Psoriasis Research Review™

Making Education Easy

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In this issue:

Abbreviations used in this issue:

AE = adverse event; **IBD** = inflammatory bowel disease; **IR** = incidence rate; **PASI** = Psoriasis Area and Severity Index; **PRO** = patient-reported outcome; **RA** = rheumatoid arthritis; **TNF** = tumour necrosis factor.

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Welcome to the thirty-first issue of Psoriasis Research Review.

A couple of papers in this issue highlight the increased risk of malignancy associated with psoriasis. The findings illustrate an increased risk of melanoma and haematological cancers in patients with psoriasis compared with the general population. Notably, this risk is not increased by systemic or biologic psoriasis therapies.

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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Should tumour necrosis factor antagonist safety information be applied from patients with rheumatoid arthritis to psoriasis? Rates of serious adverse events in the prospective rheumatoid arthritis BIOBADASER and psoriasis BIOBADADERM cohorts

Authors: García-Doval I et al.

Summary: These researchers used data from two national drug safety registries in Spain of patients with rheumatoid arthritis (RA) and psoriasis (BIOBADASER and BIOBADADERM) to determine whether the risk of biological therapy is similar in these two diseases. Only the tumour necrosis factor (TNF) inhibitors used in common between psoriasis and RA were included (infliximab, adalimumab and etanercept).

Comment: This is a very important article in that the dermatological Safety Data Sheets etc. are very much coloured by the non-dermatological use of particular medications. Many of the biologics are used both for inflammatory bowel disease patients and inflammatory arthritic patients. These of course involve different treatment groups. The question arises as to whether the side effect profile is very different in these two groups.

This study reviews the Spanish Registry data, where all patients on a biologic are entered. 1,248 serious or mortal adverse events (AEs) in 16,230 person-years of follow-up of RA patients – a cohort of 3,171 patients. 124 serious AEs in 2,760 person-years of follow-up of psoriasis patients – total cohort number of 946. Therefore, reasonable numbers. The conclusion was that patients with RA have double the risk of serious AEs versus those with only psoriasis. They have a different pattern of AEs, namely, patients with RA showed a higher rate of infections, cardiac disorders, respiratory disorders and infusion-related reactions. Patients with psoriasis had more skin and subcutaneous tissue disorders, as well as capillary disorders.

This is an interesting paper and I recommend those who use biologics to discuss the safety protocol with their patients and review this in detail.

Reference: Br J Dermatol. 2017;176(3):643-9

Abstract

RESEARCH REVIEW—The Australian Perspective Since 2007

Incidence, prevalence and mortality of patients with psoriasis: a U.K. population-based cohort study

Authors: Springate DA et al.

Summary: This paper describes changes in the prevalence and incidence of psoriasis, and mortality rates over a 15-year period in the UK. The researchers identified a steady increase in the prevalence of psoriasis from 2.3% (2,297 cases per 100,000) in 1999 to 2.8% (2,815 per 100,000) in 2013, with no apparent relationship to changes in incidence rates. The data revealed peaks in age bands characteristic of early-onset (type I) and late-onset (type II) psoriasis.

Comment: This is a study based upon data from the UK Clinical Practice Research Datalink; an analysis of longitudinal electronic health records from 1999 to 2013. Two factors came to my attention. One is that there was an increase in the prevalence of psoriasis from 2.3% in 1999 to 2.8% in 2013. This increase in prevalence did not appear to be attributable to changes in incidence rates. There were peaks in age bands, particularly in early-onset and late-onset psoriasis, as well as changes in incidence and prevalence rates, with increasing latitude in the UK. All-cause mortality rates for the general population and for patients with psoriasis have decreased over the last 15 years. However, the risk of mortality for patients with psoriasis remains elevated compared with people without psoriasis. It has a ratio of 1.21 (95% CI, 1.13 to 1.3). No significant change in the relative excess mortality gap was found over that time.

In summary, this means patients with psoriasis are more likely to die. They don't know why. The assumption is that the comorbidities associated with psoriasis have some impact but this study wasn't empowered to find that. There is, also, no comment of why we now see more psoriasis, in that the prevalence has gone from 2.3% to 2.8% in 15 years. Possibly it is because the patients have been better diagnosed.

Reference: Br J Dermatol. 2017;176(3):650-8
Abstract

Efficacy and safety of brodalumab in patients with generalized pustular psoriasis and psoriatic erythroderma: results from a 52-week, open-label study

Authors: Yamasaki K et al.

Summary: This phase 3 study recruited Japanese patients with generalised pustular psoriasis (n=12) and psoriatic erythroderma (n=18). All patients received brodalumab, a human immunoglobulin G2 monoclonal antibody against human interleukin-17-receptor A, at the dose of 140 mg on day 1 and at weeks 1 and 2, then every 2 weeks thereafter until week 52. The primary end point (Clinical Global Impression of Improvement [CGI] remission or improvement at week 52) was achieved in 11 patients with generalised pustular psoriasis and 18 with psoriatic erythroderma. The most commonly reported AE was nasopharyngitis (33.3%). None of the 5 serious AEs that occurred during brodalumab treatment was considered to be treatment-related.

Comment: For our patients, there is still a stream of newer biologic agents in the pipeline. There are several unmet needs for psoriasis patients. Generalised pustular psoriasis is rare, as is psoriatic erythroderma. Acitretin is the agent of choice for generalised pustular psoriasis. There are patients where this medication does not work particularly well. Brodalumab was used in this 52-week open-label study for Japanese patients. Only 12 patients with generalised pustular psoriasis were enrolled; 10 patients finished the study. The assessment tool used was one Clinical Global Impression of Improvement. 11 patients with pustular psoriasis were improved. For erythrodermic psoriasis, there were 18 patients, of which 16 completed the study. All 18 achieved the primary end point of Clinical Global Impression of Improvement.

The conclusion is that brodalumab provides significant improvement in symptoms of patients with both generalised pustular psoriasis and psoriatic erythroderma, with favourable safety profiles and no new safety signals.

Reference: Br J Dermatol. 2017;176(3):741-51
Abstract

Malignancy rates in a large cohort of patients with systemically treated psoriasis in a managed care population

Authors: Asgari MM et al.

Summary: This analysis sought to determine the overall malignancy rate (excluding non-melanoma skin cancer [NMSC]) and NMSC rate among 5,889 adult Kaiser Permanente Northern California health plan members with psoriasis (no data were available on disease severity) diagnosed between 1998 and 2011 and treated with ≥1 systemic antipsoriatic agent. Patients were categorised into ever-biologic or non-biologic users; 97% of the biologics users had been treated with TNF-α inhibitors. Malignancy rates were calculated per 1,000 person-years of follow-up. In Cox regression analysis adjusted for potential confounders, overall incident cancer rates were comparable between ever-biologic and non-biologic users (aHR 0.86; 95% CI, 0.66 to 1.13). NMSC rates were markedly higher among individuals ever exposed to a biologic (aHR 1.42; 95% CI, 1.12 to 1.80), largely because of their increased risk of cutaneous squamous cell carcinoma (aHR 1.81; 95% CI, 1.23 to 2.67).

Comment: This was an interesting study out of the Blue Journal from impressive authors. They looked at the Kaiser Permanente Northern California Health Plan members from 1998–2011. Most of the patients had been treated with TNF-α inhibitors, of which there were 2,214 patients. The conclusion was there were increased incidents of cutaneous squamous cell carcinoma in patients with systemically-treated psoriasis who were ever exposed to biologics. Overall incident cancer rates were comparable between biologic and non-biologic users. Non-melanoma skin cancer rates were 42% higher amongst individuals ever exposed to biologics, largely due to increased cutaneous squamous cell carcinoma risk.

Reference: J Am Acad Dermatol. 2017;76(4):632-8
Abstract

The risk of melanoma and hematologic cancers in patients with psoriasis

Authors: Reddy SP et al.

Summary: This retrospective cohort study identified 8,161 patients at Kaiser Permanente Southern California who satisfied the study's diagnostic and inclusion criteria for psoriasis and presented for medical treatment between January 2004 and December 2013; the cohort included 62 (0.87%) cases of melanoma and 47 (0.87%) cases of lymphoma or leukaemia.

Comment: This report feeds on from the last one. Again, the group that was looked at was 5,889 patients with severe psoriasis who had a systemic therapy. The results showed that patients with psoriasis had a 1.53 times greater risk of developing a malignancy compared with patients without psoriasis. There were no significant differences in malignancy risk amongst patients treated with topicals, phototherapy, systemic or biologic agents. Patients with psoriasis or malignancy did not have significantly worse survival than patients without psoriasis.

So, in conclusion, patients with psoriasis develop an increased risk of melanoma and haematological cancers compared with the general population. The risk is not increased by systemic or biologic psoriasis therapies. Again, another one to pile on the comorbidities associated with psoriasis in general.

Reference: J Am Acad Dermatol. 2017;76(4):639-47
Abstract

Efficacy and safety of guselkumab, an anti-interleukin-23 monoclonal antibody, compared with adalimumab for the continuous treatment of patients with moderate to severe psoriasis: Results from the phase III, double-blinded, placebo- and active comparator–controlled VOYAGE 1 trial

Authors: Blauvelt A et al.

Summary: This study randomised patients with moderate-to-severe psoriasis to 1 of 3 treatment groups: guselkumab 100 mg at weeks 0 and 4 and then every 8 weeks thereafter (n=329), placebo at weeks 0, 4, and 12 followed by guselkumab at weeks 16 and 20 and then every 8 weeks thereafter (n=174), or adalimumab 80 mg at week 0, followed by 40 mg at week 1 and then 40 mg every 2 weeks thereafter through week 47 (n=334). At week 16, guselkumab demonstrated significant superiority over placebo for the physician-reported outcomes of Investigator Global Assessment scores of 0/1 (cleared/minimal) (85.1% vs 6.9%; p<0.001) and ≥90% improvement from baseline in Psoriasis Area and Severity Index (PASI90) score (73.3% vs 2.9%; p<0.001). Moreover, Investigator Global Assessment 0/1 and PASI90 were improved by a significantly greater extent with guselkumab compared with adalimumab at week 16 (85.1% vs 65.9% and 73.3% vs 49.7%, respectively), week 24 (84.2% vs 61.7% and 80.2% vs 53.0%, respectively) and week 48 (80.5% vs 55.4% and 76.3% vs 47.9%, respectively); p<0.001 for all comparisons. Through week 48, patient-reported outcomes (Dermatology Life Quality Index, Psoriasis Symptoms and Signs Diary) were significantly improved from baseline by guselkumab. AE rates were comparable between all treatment groups.

Comment: There are a number of newer biologic agents in development. Guselkumab is an anti-interleukin-23 monoclonal antibody, in a newer target class. Its effectiveness is compared against adalimumab in this study. The registration authorities generally pick what is the most popular biologic in its class at that time and require the developers of a newer biologic to run a comparison trial. The trials will take some years to run and the usage patterns of biologics will have changed over the 3–5 years from initiation of the study to the final conclusion and publication. Some readers will feel that adalimumab in the Australian market is not an adequate comparator.

There are a number of anti-interleukin-23s in development. The summary of this paper is that guselkumab demonstrates superior efficacy compared with adalimumab and is well tolerated over the year of data collection that is the subject of this study.

I have included this just for the readership as to what is and will be happening in the biologic market over the next few years. This is a drug that we will be using in 3–5 years' time.

Reference: J Am Acad Dermatol. 2017;76(3):405-17
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.

Short- and long-term safety outcomes with ixekizumab from 7 clinical trials in psoriasis: Etanercept comparisons and integrated data

Authors: Strober B et al.

Summary: This analysis examined integrated safety data with ixekizumab in moderate-to-severe psoriasis from a 12-week induction period, a 12- to 60-week maintenance period, and from all ixekizumab-treated patients (n=4,209) included in 7 clinical trials. These trials enrolled adults (age ≥18 years) with psoriasis involving ≥10% of the body surface area and with baseline scores of ≥3 on the Physician Global Assessment and ≥12 on the PASI scale who were candidates for systemic therapy and/or phototherapy. Two of the trials included an etanercept arm up to week 12. Up to week 12, exposure-adjusted incidence rates (IRs) per 100 patient-years were similar between the groups for patients experiencing ≥1 treatment-emergent AE (251 with ixekizumab and 236 with etanercept); IRs for serious AEs were 8.3 in both groups. During maintenance treatment, ixekizumab resulted in IRs of 100.4 for treatment-emergent AEs and 7.8 for serious AEs. For all ixekizumab-treated patients, the IR was 2.5 for *Candida* infections. IRs of treatment-emergent AEs of special interest (including serious infections, malignancies, major adverse cardiovascular events) were comparable between ixekizumab and etanercept during the induction period.

Comment: Ixekizumab (Taltz®) was released in early 2017 on the Australian market. Questions always arise with new drugs. This is a paper that answers most of these questions. This is integrated data from 7 clinical trials looking at 4,209 patients. The total exposure here was 6,480 patient-years. The comparator was etanercept for most of these studies. This is an FDA requirement, as at the start of the research period, etanercept was the market leader. Of course, time has moved on and we now use more efficacious agents. Ixekizumab is associated with an increase in oro-cutaneous Candidiasis. Incident rates of treatment-emergent AEs of special interest including serious infections, malignancy and major adverse cardiovascular events were comparable for both drugs. For readers, there is a class-effective Candida infection in this group. We will need to watch.

Reference: J Am Acad Dermatol. 2017;76(3):432-40
Abstract

Inflammatory bowel disease among patients with psoriasis treated with ixekizumab: A presentation of adjudicated data from an integrated database of 7 randomized controlled and uncontrolled trials

Authors: Reich K et al.

Summary: Using the integrated database of 7 ixekizumab psoriasis trials that was analysed in the preceding analysis, this investigation evaluated IBD cases (Crohn's disease [CD] and ulcerative colitis [UC]) reported during the induction and maintenance periods and in all ixekizumab-treated patients. A total of 19 IBD cases were adjudicated as definite/probable (CD, n=7, IR of 1.1/1000 patient-exposure years; UC, n=12, IR of 1.9/1000 patient-exposure years). Among these, 3 occurred during induction (CD, n=1; UC, n=2) and 7 during maintenance (CD, n=4; UC, n=3).

Comment: There is a question mark with this family of medications regarding IBD. It is still very early in its history and the numbers treated are small so far. The importance of this issue will become more established as time goes by. Certainly, IBD occurs more frequently in patients with psoriasis. I have it as roughly twice as common as the normal population. There is a significant genetic overlap however the pathogenesis underlying the co-occurrence of these conditions is still unknown.

This report studies 4,209 patients who have been treated with ixekizumab (Taltz®) for a total of 6,480 patient-exposure years to this drug. There were 19 cases of definite/probable IBD. Three occurred during induction, 7 during maintenance. 12 of 16 patients with previously reported prior IBD history did not have an IBD treatment-emergent AE/serious AE.

What does this data mean to me? IBD cases were uncommon in less than 1% of this treatment group. 12 of 16 patients who had IBD before going into the study did not have a flare of their disease whilst on the study. Would I treat somebody who has IBD with this family of medication? Only if no other option was available at the moment. Would I be concerned about someone with a family history developing IBD on this agent? Again, we don't have the exact data but it would be quite rare for this to occur.

Reference: J Am Acad Dermatol. 2017;76(3):441-8
Abstract

Optimal maintenance treatment with calcipotriol/betamethasone dipropionate gel in Korean patients with psoriasis vulgaris: a multicentre randomized, controlled clinical trial

Authors: Lee JH et al.

Summary: In this phase 4 open-label trial, South Korean patients with psoriasis vulgaris on the limbs/trunk received once-daily treatment with calcipotriol monohydrate (50 µg/g)/betamethasone dipropionate (500 µg/g) Xamiol® gel for 8 weeks (induction phase). Responders (defined as an Investigator's Global Assessment of Disease Severity [IGA] grade of 'clear' or 'almost clear') were then randomised to receive 8 weeks of maintenance treatment with Xamiol® gel once daily as needed (PRN Group), once daily every day (Continuous group), or twice weekly – on Saturdays and Sundays (Weekend group). At week 16, responder rates were 63.89% for the PRN group, 67.5% for the Continuous group and 31.43% for the Weekend group. The PRN and Continuous groups did not differ statistically, but both were statistically superior to the Weekend group (p=0.0109 and p=0.0015, respectively).

Comment: There is a newer version of this combination called Enstilar® that has come on the PBS since 1 April. I think it is prudent to review optimal maintenance treatments of this combination product.

This is a study out of Korea, so may not necessarily reflect response rates in Australia. However, there is no other evidence to suggest that there is an issue with response rates between different skin types. The conclusion was that in this patient group, maintenance therapy with calcipotriol monohydrate/betamethasone dipropionate using a continuous daily regime or an 'as needed' daily regime provided similar efficacy, whereas a twice-weekly regime was significantly less efficacious than either of these regimens. As such, it seems best that patients can use it daily or wait for skin to flare and then use it daily. 62.18% were assessed by IGA scores as responders with a grade of clearance of 'clear' or 'almost clear' at week 8. At 16 weeks, the continuous therapy group had a response rate of 67.50%, whilst the PRN group had a response rate of 63.89%. There was no difference in the incidence of AEs between both groups.

Reference: J Eur Acad Dermatol Venereol. 2017;31(3):483-9
Abstract

Apremilast, an oral phosphodiesterase 4 inhibitor, improves patient-reported outcomes in the treatment of moderate to severe psoriasis: results of two phase III randomized, controlled trials

Authors: Thaçi D et al.

Summary: The ESTEEM 1 and 2 trials randomised 1,255 patients moderate-to-severe plaque psoriasis to treatment with twice-daily apremilast 30 mg or placebo for 16 weeks; all participants received apremilast thereafter through week 32. Patient-reported outcome (PRO) assessments included the Dermatology Life Quality Index (DLQI), 36-Item Short-Form Health Survey version 2 mental/physical component summary scores (SF-36v2 MCS/PCS), Patient Health Questionnaire-8 (PHQ-8), EuroQol-5D (EQ-5D) and Work Limitations Questionnaire-25 (WLQ-25). At week 16, all health-related quality of life (HRQOL) PROs were improved with apremilast compared with placebo, except for SF-36v2 PCS scores; improvements were sustained through week 32. Mean DLQI and SF-36v2 MCS improvements exceeded minimal clinically important differences. Post hoc analyses identified a weak correlation between changes from baseline in PHQ-8 and PASI at week 16. In the apremilast arm, only 35.8% of patients who achieved a ≥75% reduction from baseline in PASI score also achieved PHQ-8 scores of 0–4.

Comment: In Australia, we are still waiting for apremilast to be listed on the PBS. It is available privately, at some significant expense. This is a paper that reviews a total of 1,255 patients and looks at the quality of life indexes as well as a number of other health questionnaires that measure the effect of disease on patients' lifestyles. The recommended apremilast dosage for psoriasis is 30mg bid. There is a significant improvement in all of these measures.

I have put this in to remind readers that if and when apremilast does come onto the Australian market, it has an acceptable side effect profile and is effective for the treatment of plaque psoriasis and psoriatic arthritis. This paper reviews the significant impact apremilast has on health-related quality of life questionnaires.

Reference: J Eur Acad Dermatol Venereol. 2017;31(3):498-506
Abstract

