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Welcome to issue 43 of Psoriasis Research Review.

First up we discover that compared with adalimumab, gusekumab may be more advantageous for patients with psoriasis of the scalp, soles and palms. Following on, we have further evidence that acitretin is an effective and safe agent for treating children with pustular psoriasis. Other studies included in this issue cover the topics of psoriasis in solid organ transplant patients, monthly vitamin D supplementation in mild psoriasis, TNF inhibitors and risk of major adverse cardiovascular events, cardiovascular events after TNF-α inhibitors versus phototherapy, ixekizumab impact on cardiovascular parameters, screening tools to identify psoriatic arthritis, comparative effectiveness of targeted immunomodulators, a thymus and activation-regulated chemokine level biomarker, and the use of fumaric acid esters in psoriasis.

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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Efficacy of gusekumab compared with adalimumab and placebo for psoriasis in specific body regions: A secondary analysis of 2 randomized clinical trials

Authors: Foley P et al.

Summary: This post hoc analysis of data from the VOYAGE 1 and VOYAGE 2 double-blind, placebo- and adalimumab-controlled studies (n = 1829) examined the effect of gusekumab on moderate-to-severe plaque psoriasis (PASI score ≥12, IGA score ≥3, ≥10% BSA affected). At baseline, 1512 (82.7%) patients had scalp-specific IGA (ss-IGA) scores ≥2, 461 (25.2%) had hands and/or feet Physician’s Global Assessment (hf-PGA) scores ≥2, and 928 (50.7%) had fingernail PGA (f-PGA) scores ≥2. The proportion of patients with an ss-IGA score of 0 or 1 was higher in gusekumab than in placebo recipients at week 16 (81.3% vs 12.4%; p < 0.001) or adalimumab recipients at week 24 (85.0% vs 68.5%; p < 0.001); 69.9% versus 56.3% (p < 0.001) had an ss-IGA score of 0. The proportion of patients with an hf-IGA score of 0 or 1 was also higher in gusekumab than placebo recipients at week 16 (75.5% vs 14.2%; p < 0.001) or versus adalimumab recipients at week 24 (80.4% vs 60.3%; p < 0.001); 75.0% versus 50.3% (p < 0.001) achieved an hf-PGA score of 0. Finally, the number of patients with an f-PGA score of 0 or 1 was higher in gusekumab than in placebo recipients at week 16 (46.7% vs 15.2%; p < 0.001), but there were no differences between gusekumab and adalimumab recipients in the number of patients with a score of 0 or 1 in f-PGA at week 24 (60.0% vs 64.3), nor in the number with an f-PGA score of 0 (27.4% vs 27.9%).

Comment: In this review series I have frequently stressed that we are now blessed with an increasing variety of biologics that are performing better than anything we previously had. It would be nice to be more precise with our targeted treatments. They are an expensive medication class that less frequently than before are not effective in certain patients and certain psoriatic sites. All the biologic scientific studies involve patients with total-body generalised chronic plaque psoriasis. The companies concerned then sub-analyse the entire treatment cohort for certain specific site locations. This paper, with a well-known Australian lead author, assesses VOYAGE 1/VOYAGE 2. This study compared adalimumab with gusekumab. Because gusekumab will be released very shortly in Australia, biologic prescribers will be able to trial this drug on their patient group extremely soon. It needs to be said that in generalised chronic plaque psoriasis, gusekumab has high PASI 90/PASI 100 rates. It is therefore logical to believe it would give better clinical results in more difficult to treat areas on scalp, palms and soles, than adalimumab. I read this data as saying that if I have a patient who does have involvement in the scalp and/or palms and soles that I can feel confident that gusekumab will be of value in this group.


Abstract
Efficacy and safety of acitretin monotherapy in children with pustular psoriasis: results from 15 cases and a literature review

Authors: Chen P et al.

Summary: This retrospective study assessed the use of acitretin for pustular psoriasis in 15 children with generalised pustular psoriasis (n = 10), palmoplantar psoriasis (n = 3) or acrodermatitis continua of Hallopeau (ACH; n = 2). Of the 15 patients, 14 had a good response to treatment and one ACH case had a moderate response. Over 10-32-months’ follow-up, acitretin monotherapy showed good efficacy and safety overall. A literature review of 21 studies involving 107 childhood pustular psoriasis cases receiving acitretin as monotherapy or combination therapy suggested clinical effectiveness in 88.8% of patients, and 92.6% of patients did not report adverse effects during treatment or follow-up.

Comment: Acitretin is my go to drug for pustular psoriasis. Pustular psoriasis is an extremely rare disorder in clinical practice. I am partial to any studies in paediatrics. This is a case report series of paediatric patients of which two-thirds had generalised pustular psoriasis. There were also some of the more rare pustular variants. These patients received treatment for 10-32-months’ follow-up. They also report an extensive literature review of another 107 childhood cases. For those of us that treat paediatric patients this is a paper that you should get your local friendly rep to order in for you and enter into your case retrieval system for future reference. It is also highly worth reading right now.


Psoriasis in solid organ transplant patients: best practice recommendations from The Medical Board of the National Psoriasis Foundation

Authors: Prussick R et al.

Summary: This systematic literature review and assessment by the Medical Board of the National Psoriasis Foundation sought to develop a treatment algorithm for organ transplant recipients with psoriasis vulgaris receiving biologic or systemic agents that might increase infection or malignancies. The recommendation for mild-to-moderate disease is first-line treatment with topical therapy, while in moderate-to-severe disease, first-line treatment should be acitretin and/or narrow band UV light (NBUVB). Second-line therapy is an increase in anti-rejection drug dose, with other systemic or biologic therapies reserved for more severe or refractory cases.

Comment: This is an American article about a very rare sub-group of patients. They do, however, exist for clinicians. There is no research data and very little published information as to how to manage these individuals. The authors’ recommendation for NBUVB therapy and/or acitretin is quite logical and almost certainly what we would normally do in this situation. It is, however, nice to receive validation of our techniques from the prestigious centres in the United States. Their second-line treatment would be to increase the anti-rejection drugs and not go for other systemic biologic therapies. Another one to put in your database for that rare patient that comes along.


A randomized, double-blind, placebo-controlled trial of the effect of monthly vitamin D supplementation in mild psoriasis

Authors: Jarrett P et al.

Summary: This study of a large randomised, double-blind, placebo-controlled trial tested the use of vitamin D, 100,000IU monthly supplementation (n = 23) versus placebo (n = 42) in patients with psoriasis from a community-dwelling population. Mean baseline 25-hydroxyvitamin D level was 65.7 nmol/L, and after 12 months there were no differences between the groups in any psoriasis outcome measures (mean scores: PASI 2.2 vs 2.1; PGA 1.4 vs 1.5; Psoriasis Disability Index [PDI] 2.1 vs 1.9; Dermatology Life Quality Index [DLQI] 2.5 vs 2.0).

Comment: My main practice is based in Fremantle, which has its eclectic mix of patients. It was a short time ago a Green seat for Federal parliament. A number of my patients feel that high doses of vitamins cure all dermatological complaints. This is a study in mature adults who had properly assessed PASI, PGA, DLQI and PDI. A small number, 23, received active vitamin D and 42 received placebo. Significant doses of vitamin D supplementation were given and the results did not recommend this as a potential therapeutic treatment for our patients. It is nice to have a study that validates our present management and refutes the poly-vitamin pharmacy of health gurus and believers in alternative systems.


Anti-inflammatory therapy with tumour necrosis factor inhibitors is associated with reduced risk of major adverse cardiovascular events in psoriasis

Authors: Wu JJ et al.

Summary: This retrospective cohort study used data from the Kaiser Permanente Southern California health plan to determine the impact of tumour necrosis factor (TNF) inhibitor therapy on major adverse cardiovascular events (MACE) in psoriasis patients. After cardiovascular risk factor adjustment, patients receiving TNF inhibitors had a lower MACE risk than those receiving topical therapy (HR 0.80; 95% CI 0.66-0.98). A cohort using oral/phototherapy had a MACE risk that did not differ from that of the topical therapy cohort (HR 1.19; 95% CI 0.91-1.42).

Comment: Some years ago, there was a health scare regarding MACE in biologics. It is well known that the comorbidities of psoriasis include significant cardiovascular risk. The suspicion has been that if we reduce chronic systemic inflammation that this would be beneficial for our patients. An American study of the Kaiser Permanente group of patients. This is a very large and sophisticated database. The patients treated with TNF inhibitors had a significantly lower cardiac event profile when compared to the topical therapy cohort. The oral/phototherapy cohort had similar MACE figures compared to the topical cohort. The conclusion was that TNF inhibitors have benefits in mitigating cardiovascular risk.

Reference: J Eur Acad Dermatol Venereol. 2018;Mar 24 [Epub ahead of print]
The risk of cardiovascular events in psoriasis patients treated with tumor necrosis factor-α inhibitors versus phototherapy: An observational cohort study

Authors: Wu JJ et al.

Summary: This is another analysis of Kaiser Permanente Southern California data on the effect of cumulative treatment exposure on cardiovascular event risk in psoriasis patients receiving TNF-α inhibitors compared with phototherapy. Multivariate Cox proportional hazards model analysis of data from 11,410 TNF-α inhibitor and 12,433 phototherapy (psoriasis plus UV A n = 11,717; UV-B n = 11,316) recipients suggested a lower risk of cardiovascular events in TNF-α inhibitor recipients (adjusted HR 0.77; p < 0.05). Risk reduction over 6 months of cumulative exposure was 11.2% (p < 0.05) greater in TNF-α inhibitor versus phototherapy recipients.

Comment: This is a further study out of Kaiser Permanente with different authors, but a very similar subject. This specifically looked at very large groups of patients, over 10,000, who were on TNF-α inhibitors compared to phototherapy patients. The conclusion is the same as in the prior article. Cumulative exposure to TNF-α inhibitors was associated with an incremental cardiovascular risk reduction ahead of phototherapy.


Ixekizumab treatment shows a neutral impact on cardiovascular parameters in patients with moderate-to-severe plaque psoriasis: Results from UNCOVER-1, UNCOVER-2, and UNCOVER-3

Authors: Egeberg A et al.

Summary: This post hoc analysis of data from the phase III ixekizumab trials UNCOVER-1, UNCOVER-2, and UNCOVER-3 was conducted to assess cardiovascular-related parameters in patients with moderate-to-severe psoriasis. At baseline, cardiovascular-related parameters were within normal ranges except for elevated triglyceride and high-sensitivity C-reactive protein (hsCRP) levels; hsCRP levels were reduced versus placebo over the 12-week induction period and remained reduced during the maintenance period (weeks 12-60), although not significantly. During the maintenance period there were no differences between ixekizumab and placebo recipients in total cholesterol, low-density lipoprotein cholesterol (LDL-C), high-density lipoprotein cholesterol (HDL-C), very-low-density lipoprotein cholesterol, triglyceride, apolipoprotein A1, apolipoprotein B, fasting glucose levels, or systolic/diastolic blood pressure. LDL-C/HDL-C ratios remained stable during both induction and maintenance.

Comment: Further to concerns that the IL-17s may aggregate MACE (see the prior two reports). This report looks at the UNCOVER series of pivotal trials comparing placebo, ixekizumab and etanercept. There were no changes in cholesterol levels on treatment. There were no changes in glucose levels or blood pressure. Over the 60 weeks on these trials, ixekizumab had a neutral effect on cardiovascular-rated problems. From the previous reports in this review, the TNF inhibitors appear cardioprotective. Certainly ixekizumab over 60 weeks was not shown to aggravate systemic measures that lead to heart disease.


Assessment of two screening tools to identify psoriatic arthritis in patients with psoriasis

Authors: Coates LC et al.

Summary: This study compared two psoriatic arthritis screening tools, the current standard Psoriasis Epidemiology Screening Tool (PES) and a new, composite, 8-item screening questionnaire (CONTEST) that combines the most discriminative questions from three questionnaires (PES, Psoriatic Arthritis Screening Evaluation, Toronto Psoriatic Arthritis Screen) in 451 dermatology patients with psoriasis, but not diagnosed with psoriatic arthritis. In total, 35% of the screened patients were reviewed and 27 (17%; 95% CI 12.3-21.7) were found to have unidentified psoriatic arthritis. The sensitivity and specificity of PEST were 0.60 (95% CI 0.42-0.78) and 0.76 (95% CI 0.69-0.83) and the sensitivity and specificity for CONTEST were 0.53 (95% CI 0.34-0.72) and 0.71 (95% CI 0.63-0.79). The area under the receiver operating curve (AUC) confidence limits overlapped with an AUC for PEST of 0.72 (95% CI 0.61-0.84) and an AUC for CONTEST of 0.66 (95% CI 0.54-0.77), indicating no difference between tools.

Comment: Recently the Skin and Cancer Foundation in Melbourne conducted a clinical program with Prof. Kristian Reich of Hamburg, Germany. Part of his presentation was discussing screening tools for psoriatic arthritis. There are differences in his, as well as the Germans’ clinical screening tools, and in what some of us here in Australia use. This is a very interesting paper out of Leeds. The PEST is a very simple, patient-completed, one-sheet tool that has been validated in the past. A new questionnaire, CONTEST, was compared to PEST. In this paper, 451 patients were approached, 27 had unidentified psoriatic arthritis. Their conclusion was that the PEST and CONTEST questionnaires were equally reliable. I will stick with PEST for now as this is something I am used to.

Reference: J Eur Acad Dermatol Venereol. 2018;Mar 26 [Epub ahead of print]

Comparative effectiveness of targeted immunomodulators for the treatment of moderate-to-severe plaque psoriasis: A systematic review and network meta-analysis

Authors: Loos AM et al.

Summary: This meta-analysis examined the comparative effectiveness of targeted immunomodulators in adults with moderate-to-severe plaque psoriasis. Using a network meta-analysis procedure to adjust for placebo response and allow indirect comparisons between agents, the likelihood of achieving PASI 75 (increasing relative risk were: apremilast (6.2), etanercept (9.6), adalimumab (13.0), ustekinumab (14.0), secukinumab (15.4), infliximab (16.2), brodalumab (17.3), ixekizumab (17.9), lefunomide, brodalumab and infliximab were superior to ustekinumab, adalimumab, etanercept and apremilast.

Comment: With the increasing numbers of biologic agents that we can utilise on our PBS in our severely affected patients, it is worth trying to establish which agents will give our patients a superior outcome. This is a systematic literature review of placebo-controlled head-to-head randomised trials, which looked at eight separate immunomodulators. The limitation of this paper was that the evidence provided was short term, 10-16 weeks only. The conclusion is that presently, IL-17a inhibitors are more effective in achieving clearance than ustekinumab. Both these agents are generally more effective than etanercept, adalimumab and apremilast. Certainly this would mimic everyone’s personal prescribing habits. The next clinical issue for me will be which of the IL-17s is superior. In their ranking system, ixekizumab was first, brodalumab was marginally less, followed by infliximab and finally secukinumab. However, it is very difficult to compare drugs when not in the same study population or trial design.


Selection of papers and comments are provided by

Clinical Associate Professor Kurt Gebauer MBBS, FACC, 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.
Alteration of serum thymus and activation-regulated chemokine level during biologic therapy for psoriasis: Possibility as a marker reflecting favorable response to anti-interleukin-17A agents

Authors: Shibuya T et al.

Summary: This single-centre study examined the use of serum thymus and activation-regulated chemokine (TARC) level as an indicator for step down of biologic therapy in 70 psoriatic patients. Analysis of TARC level and severity, of skin lesions suggested that psoriatic patients can be separated into a population in whom serum TARC level is positively correlated with skin lesion severity and a population with low severity but high TARC. Serum TARC was higher in patients receiving biologics achieving a PASI-clear rating than in those not achieving PASI-clear. Those receiving secukinumab had higher TARC levels than those receiving anti-TNF agents.

Comment: For those that are more scientifically minded, the search is on for a biological marker either on biopsy of skin or analysis of body fluids to help establish which biologic agents would work better in a particular patient. An interesting paper out of Japan looking at serum thymus and activation-regulated chemokine. This paper is of a scientific interest only and it has been placed in this review series for those that like to read a little bit wider around clinical data.

Reference: J Dermatol. 2018;45(6):710-14

Abstract

Long-term real-life safety profile and effectiveness of fumaric acid esters in psoriasis patients: a single-centre, retrospective, observational study

Authors: Dickel H et al.

Summary: This German single-centre, retrospective, observational study in 859 patients with psoriasis, examined the long-term safety and effectiveness of fumaric acid esters (FAEs) alone (n = 626) or in combination with phototherapy (n = 123) or methotrexate (n = 110). Over up to 32.5 years of follow up, 566 adverse events occurred in 49.0% of patients, most involving the gastrointestinal tract. Serious adverse events (more considered causally related to treatment) occurred in 2.3% of patients and severe events leading to discontinuation occurred in 12.9% of patients. From initiation of FAE to a 50% response rate (cumulative static PGA score of ‘light’ and ≥2-point reduction in baseline PGA) required a median of 1 year for all three treatments. A 50% PASI 75 response rate was achieved in a median of 3 years with FAE monotherapy, in 6.7 years in FAEs plus phototherapy recipients and in 8.1 years in FAEs plus methotrexate recipients (p = 0.001).

Comment: The fumaric acid esters have always fascinated me as these agents are commonly used in Europe and rarely in our health care system. It is highly unlikely that we are ever going to have exposure to this medication except through patients who have lived and been treated in Europe for their psoriasis and then moved to Australia. I have managed two or three patients over the years who were continuing to obtain their medication out of Europe. I have tried through the Hospital Pharmacy to treat another two or three with Australian FAEs that are available for multiple sclerosis. Consequently I have very limited experience with this therapeutic group. It is highly likely with the explosion of biologic agents and now the investigation of Janus kinase oral small molecules that FAEs will go by the wayside. I have included this review for those who read more widely and are interested in what is on the worldwide market. They are an effective medication in a significant group of patients with minimal toxicity.

Reference: J Eur Acad Dermatol Venereol. 2018;Apr 28 [Epub ahead of print]

Abstract

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