a US claims database
Authors: Ou Y et al.
Summary: This US retrospective cohort study compared malignancy risk in biologic-naive paediatric psoriasis (n = 9045) and non-psoriasis (n = 77,206) patients using data from the IMS LifeLink Health Plan Claims database (1998-2008). In total, 18 probable or highly probable cancers occurred and paediatric psoriasis patients did not differ in cancer incidence from the comparison population (HR 0.43; 95% CI 0.05-3.54). HR increased to 1.67 (95% CI 0.54-5.18) if cancer was probable. Paediatric psoriasis patients did not differ in cancer incidence than comparators (HR 0.43; 95% CI 0.05-3.54). The paediatric psoriasis cohort had a higher rate of lymphoma than comparator data from the US Surveillance, Epidemiology, and End Results (SEER) database (standardised IRs 5.42; 95% CI 1.62-12.94), but not compared to the control cohort.

Comment: Any studies on paediatric psoriasis patients should be brought to the dermatology community. They are so rare. This is an extremely esoteric topic and one would expect a small percentage of the paediatric patients to develop a malignancy. This is a study from the US looking at IMS LifeLink Health Plan Claims data covering the years 1998-2008. 9045 paediatric psoriasis patients were compared to 77,206 normal controls. 18 probable or highly probable cancers were identified. Paediatric psoriasis patients had a not significantly lower incidence than comparators (HR 0.43; 95% CI 0.05-3.54). The paediatric psoriasis cohort had a significantly increased lymphoma rate compared with the US SEER data. However there was no significant increase relative to the comparator cohort. The conclusion was that these paediatric psoriasis patients showed no significant increase in overall cancer risk compared with those without psoriasis. There is a potential increased risk for lymphoma when observed compared with the general population.

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*At week 52, PASI 100 responses to secukinumab and ustekinumab were 45.9% and 35.8% respectively ($p=0.0103$). Primary study endpoint was achieved with secukinumab demonstrating superiority in PASI 90 response (79%) to ustekinumab (57.6%; $p<0.0001$) at Week 16.

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New interleukins in psoriasis and psoriatic arthritis patients: the possible roles of interleukin-33 to interleukin-36 in disease activities and bone erosions

Authors: Li J et al.

Summary: This Chinese study examined the effect of new interleukins (ILs), especially the IL-1 and IL-12 families, in patients with psoriasis (n = 20) and PsA (n = 40) and healthy controls (n = 20). Serum levels of TNF-α, IL-12/23p40, and IL-33 were higher in psoriasis and PsA patients, while serum IL-34 and IL-35 levels were higher in PsA patients than in psoriasis patients or healthy controls. Pustular psoriasis patients had higher serum levels of IL-36α and IL-38 than psoriasis vulgaris patients or healthy controls and the elevated serum IL-36α levels correlated positively with Psoriasis Area and Severity Index (PASI) scores.

Comment: This is a study from China. New ILs, especially members of IL-1 and IL-12 families, have recently been reported to be involved in the development and regulation of autoimmune and inflammatory diseases. In this study they were looking particularly at this group. To date we are all aware that there are increased levels of TNF-α, IL-12/23p40, and IL-33. Serum levels of IL-34 and IL-35 were higher in PsA patients than in psoriasis patients and patients with pustular psoriasis had higher serum levels of IL-36α and IL-38 than patients with psoriasis vulgaris or healthy controls. This study was put in for those who are more scientifically minded and interested with the newer developing potential pathways of inflammation in this disease.

Reference: Dermatology 2017;233:37-46

Efficacy and safety of adalimumab every other week versus methotrexate once weekly in children and adolescents with severe chronic plaque psoriasis: a randomised, double-blind, phase 3 trial

Authors: Papp K et al.

Summary: This multinational, randomised, controlled, double-blind, phase III trial assessed the use of adalimumab 0.8 mg/kg (n = 39), adalimumab 0.4 mg/kg (n = 39) or methotrexate (n = 37) in children and adolescents with severe plaque psoriasis. After 16 weeks of treatment, a 75% improvement in PASI 75 score was achieved by 22 (58%) adalimumab 0.8 mg/kg recipients versus 12 (32%) methotrexate recipients (p = 0.027); a clear or minimal physician global assessment (PGA) was achieved by 23 (61%) adalimumab 0.8 mg/kg versus 15 (41%) methotrexate recipients (NS). Among adalimumab 0.4 mg/kg recipients, 17 (44%) achieved PASI 75 and 16 (41%) achieved clear or minimal PGA. The most frequent adverse events were infections, occurring in 45% of adalimumab 0.8 mg/kg, 56% of adalimumab 0.4 mg/kg and 57% of methotrexate recipients.

Comment: A further study in youngsters, hence I have included it. This reports a randomised, double-blind, multiperiod, phase III trial performed at 38 clinics in 13 countries. Patients (aged ≥4 to <18 years) with severe plaque psoriasis who had not responded to topical therapy were randomly assigned to adalimumab or oral methotrexate. The adalimumab dose was 0.8 mg/kg or 0.4 mg/kg subcutaneously every other week. The oral methotrexate dose was 0.1-0.4 mg/kg for 16 weeks. The interpretation was that treatment with adalimumab 0.8 mg/kg in children and adolescents with severe plaque psoriasis provided significant improvements. A non-significant increase in the proportion of patients who achieved clear or minimal PGA compared with methotrexate. One concern I have about this study is that a treatment course of 16 weeks is in my opinion a little short for a methotrexate study.


Tildrakizumab versus placebo or etanercept for chronic plaque psoriasis (reSURFACE 1 and reSURFACE 2): results from two randomised controlled, phase 3 trials

Authors: Reich K et al.

Summary: The multinational three-part, parallel group, double-blind, randomised controlled phase III reSURFACE 1 (n = 772) and reSURFACE 2 (n = 1090) studies examined the use of tildrakizumab compared to placebo and etanercept for the treatment of chronic plaque psoriasis. In reSURFACE 1, after 12 weeks 192 (62%) tildrakizumab 200 mg and 197 (64%) tildrakizumab 100 mg recipients versus nine (6%) placebo recipients achieved PASI 75 (p < 0.001 for tildrakizumab vs placebo). PGA responses (score of 0-1 with ≥2 grade score reduction from baseline) were achieved by 182 (59%) tildrakizumab 200 mg and 179 (58%) tildrakizumab 100 mg recipients versus 11 (7%) placebo recipients (p < 0.001 for tildrakizumab vs placebo). In reSURFACE 2, by week 12 a PASI 75 had been achieved by 206 (66%) tildrakizumab 200 mg, 188 (61%) tildrakizumab 100 mg recipients, nine (6%) placebo, and 151 (48%) etanercept recipients (p < 0.001 for tildrakizumab vs placebo; p < 0.001 for tildrakizumab 200 mg vs etanercept; p = 0.0010 for tildrakizumab 100 mg vs etanercept). A PGA response was achieved by 186 (59%) tildrakizumab 200 mg, 168 (55%) tildrakizumab 100 mg, seven (4%) placebo, and 149 (48%) etanercept recipients (p < 0.001 for tildrakizumab vs placebo; p = 0.0031 for tildrakizumab 200 mg vs etanercept).

Comment: This is one of the newer biologic agents originally developed by Merck, Sharp and Dohme and now under the control of marketing of Sun Pharmaceuticals. They have applied for Australian licensing so this is a drug that we should all become familiar with. This is a review of their two pivotal randomised control phase III trials. Significant patient numbers were involved. Dosing with tildrakizumab 200 mg and 100 mg was assessed. At week 12, 62% of those in the 200 mg group and 64% in the 100 mg group achieved a PASI 75. The placebo group was 6%. 59% of the 200 mg group compared to 58% of the 100 mg group achieved a PGA response of 0-1. Only 7% of the placebo group did. Serious adverse events were similar and low in all groups in both trials. What is interesting about this drug is that it was administered subcutaneously at week 4 in the first study and at 4 and 16 weeks in the second study. Etanercept was given in the standard dose. This is a drug that is a little slow in onset; however, it needs to be administered far less frequently than the more recently released biologics. It will be an agent that we dermatologists will look at seriously. So far there is no PsA data.

Reference: Lancet 2017;390(10091):276-88

Selection of papers and comments are provided by Clinical Associate Professor Kurt Gebauer MBBS, FACD, FACP

Clinical Associate Professor Kurt Gebauer has been practicing dermatology for 20 years in Australia. Dr. Gebauer has a busy private practice located in Fremantle and can also be found lecturing locally and internationally on different medical topics. As a contributing author on many publications, Dr. Gebauer is a well-known authority on dermatological conditions. Along with his dermatology practice Dr. Gebauer also participates in clinical research studies in order to offer new and innovative treatments for dermatological conditions including acne, atopic dermatitis, psoriasis, actinic keratoses, onychomycosis, and skin cancer.