Psoriasis Research Review™

Making Education Easy

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In this issue:

Abbreviations used in this issue:

DLQI = Dermatology Life Quality Index;
HADS = Hospital Anxiety and Depression Scale; **HR** = hazard ratio;
JAK = Janus kinase; **MACE** = major adverse cardiac events;
OR = odds ratio; **PASI** = Psoriasis Area and Severity Index;
PGA = Physician's Global Assessment;
PPPGA = Palmoplantar Psoriasis Physician Global Assessment;
PSI = Psoriasis Symptom Inventory; **SF-36** = Short Form (36) Health Survey;
TAPSE = tricuspid annular plane systolic excursion;
TNF = tumour necrosis factor.

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

We begin this issue with a detailed study on ixekizumab, a well-received biologic for moderate-to-severe plaque psoriasis. We then take a look at another biologic for this condition, baricitinib, an oral Janus kinase (JAK) 1/JAK2 inhibitor. Also in this issue we investigate another new JAK inhibitor for chronic plaque psoriasis, psoriasis and adverse pregnancy outcomes, the influence of family history on MACE in young adults with psoriasis, the clinical meaningfulness of complete skin clearance in psoriasis, apremilast efficacy and safety in palmoplantar psoriasis, anxiety and depression in Singaporean psoriasis patients, biologic drug survival in a large psoriasis registry and TNF-α inhibitor therapy and improvement in cardiovascular disease.

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

kurt.gebauer@researchreview.com.au

Phase 3 trials of ixekizumab in moderate-to-severe plaque psoriasis

Authors: Gordon KB et al.

Summary: This paper reports 60-week data from the randomised, placebo- and active-comparator- (etanercept 50 mg twice weekly) controlled phase III UNCOVER-1 (n = 1296), UNCOVER-2 (n = 1224) and UNCOVER-3 (n = 1346) trials of the interleukin-17A monoclonal antibody ixekizumab (starting dose 160 mg; maintenance dose 80 mg every 2 weeks [2-wk group], or 80 mg every 4 weeks [4-wk group]) in patients with moderate-to-severe psoriasis. At week 12, patients entered a long-term extension receiving ixekizumab 80 mg every 4 weeks (UNCOVER-3); or responding patients (static [s] PGA score of 0 [clear] or 1 [minimal psoriasis]) were re-randomised to placebo or ixekizumab 80 mg every 4 or 12 weeks (UNCOVER-1; UNCOVER-2) through week 60. At week 12, ixekizumab recipients had better responses than placebo recipients (UNCOVER-1); 81.8% of the 2-wk group had an sPGA score of 0 or 1 while a PASI 75 response occurred in 89.1%. 76.4% of the 4-wk dosing group had an sPGA score of 0 or 1 while the PASI 75 response rate was 82.6%. Placebo rates were 3.2% and 3.9% ($p < 0.001$ for all comparisons). In patients receiving ixekizumab 80 mg every 4 weeks or 12 weeks from week 12, an sPGA score of 0 or 1 was maintained by 73.8% or 39.0%; among placebo recipients only 7.0% of patients maintained a score of 0 or 1 (UNCOVER-1; UNCOVER-2). In patients receiving continuous ixekizumab 80 mg every 4 weeks to week 60 (UNCOVER-3) ≥73% had an sPGA score of 0 or 1 and ≥80% had PASI 75 response. Ixekizumab adverse events included neutropaenia, candidal infections and inflammatory bowel disease.

Comment: This seems to be the next biologic that will be off the block. I understand it is to go to the PBAC for November. It is highly likely we will have this medication available by the end of the year. As such, this paper is a very detailed summary of all of the pivotal studies that we clinical dermatologists need to know about. This is an interleukin-17A monoclonal antibody. It is in the same family class as secukinumab. This later drug has been well received over the last year or so that we have had it available both in joints and in skin. A detailed study that all biologic users should read and keep.

Reference: N Engl J Med. 2016;375(4):345-56

Abstract

A randomized phase 2b trial of baricitinib, an oral Janus kinase (JAK) 1/JAK2 inhibitor, in patients with moderate-to-severe psoriasis

Authors: Papp KA et al.

Summary: A randomised, double-blind, placebo-controlled, dose-ranging phase IIb study was conducted to determine the effect of a new oral Janus kinase (JAK) 1/JAK2 inhibitor, baricitinib (2, 4, 8 or 10 mg), in 271 patients with moderate-to-severe psoriasis. At week 12, PASI-75 was achieved by more baricitinib 8 mg (43%) and 10 mg (54%) than placebo (17%; p < 0·05) recipients. Baricitinib recipients had greater mean PASI score changes and higher rates of PASI-50 (except 2 mg) than placebo recipients (p < 0·05). Significant PASI-90 responses were also achieved in baricitinib 8 and 10 mg recipients at 8 and 12 weeks. Of those with a PASI-75 response, ≥81% maintained their response score through 24 weeks. Study discontinuations due to adverse events in placebo and baricitinib 2, 4, 8 and 10 mg recipients were 0%, 0%, 2·8%, 6·3% and 5·8% while the treatment-emergent adverse event rates were 44%, 50%, 47%, 58% and 64%.

Comment: We have had one JAK inhibitor developed for psoriasis by Pfizer. They are now looking at how effective this drug is working in atopic dermatitis. For various reasons this particular product did not get released in Australia. My understanding is it was acceptable to the American regulatory authorities and was released for psoriasis. These are oral agents and with a variety of JAK inhibitors it seems highly likely that one of these will be acceptable for psoriasis patients when compared to apremilast and the biologics. This article is for those of us who are interested in newer products that are in the pipeline.

Reference: Br J Dermatol. 2016;174(6):1266-76
Abstract

A randomized, double-blind, placebo-controlled, dose-escalation study of the safety and efficacy of INCB039110, an oral Janus kinase 1 inhibitor, in patients with stable, chronic plaque psoriasis

Authors: Bissonnette R et al.

Summary: Another JAK inhibitor (INCB039110) has been tested in a randomised, double-blind, placebo-controlled, phase II, dose-escalation (100 or 200 mg once daily, 200 mg twice daily, 600 mg once daily) trial in 48 patients with stable, chronic plaque psoriasis. Mean percent reduction from baseline in sPGA at day 28 with placebo was 12.5% versus 22.2% for 100 mg once daily (p = 0.270), 29.4% for 200 mg once daily (p = 0.118), 35.2% for 200 mg twice daily (p = 0.053), and 42.4% for 600 mg once daily (p = 0.003). In total, 11.1% to 45.5% INCB039110 recipients had an sPGA score of 1 versus 0% with placebo. The most common treatment-emergent adverse event was nasopharyngitis (18.4%).

Comment: Similar to the previous article. More work being done on this group of medications. The conclusion is that this drug provides significant improvement in sPGA in chronic plaque psoriasis. This is another "watch this space".

Reference: J Dermatolog Treat. 2016;27(4):332-8
Abstract

Psoriasis and adverse pregnancy outcomes: a systematic review of observational studies

Authors: Bobotsis R et al.

Summary: These authors searched PubMed, Embase and the Cochrane database for published articles investigating psoriasis and adverse pregnancy outcomes. For their analysis they included nine observational studies and clinical trials evaluating direct measures of maternal and fetal morbidity and mortality. A statistically significant increase in the risk of at least one outcome, including spontaneous abortion, caesarean delivery, macrosomia, low birth weight, large-for-gestational age, and a composite outcome consisting of both prematurity and low birth weight were reported in four of the nine studies. However, these associations were not always consistent across studies and there was no clear evidence of increased adverse outcomes in this patient group.

Comment: This is a very important review study as many women in their reproductive years are being treated with a variety of agents. It is worth reading in detail. However it concludes there was no clear evidence of increased adverse outcomes in pregnant women with psoriasis.

Reference: Br J Dermatol. 2016;Jul 24 [Epub ahead of print]
Abstract

Family history predicts major adverse cardiovascular events (MACE) in young adults with psoriasis

Authors: Egeberg A et al.

Summary: The risk of first-time MACE in patients with psoriasis with or without a family history of cardiovascular disease was investigated in this study. A search of administrative databases between January 1997 and December 2011 identified 2,722,375 individuals with a mean baseline age of 26.6 years, including 25,774 with mild psoriasis and 4504 with severe psoriasis. Among 16,080 (62.4%) patients with mild psoriasis and 3009 (66.8%) with severe psoriasis there was a family history of cardiovascular disease. These patients has adjusted incidence rate ratios for MACE of 1.28 (95% CI 1.12-1.46) and 1.62 (95% CI 1.14-2.30) for mild and severe disease, respectively. No increased risk of MACE was found in patients without a family history of cardiovascular disease.

Comment: One of the biologics in development was withdrawn from further study because of an abnormal MACE profile. There is still a lot of argument whether this profile was clinically real or not. It is always difficult when we are factoring in comorbidities, e.g. obesity. Additionally the biologic-treated group have been treated with a number of agents e.g. acitretin and other agents that increase cholesterol – cyclosporine pushes up blood pressure. This is a study out of Copenhagen looking at registry data. A large number, 2,700,000 plus individuals including 25,774 who had mild and 4504 patients with severe psoriasis. A family history of cardiovascular disease predicted the risk of first time MACE episodes in young adults with psoriasis. This highlights that really the cardiac issues may be more an independent factor of psoriasis and their family as opposed to treatments itself. I understand a number of the biologic companies were concerned about the cardiac profile particularly of Stelara® and others in that family.

Reference: J Am Acad Dermatol. 2016;75(2):340-6
Abstract

Clinical meaningfulness of complete skin clearance in psoriasis

Authors: Strober B et al.

Summary: This analysis of pooled data from 3 phase-III trials investigated whether complete skin clearance (PASI 100 or static PGA score 0) is clinically meaningful to patients with psoriasis compared with treatment responses without complete skin clearance (PASI 75 to <100 or static PGA score 1) based on PSI and DLQI. Complete skin clearance was found to represent a clinically meaningful end point and outcome for patients, with 45% of those achieving a PASI 100 exhibiting a PSI score of 0 compared to only 8% of those achieving a PASI 75 <100 ($p < 0.001$), and 80% and 55%, respectively, achieving a DLQI score of 0/1 ($p < 0.001$). Furthermore, a PASI 100 resulted in incremental improvement over PASI 90 to <100 (incremental differences of 28% for PSI score 0 and 18% for DLQI score 0); similar results were seen for static PGA scores 0 versus 1.

Comment: Researchers have progressed the effectiveness of the biologic agents especially in skin as well as joints. Although we are to utilise PASI 75% for our Governmental Authorities, several of the newer agents are publishing PASI responses far higher than that including the Holy Grail of PASI 100. This paper argues that complete skin clearance represents a clinically meaningful end point and outcome for patients. Certainly it seems that our patients are no longer satisfied with the lesser effective treatments.

Reference: J Am Acad Dermatol. 2016;75(1):77-82
Abstract

Apremilast, an oral phosphodiesterase-4 inhibitor, in the treatment of palmoplantar psoriasis: Results of a pooled analysis from phase II PSOR-005 and phase III Efficacy and Safety Trial Evaluating the Effects of Apremilast in Psoriasis (ESTEEM) clinical trials in patients with moderate to severe psoriasis

Authors: Bissonnette R et al.

Summary: This was a post hoc analysis of data pooled from the phase IIb (PSOR-005) and phase III (Efficacy and Safety Trial Evaluating the Effects of Apremilast in Psoriasis [ESTEEM] 1 and 2) clinical studies, undertaken to determine the efficacy and safety of apremilast in palmoplantar psoriasis. Patients with moderate-to-severe plaque psoriasis with active palmoplantar psoriasis (baseline PPPGA score ≥1) received apremilast 30 mg twice daily or placebo. After 16 weeks of treatment, apremilast was associated with a significantly higher percentage of patients with a baseline PPPGA score ≥3 achieving a PPPGA score of 0 (clear) or 1 (almost clear) compared with placebo recipients (48% vs 27%; $p = 0.021$). At week 16, 46% of the apremilast recipients with baseline PPPGA score ≥1 achieved a PPPGA score of 0 versus 25% of placebo recipients ($p < 0.001$); 59% of the apremilast group had a PPPGA score of 0 or 1 with 1-point or more improvement versus 39% receiving placebo ($p < 0.001$).

Comment: This is a drug highlighted in a number of previous reviews over the last year or so. We are still waiting to see whether this drug will be available for us to use routinely in our patients in Australia. This article specifically deals with the treatment of palmoplantar psoriasis. This is a separate sub-group which can be quite difficult to treat. A number of the biologic agents do not seem to be as effective in this location as on the general body or scalp. This study was a post hoc analysis limited to 16 weeks. It did not deal with palmoplantar pustulosis or measures of surface area. 46% of the apremilast treated group scored a clear or almost clear rating versus 25% of the placebo group. This is indeed a very high placebo response rate. This article highlights that in difficult to treat areas like palmoplantar psoriasis, apremilast may be an oral drug that we would like to use.

Reference: J Am Acad Dermatol. 2016;75(1):99-105
Abstract

A prospective cross-sectional study of anxiety and depression in patients with psoriasis in Singapore

Authors: Tee SI et al.

Summary: The frequency of anxiety and depression in a cohort of Singaporean patients with psoriasis and its relationship to physical disease severity and subjective quality of life was assessed in this prospective cross-sectional study involving 100 patients aged 21-60 years who attended The National Skin Centre, Singapore between 2008 and 2009. The mean score on the Hospital Anxiety and Depression Scale (HADS) was 6.9 and for depression was 4.7. Anxiety disorder and depressive disorder rates for the study population were suggested to be 17% and 15%, respectively. A significant correlation was found between all eight domains of the Short Form (36) Health Survey (SF-36) and both anxiety and depression scores. Worse depression scores were seen in those with moderate or severe psoriasis (according to PASI) than those with mild psoriasis; there was no correlation between anxiety scores and PASI. Patients' age, monthly income and duration of psoriasis also showed no correlation with anxiety and depression scores.

Comment: Depression is the new bogyman for biologic trials. Both MACE and depression are being observed with this family class. Whether it is a drug dependent effect or an effect of the disease itself is still being worked out. This study is helpful in making up your own mind. A small study of younger patients, only 100 aged between 21-60 years old from the National Skin Centre were studied. This unit is a centre of excellence in South East Asia. Simple tools to assess anxiety and depression were used. Anxiety disorder was suggested in 17% whilst a depressive disorder was suggested in 15% of the study population. The conclusion was that there is a strong psychiatric morbidity in patients with psoriasis and further investigations of this sort should be carried out. My conclusion is that we need to be aware that our patients suffer high levels of anxiety and depression at their presentation and we need to be mindful of this when assessing the so called complications of the medications we are using.

Reference: J Eur Acad Dermatol Venereol. 2016;30(7):1159-64
Abstract

Psoriasis Research Review™

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 survival of biologic therapy in a large, disease-based registry of patients with psoriasis: results from the Psoriasis Longitudinal Assessment and Registry (PSOLAR)

Authors: Menter A et al.

Summary: Biologic drug survival (defined as the time from initiation to stopping or switching of therapy) in the PSOriasis Longitudinal Assessment and Registry (PSOLAR), a large, prospective, international, disease-based registry of patients with psoriasis receiving (or eligible for) systemic therapy in a real-world setting was assessed. The time to discontinuation was compared across cohorts (n = 3500) undergoing first-, second- or third-line treatment with ustekinumab, infliximab, adalimumab or etanercept. The most common reason for discontinuation across biologic therapies was lack of effectiveness. Multivariate analysis revealed significantly shorter times to discontinuation with infliximab (HR 2.73; 95% CI 1.48-5.04: p = 0.0014), adalimumab (HR 4.16; 95% CI 2.80-6.20: p < 0.0001) and etanercept (HR 4.91; 95% CI 3.28-7.35: p < 0.0001) compared with ustekinumab (reference treatment) for first-line biologic use; similar results were found for treatment effects for second/third-line therapies.

Comment: This is a study coming out of America looking at the PSOLAR registry data. The American system of course is very different to what we have in Australia. Patients will change biologics for economic and insurance reasons very frequently as opposed to what we do. This study needs to be reviewed with this factor being paramount. Lack of effectiveness was noted as being the most common reason for discontinuation across biologic therapies in the 12,000 patients in this registry. Ustekinumab when compared with infliximab, adalimumab and etanercept gave superior drug survival in their USA database.

Reference: J Eur Acad Dermatol Venereol. 2016;30(7):1148-58
Abstract

Subclinical cardiovascular disease and it's improvement after long-term TNF-α inhibitor therapy in severe psoriatic patients

Authors: Herédi E et al.

Summary: Signs of subclinical cardiovascular disease (echocardiographic abnormalities) in severe psoriatic patients without clinically overt heart disease and the influence of long-term treatment with TNF-α inhibitors on ventricular functions were investigated in this study involving 44 psoriatic patients and 45 age- and sex-matched controls. At baseline, psoriatic patients exhibited a higher right ventricular Tei index (p < 0.001), whereas the tricuspid annular plane systolic excursion (TAPSE) and right ventricular free wall peak systolic velocity were lower (p < 0.001 and p < 0.0001, respectively) than in controls. TAPSE and right ventricular free wall peak systolic velocity significantly improved (p < 0.0001 for both parameters) after treatment with anti-TNF-α inhibitors. Also, the Tei index of both ventricles improved during biological therapy, but the change was not statistically significant.

Comment: There is a theme in this month's reviews of cardiac and psychiatric effects. This is a Hungarian study of a very limited number of patients. Echocardiogram parameters were measured before anti-TNF-α treatment compared with controls. As a second step, the effects of long-term anti-TNF were measured on the heart. We all accept and understand comorbidities and the heightened medical risks our psoriatic patients run into. What hasn't been shown clearly yet is a cardiac benefit from treatment. There is some evidence that the long-term use of oral methotrexate acts in a positive way on improving patients health and certainly biologic agents in registries have been shown to reduce a number of significant internal medical issues. Whether we are improving cardiac effects by treating our patients more aggressively hasn't been conclusively proven but this study suggests that it may.

Reference: J Eur Acad Dermatol Venereol. 2016;Jul 9 [Epub ahead of print]
Abstract

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