Psoriasis Research Review™

Making Education Easy

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In this issue:

Abbreviations used in this issue:

BMI = body mass index; **BSA** = body surface area;
NMSC = nonmelanoma skin cancer;
PASI = Psoriasis Area and Severity Index;
PGA = Physician's Global Assessment; **PYE** = person-years of exposure;
PYO = person-years of observation ; **SCC** = squamous cell carcinoma;
VEGF = vascular endothelial growth factor.

Welcome to the twenty-fourth issue of Psoriasis Research Review.

It may come as no surprise that psoriasis is significantly associated with major depression. What may be surprising is that the risk of major depression does not appear to differ between patients with limited versus extensive disease. Such are the findings of the large US population-based National Health and Nutrition Examination Survey reviewed first-up in this issue. Following on from this study we look at another study involving a large data set, this time the German Psoriasis Registry PsoBest, from which researchers assessed the drug safety of systemic treatments for psoriasis including conventional and biologic agents. Among other studies included in this issue we look at the efficacy and safety of apremilast, malignancies and hospitalised infections in psoriasis patients, the long-term use of etanercept in children and adolescents, and adverse effects associated with biologics.

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

Kind Regards,

Clinical Associate Professor Kurt Gebauer

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Psoriasis and the risk of depression in the US population: National Health and Nutrition Examination Survey 2009-2012

Authors: Cohen BE et al.

Summary: This analysis of data from the US National Health and Nutrition Examination Survey (2009-12) investigated the relationship between psoriasis and depression. Among 12,382 US citizens, 351 (2.8%) psoriasis cases and 968 (7.8%) major depression cases were observed; 58 (16.5%) psoriasis patients met major depression criteria. The mean Patient Health Questionnaire-9 score was higher among psoriasis patients than those without psoriasis (4.54 vs 3.22; $p < 0.001$). After adjustment for sex, age, race, BMI, physical activity, smoking history, alcohol use, myocardial infarction, stroke and diabetes mellitus, psoriasis remained associated with major depression (OR 2.09; 95% CI 1.41-3.11; $p < 0.001$). The risk of major depression did not differ between patients with limited vs extensive psoriasis (OR 0.66; 95% CI 0.18-2.44).

Comment: This is an important topic considering the investigational agent brodalumab was recently withdrawn from research and marketing because of a perception of heightened depression risk. There is an argument that depression is now more common in America because of the economy in general, particularly affecting certain classes of people i.e. the poorer patients without insurance who are at the bottom of the economic tree that are entered into trials and are without economic means and are at heightened risk of psychological adverse affects. This article assesses patients diagnosed with major depression who have psoriasis. In this study the severity of psoriasis was unrelated to the risk of major depression. A history of cardiovascular events did not modify the risk of major depression. Psoriasis was significantly associated with major depression even after adjustments for sex, age, race, body mass, physical activity, smoking history, alcohol use, myocardial Infarction, stroke and diabetes.

Reference: JAMA Dermatol. 2016;152(1):73-9

Abstract

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.

Drug safety of systemic treatments for psoriasis: results from The German Psoriasis Registry PsoBest

Authors: Reich K et al.

Summary: Using data from the German Psoriasis Registry PsoBest, researchers assessed the use of antipsoriatic drugs in 2444 patients (40 % female; mean age 47.3 years; mean disease duration 18.2 years) with special focus on serious adverse events for infections, malignancies and major cardiac events. Conventional systemic drugs were used by1791 patients (3842 patient years) and biological agents by 908 patients (3442 patient years). Overall serious adverse event rates did not differ between conventional systemic drugs and biologics (1.3 vs 1.5 per 100 patient years; $p > 0.5$). The single severe adverse event rate ratios (per 100 patient years) for conventional systemic/biologics were also nonsignificant (0.33/0.65 for serious infections, 0.56/0.77 for major cardiac events, and 0.46/0.49 for malignancies [except non-melanoma skin cancer]).

Comment: Registry data is really the only way that we can get a longitudinal long-term outcome and safety assessment of systemic treatments. They have their limitations, however, they are one of the very few ways of accessing this information. The overall rate of serious adverse events per 100 patient years was 1.3 with conventional systemics and 1.5 in biologic patients. There was no significant p value here. There were also no significant differences between single drugs in any of the safety parameters.

Reference: Arch Dermatol Res. 2015;307(10):875-83
Abstract

Efficacy and safety of apremilast, an oral phosphodiesterase 4 inhibitor, in patients with moderate-to-severe plaque psoriasis over 52 weeks: a phase III, randomized controlled trial (ESTEEM 2)

Authors: Paul C et al.

Summary: The ESTEEM 2, 52 week double-blind, placebo-controlled phase III trial tested the efficacy and safety of apremilast 30 mg twice daily (n = 274) vs placebo (n = 137) in patients with moderate-to-severe plaque psoriasis. After 16 weeks, more apremilast patients achieved PASI 75 (28·8%), PASI 50 (55·5%) and static Physician's Global Assessment (PGA) scores of 0 or 1 (20·4%) than did placebo recipients (5·8%, 19·7%, and 4·4%, respectively; $p < 0·001$). At week 16, placebo patients were switched to apremilast. Patients achieving ≥ 50% reduction in PASI 50 at week 32 were rerandomised to apremilast and most had a PASI 50 response at week 52 (80%). Apremilast recipients also experienced improvements in quality of life (Dermatology Life Quality Index) and pruritus at week 16 versus placebo ($p < 0·001$). Exposure-adjusted incidence of adverse events was not altered by apremilast treatment for up to 52 weeks.

Comment: Apremilast is a small agent oral tablet that is not formally in Australia yet. It is under consideration for PBS supply. There is a company provided Provider Access Scheme that a number of dermatologists and rheumatologists have enrolled patients in. This article is based on the ESTEEM 2 trial data. The results, specifically at week 16, show significantly more apremilast patients achieved PASI 75, PASI 50 and static PGA score of 0 or 1 than did patients receiving placebo. Most common adverse events were nausea, diarrhoea, nasopharyngitis and upper respiratory tract infection.

Reference: Br J Dermatol. 2015;173(6):1387-99
Abstract

Cohort study of malignancies and hospitalized infectious events in treated and untreated patients with psoriasis and a general population in the United States

Authors: Kimball AB et al.

Summary: This retrospective cohort study analyses data from MarketScan® databases to assess the rates of malignancies and hospitalised infectious events in patients with psoriasis. Incidence rates for all malignancies except nonmelanoma skin cancer (NMSC) were 129 (95% CI 127-130; 51,071,587 person-years observation [PYO]) for the general population and 142 (95% CI 135-149; 119,432 PYO) for psoriasis patients. Lymphoma rates were 10·9 (95% CI 10·5-11·3) and 12·9 (95% CI 10·9-14·8) and NMSC rates were 145 (95% CI 144-147) and 180 (95% CI 173-188). Rates for all malignancies except NMSC did not differ between treatments (nonbiologics, adalimumab, etanercept, infliximab or phototherapy), but were variable for lymphoma and nonmelanoma skin cancer. Incidence rates for hospitalised infectious events were 332 (95% CI 256-408; 3528 person-years of exposure [PYE]) for the nonbiologic cohort, 288 (95% CI 206-370; 6563 PYE) for etanercept, 325 (95% CI 196-455; 2772 PYE) for adalimumab; 521 (95% CI 278-765; 1058 PYE) for infliximab; and 334 (95% CI 242-427, 1797 PYE) for phototherapy. The hospitalised infectious event incidence rates were lowest for etanercept recipients and were higher in patients on systemic corticosteroids across all treatment cohorts.

Comment: The background premise is that psoriasis is associated with risk of malignancy. The objectives of this study were to evaluate rates of malignancy and hospital infectious events in such patients. This is an American study where general population patients, patients with psoriasis and patients on systemic, biologic and phototherapy were compared to each other. Incidence rates for cancer were similar amongst treatment groups with some variability for lymphoma and non-melanoma skin cancers. Incidence rates for hospital infectious events were the lowest for etanercept and higher with those on baseline systemic corticosteroids, however balanced amongst other treatments.

Reference: Br J Dermatol. 2015;173(5):1183-90
Abstract

Long-term safety and efficacy of etanercept in children and adolescents with plaque psoriasis

Authors: Paller AS et al.

Summary: This 5-year, open-label extension study in the US evaluated the long-term safety and efficacy of etanercept in children and adolescents (aged 4-17 years) with moderate-to-severe plaque psoriasis who had participated in a 48-week study. Among 182 patients enrolled, 181 received etanercept, with 69 completing 264 weeks of treatment, during which time 161 (89.0%) reported an adverse event; most commonly upper respiratory tract infection (37.6%), nasopharyngitis (26.0%) and headache (21.5%). Seven patients reported eight serious adverse events, but only one, cellulitis, was considered treatment-related. There were no cases of malignancy or opportunistic infections. PASI 75 and 90 rates of 60-70% and 30-40%, and static PGA status of clear/almost clear rates of 40-50% were maintained throughout week 264.

Comment: Each time I do this report there are now more studies on children and adolescents. Etanercept is approved in Australia for adolescents. This article is a summary of a 5-year open-label extension study. The conclusion was etanercept was generally well tolerated and efficacy was maintained in those who remained in the study for up to 264 weeks, however the numbers at that end point were quite small. The most common adverse events were upper respiratory tract infections, nasopharyngitis and headaches. Seven of the 182 patients enrolled had a serious adverse event, only one, a cellulitis, was considered treatment related. No cases of opportunistic infection or malignancy were recorded. The response rates for psoriasis were good. An interesting study for those who treat this group.

Reference: J Am Acad Dermatol. 2016;74(2):280-87
Abstract

Evidence-based adverse effects of biologic agents in the treatment of moderate-to-severe psoriasis: Providing clarity to an opaque topic

Authors: Sorenson E and Koo J

Summary: This review of data from 17 clinical trials, two open-label extension studies and eight meta-analyses reporting statistical analysis of adverse events associated with the use of etanercept, adlimumab and ustekinumab for the treatment of moderate-to-severe plaque psoriasis found the rates of the following to be significantly increased; squamous cell carcinoma (SCC), injection-site reaction, and headache associated with etanercept, and overall NMSC, SCC, and upper respiratory tract infection associated with adalimumab. However, there was no significantly increased adverse event rate associated with ustekinumab.

Comment: The background of this study was that previous reviews of the safety of biologic agents included patients with conditions other than psoriasis. The authors claim that this report is a more focused review of current literature dealing only with biologics used for the treatment of moderate-to-severe plaque psoriasis. The results conclude that adverse events were reported to be significantly increased including SCC, injection site reactions and headaches associated with etanercept. Overall, more NMSC, SCC and upper respiratory tract infections were associated with adalimumab and there was no significant increase in adverse events associated with ustekinumab. However, in the conclusion it suggests that few adverse events in the biologic agents have reached statistical significance and further studies should be performed. I read nothing in this review that would alter prescribing habits.

Reference: J Dermatolog Treat. 2015;26(6):493-501
Abstract

Psoriasis patients' willingness to accept side-effect risks for improved treatment efficacy

Authors: Kauf TL et al.

Summary: The risks psoriasis patients are willing to accept for improvements in their symptoms was assessed in this study involving adults (n = 1608) with a self-reported physician diagnosis of psoriasis, recruited through the National Psoriasis Foundation. Patients completed a series of nine choice questions, each including a pair of hypothetical treatments with treatments defined by severity of plaques, body surface area (BSA), and 10-year risks of tuberculosis, lymphoma and serious infection. Overall, for complete clearance of mild plaques with a BSA of 25%, respondents were willing to accept a 20% (95% CI 9-26%) risk of serious infection, a 10% (95% CI 5-15%) risk of tuberculosis and a 2% (95% CI 1-3%) risk of lymphoma. For complete clearance of severe plaques with a BSA of 25%, respondents were willing to accept a 54% (95% CI 48-62%) risk of serious infection, a 36% (95% CI 28-49%) risk of tuberculosis and an 8% (95% CI 7-9%) risk of lymphoma.

Comment: The title of this caught my eye as now we have newer agents with high response rates, but how the general public will behave is yet to become apparent. Previous studies suggest that efficacy is more important than side effect risk profile for psoriasis patients. It claims that these studies did not consider potentially fatal risks of biologic treatments. Psoriasis patients recruited through the National Psoriasis Foundation were asked to complete a questionnaire which contained hypothetical scenarios. The conclusion was that patients were willing to accept risks above likely clinical exposures for improvements in psoriasis symptoms. How this works out for patients who do get a side effect is not clear to me.

Reference: J Dermatolog Treat. 2015;26(6):507-13
Abstract

Calcipotriol/betamethasone for the treatment of psoriasis: efficacy, safety, and patient acceptability

Author: Rogalski C

Summary: These authors reviewed the efficacy, safety and acceptability of the fixed-dose combination calcipotriol/betamethasone for mild-to-moderate psoriasis of the body and scalp, by undertaking a literature search for all relevant articles comparing the fixed-dose combination with the individual components, published before February 2015. Among 70 suitable studies, there was a significantly higher proportion of patients whose psoriasis improved in the two-compound group compared with the group treated with the individual components. The fixed dose combination was also generally associated with a lower risk of adverse events and led to a significant improvement in quality of life.

Comment: When this medication first came on the market there was some discussion locally from senior dermatologists about the safety of long-term betamethasone in this combination therapy. This is a literature search of all articles regarding this medication class. In their results section, 70 references were reviewed. The authors state the fixed combination was generally associated with lower risk of adverse events. The fixed combination lead to a significant improvement in the quality of life. The two compound product was more convenient to handle and time saving compared to former treatments.

Reference: Dove Medical Press Ltd. 2015;5:97-107
Abstract

Subcutaneous methotrexate for symptomatic control of severe recalcitrant psoriasis: safety, efficacy, and patient acceptability

Authors: Manalo IF et al.

Summary: This literature review investigated the safety, efficacy and patient acceptability of subcutaneous methotrexate for severe recalcitrant psoriasis. A search of PubMed, Ovid and ClinicalTrials.gov databases identified only three relevant studies, with only one (an unpublished study) directly investigating the use of subcutaneous methotrexate in psoriasis patients. Due to the paucity of original evidence-based studies evaluating the use of subcutaneous methotrexate specifically for the treatment of psoriasis, the authors point to the more extensively researched data on subcutaneous methotrexate in rheumatoid arthritis patients and conclude that this data suggests that its application for the treatment of moderate-to-severe psoriasis is promising. More evidence-based studies on the subcutaneous use of this agent in psoriasis are warranted.

Comment: Having worked in England, I got used to using injected methotrexate rather than oral therapy. It was rare for my unit in Derby, UK to use oral methotrexate therapy at all. Patients presented routinely for their injections at the Clinic. This is a study of literature searches. Only three relevant papers were found. As such there was a lack of original evidence-based information evaluating the use of subcutaneous methotrexate specifically for the treatment of psoriasis. The authors recommend that we use the reviews of methotrexate in rheumatoid arthritis as our evidence base.

Reference: Dove Medical Press Ltd. 2015;5:65-70
Abstract

Clinical symptoms and self-reported disease severity among patients with psoriasis - Implications for psoriasis management

Authors: Korman NJ et al.

Summary/comment: Interestingly, patients complain of pain, itching, burning and irritation most commonly. Our training would suggest that it is the visual aspects of psoriasis that are the most concerning and distressing to patients, however, when surveyed this is not the case. This paper actually uses syndicated patients survey data of 1050 subjects classified into mild (610) or moderate-to-severe psoriasis (440). The presence and level of particular symptoms increases with self-reported disease severity in patients with psoriasis. Of the moderate-to-severe patients, 35% reported severe pain between, and 68% during, flare ups, and over 79% reported frequent bothersome itching. After controlling for between-group differences, patients with moderate-to-severe psoriasis exhibited worse pain, reported more bothersome symptoms, were more likely to have continual flare-ups (OR 3.0), and flare-ups more than once monthly (OR 3.0) than those with mild disease (all $p < 0.05$).

Reference: J Dermatolog Treat. 2015:26(6):514-9
Abstract

Correlation between vascular endothelial growth factor and subclinical atherosclerosis in patients with psoriasis

Authors: Shahidi-Dadras M et al.

Summary/comment: Most of the pages in this series were of a clinical nature and I was looking for something for the scientists amongst us. This time around scientific papers were scarce. This is a paper out of Iran looking at why psoriasis is associated with increased risk of atherosclerotic disorders. 60 patients with moderate-to-severe psoriasis were compared against age- and gender-matched controls. Serum vascular endothelial growth factor (VEGF) levels were significantly ($p < 0.0001$) higher in the psoriatic patients. Mean intima-media thickness of the common carotid artery was also significantly ($p < 0.0001$) greater in psoriatic patients. 45% of the patients and 6.7% of the healthy controls had sub-clinical atherosclerosis.

Reference: Int J Dermatol. 2016;55(1):52-9
Abstract

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