Psoriasis Research Review™

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In this issue:

Abbreviations used in this issue:

AST = aspartate aminotransferase; **DLQI** = Dermatology Life Quality Index; **IL** = interleukin; **MACE** = major adverse cardiac events; **PASI** = Psoriasis Area and Severity Index; **sPGA** = static Physician's Global Assessment; **UVB** = ultraviolet B.

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Welcome to issue 58 of Psoriasis Research Review.

We begin this issue with a review of the ECLIPSE trial in which guselkumab showed superior long-term efficacy compared with secukinumab for treating moderate-to-severe psoriasis. Following on, in a systematic review we discover shorter time to onset of action in studies assessing approved dosing ranges of IL-17 inhibitors compared with studies assessing IL-23 inhibitors. Other studies included in this issue cover the topics of the prevalence of advanced liver fibrosis in severe psoriasis, tildrakizumab continuous dosing, interruption, dose adjustments and switching, factors predicting biologic drug persistence in psoriasis, adalimumab and phototherapy in the Vascular Inflammation in Psoriasis Trial, and narrowband ultraviolet B phototherapy for psoriasis/atopic dermatitis.

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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Guselkumab versus secukinumab for the treatment of moderate-to-severe psoriasis (ECLIPSE): results from a phase 3, randomised controlled trial

Authors: Reich K et al.

Summary: The multinational, double-blind, randomised, comparator-controlled, phase III ECLIPSE trial compared the interleukin (IL)-23p19 inhibitor guselkumab with the IL-17A inhibitor secukinumab in 1048 patients with moderate-to-severe plaque-type psoriasis. PASI 90 response at week 48 (primary endpoint) was greater in guselkumab (84%) than secukinumab (70%; $p < 0.0001$) recipients. The non-inferiority margin (10%) was met for the major secondary endpoint, PASI 75 response at 12 and 48 weeks (85% vs 80%), but superiority was not established ($p = 0.0616$). As statistical testing was conducted in a fixed sequence to control the type I error rate, further formal statistical testing of other secondary endpoints was not conducted. Adverse event, infection, and serious adverse event rates did not differ between treatments and safety findings were generally consistent with registration trials.

Comment: The ECLIPSE study was a worldwide study in which Australia participated. Essentially guselkumab was compared to secukinumab. There are a number of statistical issues that are important in the interpretation of this study. The proportion of patients with PASI 90 response at week 48 was greater in the guselkumab group (84%) than in the secukinumab group (70%.) However, only non-inferiority was established for the first major secondary endpoint around PASI 75 response. Consequently, detailed statistical analyses of other endpoints were not performed. Adverse events, infection, safety findings etc., were consistent with all such biologic studies. Presently dermatologists are blessed with a number of IL-17 and IL-23 drugs at our disposal. It is confusing to some as to which is our preferred option. The study designs for pivotal studies for generalised chronic plaque psoriasis are very homogeneous with very little in the studies to differentiate products. This head-to-head study does give a lot of data. I would suggest readers obtain a copy and look at the publication in detail. Certainly, from my point of view, most of these agents give brilliant PASI 75 and excellent PASI 90. A difference of 1-2% points may not be so important when we are analysing a number of factors in choosing which agent we use.

Reference: Lancet 2019;394(10201):831-9

Abstract

Systematic review on rapidity of onset of action for interleukin-17 and interleukin-23 inhibitors for psoriasis

Authors: Egeberg A et al.

Summary: This systematic review analysed time to onset for IL-17 and IL-23 inhibitors (ixekizumab, secukinumab, brodalumab, risankizumab, guselkumab, tildrakizumab) in psoriasis treatment based on the weighted mean time for 25% and 50% of patients to achieve PASI 90 in 26 studies. The fastest time to PASI 90 for 25% (3.5 weeks) and 50% (6.2 weeks) of patients was observed for brodalumab 210 mg every 2 weeks, followed by ixekizumab 80 mg every 2 weeks (4.1 and 7.4 weeks) and ixekizumab 80 mg every 4 weeks (4.6 and 8.1 weeks).

Comment: This article compliments the last one in that it has discussed IL-17 and IL-23 biologic agents. This is another paper for those who prescribe biologics. Users of these agents should obtain a copy of this paper and review it individually. Not just take my word for it! Brodalumab is coming and may be on the Australian market in 2020, but that is by no means clear. Ixekizumab is an IL-17 inhibitor that clears patients faster than IL-23 agents. As stated in the last review, there are many other factors that I use in choosing which medication I will prescribe for a particular patient. Occasionally the speed of onset is a primary factor.

Reference: J Eur Acad Dermatol Venereol. 2019;Aug 29 [Epub ahead of print]

Abstract

Prevalence of advanced liver fibrosis in patients with severe psoriasis

Authors: Maybury CM et al.

Summary: The prospective observational Co-morbidities in Severe Psoriasis study sought to describe the prevalence and clinical factors associated with advanced liver fibrosis in 333 severe psoriasis (PASI ≥10) patients with a successful transient elastography scan. Advanced liver fibrosis was diagnosed in 47 patients (14.1%; 95% CI 10.4-17.9). The best-fit model ($r^2 = 0.54$) for advanced fibrosis identified clinical factors including central obesity, insulin resistance, AST level, platelet count, psoriasis disease severity and reduced alcohol use.

Comment: Occasionally with the papers coming through for me to assess, this review becomes quite biologic heavy. This is an excellent English paper that makes the point that advanced fibrosis is common in patients whose PASI is greater than 10. Being found in 14.1% of the 400 patients recruited into this study. The factors related with hepatic cirrhosis include central obesity, insulin resistance, AST level, platelet count, psoriasis disease severity and reduced alcohol use. Of these the most important were abdominal obesity and insulin resistance. Unfortunately, that is roughly 85% of my patients. Liver function assessment, monitoring and management is a significant part of my workload in this patient group. This is a study that reminds us to keep it in mind.

Reference: JAMA Dermatol. 2019;Jun 5 [Epub ahead or print]
Abstract

Efficacy and safety of tildrakizumab for plaque psoriasis with continuous dosing, treatment interruption, dose adjustments, and switching from etanercept: results from phase 3 studies

Authors: Kimball AB et al.

Summary: This pooled analysis of data from the double-blind, randomised, controlled phase III reSURFACE studies (n = 1862) assessed the use of tildrakizumab in subgroups receiving continued (100/100 or 200/200 mg), increased (100/200 mg) or lowered (200/100 mg) dosage at week 28, treatment interruption/re-initiation and initiation after switching from etanercept. Among tildrakizumab 100/100 mg and 200/200 mg partial-responders (PASI 50-75%), the proportion of patients who achieved PASI 75 responses after 28 weeks increased with time, while in tildrakizumab 100/200 mg partial-responders, the number achieving PASI 75 increased from 32 weeks (38.5%) to 52 weeks (63.2%). PASI 75 numbers remained constant in tildrakizumab 200/100 mg responders (PASI ≥75%). In relapsed tildrakizumab recipients (100/placebo and 200/placebo patients) 86% and 83% who re-initiated tildrakizumab achieved PASI 75 by 64 weeks. Among etanercept/tildrakizumab 200 mg partial-responders, PASI 75 responses increased from 32 (24.1%) to 52 (74.7%) weeks.

Comment: Tildrakizumab came on the Australian market earlier this year. It is an IL-23 agent with a dosing regimen very similar to ustekinumab. The theme of this review is helping choose which agent you would prefer to use. This paper gives detailed information on dosing, switching and re-commencement of therapy. PASI response rates are very high in the IL-17 and IL-23 group. My choice of drug is increasingly individualised according to patient preferences, pain of injection, frequency of injection, presence of systemic disease, particularly the potential for psoriatic arthritis, past experience etc... It is very much like when a GP rings you and asks you what is your go-to drug for eczema, there are many factors that we weigh up before we prescribe.

Reference: Br J Dermatol. 2019;Sep 5 [Epub ahead of print]
Abstract

Factors predicting persistence of biologic drugs in psoriasis: a systematic review and meta-analysis

Authors: Mourad A et al.

Summary: This systematic review and meta-analysis aimed to identify factors predictive of biologic drug persistence or discontinuation. Analysis looked at female sex (n = 28,090), obesity (n = 9311) and psoriatic arthritis (n = 24,444). Treatment discontinuation was predicted by obesity (HR 1.21; 95% CI 1.10-1.32; I^2 0%) and female sex (HR 1.22; 95% CI 1.07-1.38; I^2 84%). Persistence was predicted by concomitant psoriatic arthritis (HR 0.83; 95% CI 0.80-0.86; I^2 0%). Female sex was predictive of biologic discontinuation due to adverse events (HR 2.16; 95% CI 1.39-3.35; I^2 67%). Insufficient data for analysis were reported for other factors (smoking, metabolic syndrome, biologic naivety, age, DLQI, dyslipidaemia, high socioeconomic status, concomitant methotrexate).

Comment: This article covers a point that is becoming more and more important. The papers presented in this review in the past have demonstrated that the cost of biologic treatments is maximal in the first year because of the loading dose. Changing biologics by switching and swapping increases resistance rates and reduces the benefit of response. Essentially, as a practitioner, I want to prescribe a drug that the patient will find agreeable, acceptable and effective for their disease. This paper reviews 16 cohort studies looking at 32,194 patients and comes from authors who are well known. Interestingly they found female sex predicted biological discontinuation due to side effects. Obesity was also a negative factor. Those who use biologics understand that the super fatties, those 140 kg or above, pose a special treatment resistant group. The IL-23s and IL-17s seem to do quite well up to 120 kg. I have one patient I struggle with who is 180 kg when he should be 80 kg. He is my only patient now that really has not responded to a biologic. I have recommended lap banding as an excellent way of treating his psoriasis.

Reference: Br J Dermatol. 2019;181(3):450-8
Abstract

Coronary artery disease assessed by computed tomography in patients with psoriasis: A systematic review and meta-analysis

Authors: Kaiser H et al.

Summary: This meta-analysis assessed data on coronary artery disease (CAD) among psoriasis patients compared with controls using coronary calcium score (CCS) and cardiac computed tomography angiography (CCTA). Pooled data across 14 studies (1427 patients; 9670 controls) demonstrated that psoriasis patients had an increased risk of CAD (RR 1.14; 95% CI 1.04-1.26; p = 0.004), and in those with more severe CAD (CCS >100) the risk was further increased (RR 1.71; 95% CI 1.28-2.30; p < 0.001). The weighted mean difference for CCS was higher in psoriasis patients (12.74; 95% CI 10.70-14.78; p < 0.001). High-risk coronary plaques identified by CCTA also showed a higher risk in psoriasis patients (RR 1.77; 95% CI 1.37-2.28; p < 0.001).

Comment: I have included this just to remind all readers that patients with psoriasis are at higher risk of coronary heart disease. It is not the treatments that cause coronary heart disease, but it is linked to obesity, comorbidities and psoriasis itself. We need to be mindful to try to encourage patients to stop smoking, lose weight and get their blood pressure and other co-factors addressed.

Reference: Dermatology 2019;Sep 3 [Epub ahead of print]
Abstract

Outcomes of prolonged and low-dose ciclosporin in an Asian population

Authors: Choi E et al.

Summary: This single centre, retrospective study examined response to low doses of cyclosporine A in 92 patients (64 eczema; 17 psoriasis). Mean initiation dose was 1.53 mg/kg/day, increasing to 2.61 mg/kg/day at 6 months; median duration of treatment was 180 days. Response was observed as early as 2 weeks, with greatest disease control at 6 months. 32 patients received cyclosporine for ≥1 year; only 1 had a >30% increase in creatinine crossing the upper limit of normal.

Comment: This is a study that is extremely relevant to our practice in Australia as we have a large Asian population. This doesn't just look at psoriasis, as of 92 patients in this study, 64 had eczema. Most dermatologists don't use cyclosporine at all. I certainly use this drug frequently. I prefer cyclosporine as a short-term steroid-sparing agent particularly in acute eczema. I find it gives me at least 1 month to several months to calm down their skin and arrange for a long-term immune-modulating drug or a better treatment plan with topicals and/or phototherapy. It buys me time without causing significant psychological, psychiatric, gastrointestinal and other medical issues that arise from the use of oral steroids. I worry about hypertension, particularly in those of my age group or above, and we all worry about long-term renal impairment. However, I have rarely had patients whose renal function deteriorates significantly in the very short-term (2-4 weeks). It is a drug with significant toxicity and issues. I will encourage people to get a copy of this paper, as well as read it, as it discusses a number of factors, particularly low-dose longer-term therapy.

Reference: J Dermatolog Treat. 2019;Sep 10 [Epub ahead of print]
Abstract

Factors associated with patient-reported importance of skin clearance among adults with psoriasis and atopic dermatitis

Authors: Egeberg A and Thyssen JP.

Summary: A cross-sectional study of 4016 psoriasis and 3842 atopic dermatitis patients was conducted to ascertain factors that are associated with patient views of the importance of obtaining complete or almost complete skin clearance. Almost complete or complete skin clearance was more important for atopic dermatitis than psoriasis patients. In both groups, almost complete clearance was more important than complete clearance, and greater disease severity and itch and skin pain were associated with the perceived importance of skin clearance. Atopic dermatitis and psoriasis of the face or neck and psoriasis of the palms, soles or genitals were associated with the patient-perceived importance of almost complete clearance. Only 7% of patients with severe atopic dermatitis and 27% of patients with severe psoriasis were receiving systemic therapy.

Comment: This study looks at both psoriasis and atopic dermatitis and assesses what patients want from their interaction with their dermatologist. It may be quite obvious to those who have been looking after patients for some time, but itch and skin pain are the most significant symptoms that patients want to improve. Again, increasing disease severity is something that patients want to stop. Disease on the face and neck, palms and soles, and genitals are also high priority sites. Only a very small percentage of the patients studied, from Denmark, were receiving a systemic therapy. I find this very interesting, in that they have a very socialised system with lots of dermatologists but their patients seem not to be getting very well treated. We have, of course, no data on Australia.

Reference: J Am Acad Dermatol. 2019;81(4):943-9
Abstract

Patient-reported outcomes of adalimumab, phototherapy, and placebo in the Vascular Inflammation in Psoriasis Trial

Authors: Noe MH et al.

Summary: Results of the multicentre, randomised, placebo-controlled Vascular Inflammation in Psoriasis trial were analysed to determine the effects of adalimumab and phototherapy on health-related quality of life in 97 patients. After 12 weeks, a minimal clinically important difference was observed in DLQI in adalimumab (OR 2.88; 95% CI 1.02-8.17) and phototherapy (OR 8.83; 95% CI 2.47-31.57) recipients versus placebo recipients. The odds of achieving a minimal clinically important difference in EQ-5D-3L (EQ-5D three-level version) were higher with phototherapy versus placebo (OR 9.78; 95% CI 2.99-31.95) and phototherapy versus adalimumab (OR 4.07; 95% CI 1.42-11.70).

Comment: I included this study not because of adalimumab, which is a drug that most dermatologists do not use as first line, but rather phototherapy. With the emphasis on biologic treatment some systemic treatments are not so popular. This study makes the point that phototherapy gave better quality of life changes than adalimumab. For those of us who still use phototherapy, I have always wondered why some patients who in my opinion would benefit from a switch to a biologic stay with phototherapy. Equally, I have a number of patients who are quite comfortable coming once a fortnight for their light treatment when other agents would free them up from having to attend the clinic. This is an interesting paper that explains in some way why patients choose phototherapy over a systemic agent.

Reference: J Am Acad Dermatol. 2019;81(4):923-30
Abstract

Narrowband ultraviolet B phototherapy improves quality of life of psoriasis and atopic dermatitis patients up to 3 months: Results from an observational multicenter study

Authors: Väkevä L et al.

Summary: This multicentre observational study assessed the efficacy and cost of narrowband ultraviolet B (UVB) phototherapy in psoriasis (n = 207) and atopic dermatitis (n = 144) patients. In both patient groups Self-Administrated PASI/Patient-Oriented SCORAD and DLQI scores improved and remained improved for at least 3 months. Pruritus alleviation was correlated with greater quality of life in both patient groups. Slight redness and burning adverse events occurred as a result of lack of minimal erythema dose testing. Mean patient costs were 21 hours of their time and €310, and the mean healthcare provider cost was €810.

Comment: This study runs on from the last one and again just makes a point that narrowband UVB is a very effective treatment for psoriasis. It also discusses atopic dermatitis, which is the patient group that we are still struggling with. Again this study has been put in to compliment the last one but also to remind readers not to forget the older traditional treatments we have used.

Reference: Photodermatol Photoimmunol Photomed. 2019;35(5):332-8
Abstract

Efficacy, safety, and patient-reported outcomes in patients with moderate-to-severe plaque psoriasis treated with brodalumab for 5 years in a long-term, open-label, phase II study

Authors: Lebwohl MG et al.

Summary: This open-label extension to a 12-week, phase II dose-ranging trial examined the use of the fully human anti-interleukin-17 receptor A monoclonal antibody brodalumab 210 mg every 2 weeks in 181 patients with moderate-to-severe plaque psoriasis. After a median follow-up of 264 weeks, brodalumab improvements were maintained in sPGA, PASI, and DLQI scores. A PASI score of 90-100 or PASI 100 after 12, 240 and 264 weeks was associated with greater likelihood of DLQI scores of 0 or 1 versus PASI 75-90. One adverse event of suicidal ideation was identified, but no suicides occurred.

Comment: Brodalumab has been mentioned earlier in this review. It is an IL-17 drug which seems to work a little faster than IL-23s. They also seem to be more effective at controlling joint disease than IL-23s. This medication originally had some issues with depression in its early onset research development pathway. That is why going onto the market has been a little bit slower. Certainly this drug has been well and truly assessed from a cardiac (MACE) point of view as well as the mental health aspects. There were no safety signals. I have had limited experience with this of late. I would be interested to see how painful the injections are. My usage of this medication will probably be driven by select patient details or/and the functionality of the actual medication injector, dosing frequency, pain, local reactions etc.

Reference: Am J Clin Dermatol. 2019;Sep 6 [Epub ahead of print]
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.