Biologics (Dermatology) Research Review™

Making Education Easy

Issue 67 - 2023

In this issue:

Abbreviations used in this issue:

AE = adverse event; **(a)OR** = (adjusted) odds ratio; **BSA** = body surface area; **DLQI** = Dermatology Life Quality Index; **HR** = hazard ratio; **ICU** = intensive care unit; **QoL** = quality of life; **PASI** = Psoriasis Area and Severity Index; **PBS** = Pharmaceutical Benefits Scheme; **PSP** = patient support programme; **RR** = relative risk; **sPGA** = static Physician's Global Assessment.

RACP MyCPD participants can claim **the time spent reading and evaluating research reviews** as CPD in the online **MyCPD program**.

Please contact MyCPD@racp.edu.au for any assistance.

Welcome to Issue 67 of Biologics Research Review.

We begin this issue with the open-label, extension study, LIBERTY AD OLE, which assessed the incidence of infections in adults with moderate-to-severe atopic dermatitis treated with dupilumab for up to 4 years. This is followed by an interesting pooled analysis of five randomised, double-blind, placebo-controlled phase 2 and 3 clinical trials which examined the safety of tralokinumab in patients with moderate-to-severe atopic dermatitis. The next paper reports on results from the global SECURE-AD registry, that explored COVID-19 outcomes in patients with atopic dermatitis receiving systemic immunomodulatory treatments. We conclude this issue with a retrospective observational study which investigated patient adherence and persistence of ixekizumab while participating in a patient support programme.

We hope you find this update in Biologics in Dermatology research interesting and informative for clinical practice, and we look forward to reading your comments and feedback.

Kind Regards,

Clinical Professor Saxon D Smith AM
saxon.smith@researchreview.com.au

No increased risk of overall infection in adults with moderate-to-severe atopic dermatitis treated for up to 4 years with dupilumab

Authors: Blauvelt A et al.

Summary: The incidence of infections in adults with moderate-to-severe atopic dermatitis treated with dupilumab for up to 4 years was quantified in this open-label, extension study, LIBERTY AD OLE. A total of 2,677 patients from 28 countries across North America, Europe and Asia-Pacific were treated with dupilumab 300mg weekly; a subset of 8.4% changed to 300mg 2-weekly during the trial, and 13.1% of all patients received treatment up to week 204. Patients were permitted to use topical corticosteroids and calcineurin inhibitors. Incidence rates were recorded as nP/100 PY (number of patients with ≥1 event per 100 patient-years). The rate of overall infections was 71.27nP/100 PY, while serious and/or severe infections occurred in 1.39nP/100 PY and discontinuation as a result of infection in 0.34nP/100 PY. These data reflected the earlier 3-year results of this study and were lower than the 1-year data of adults treated with placebo plus topical corticosteroids. Each year of treatment saw decreases in the numbers of patients with treatment-emergent serious/severe infections, herpetic/non-herpetic infections and total skin infections.

Comment: The introduction of advanced medical therapies in the management of severe atopic dermatitis is causing a transformational shift in how we can look after these patients. Whilst conventional oral systemic agents have been the standard for the decades preceding this shift, we now have medical therapies which are able to much more reliably and reproducibly achieve substantial control of this common, but often challenging to treat condition. This has also allowed our understanding of the complex pathophysiology that underpins atopic dermatitis to evolve. Dupilumab, as a monoclonal antibody targeting IL4/IL13, takes advantage of this evolved understanding and can achieve clear or almost clear results in many patients. While it does not have the same level of efficacy in all patients, even a 50-75% improvement on control can be a life-changing moment for many of these patients who have suffered for years, often since childhood. However, as with all new medications we must maintain an eye on AEs. Infections such as herpes simplex and herpes zoster may have occurred somewhat more frequently in the active treatment arms compared to placebo during the phase 3 trials. Obviously, there must be consideration to the fact that atopic dermatitis patients have an increased risk because of the pathophysiologic alteration in their skin barrier function and innate immunity. However, it is very reassuring to see that there is not an increased risk of overall systemic or cutaneous infections in this first of hopefully many timepoints to come.

Reference: Adv Ther. 2023;40(1):367-80

Abstract

Safety of tralokinumab in adult patients with moderate-to-severe atopic dermatitis

Authors: Simpson EL et al.

Summary: This was a pooled analysis of five randomised, double-blind, placebo-controlled phase 2 and 3 clinical trials which examined the safety profile of tralokinumab in patients with moderate-to-severe atopic dermatitis. Across the studies, a total of 2,285 patients were randomly assigned to either tralokinumab (n=1,605) or placebo (n=680). AEs occurred in 65.7% and 67.2% of patients treated with tralokinumab and placebo, respectively (640 and 678 events per 100 patient-years of exposure [ep100PYE]; rate ratio 1.0), while serious AEs occurred in 2.1% and 2.8% (7.4 and 11.9 ep100PYE; rate ratio 0.7). Compared with placebo, patients who received tralokinumab experienced higher rates of viral upper respiratory tract infection (15.7% vs. 12.2%), upper respiratory tract infection (5.6% vs. 4.8%), conjunctivitis (5.4% vs. 1.9%) and injection-site reaction (3.5% vs. 0.3%). Continued maintenance of treatment did not lead to an increase in common/serious AEs or discontinuation of treatment due to AEs. At 1 year, no clinically meaningful changes in laboratory measures were recorded.

Comment: We have been witnessing in the past decade the transformative impact that monoclonal antibody biologics have had on disease and patient QoL in psoriasis. With the third generation of these agents, we now can reliably and reproducibly have the majority of patients clear or almost clear of their psoriasis. And now in the setting of atopic dermatitis, we are witnessing another wave of transformative impact from monoclonal antibody biologics. Even though it may have taken a few years through government reimbursement regulations, dupilumab has changed the lives of many severe atopic dermatitis sufferers. However, having more options in the armoury to assist us in managing atopic dermatitis are needed. The Janus Kinase inhibitors have been shown to be efficacious in their phase 3 trial programs as well as in our own real-world experience with upadacitinib. However, there remains some clarification from the recent FDA black box warning which adorns all Janus Kinase inhibitors as a result of a single, small, open-label extension study in patients with rheumatoid arthritis of tofacitinib - the first-generation Janus Kinase inhibitor. This 'lumping' approach to all Janus Kinase inhibitors by regulatory bodies is slowing the possible availability of these medications in severe atopic dermatitis as well as in other disease states such as vitiligo and alopecia areata. This is unfortunate for the patients, and also because at present, the concerns around Major Acute Cardiac Events and all malignancies has not been seen as a signal in these skin conditions. Regardless, it means that now, more than ever, we look to the next wave of available monoclonal antibody inhibitors as the most likely next options for our patients. Tralokinumab is a fully human monoclonal antibody that inhibits the activity of interleukin-13 selectively. To date, their phase 3 clinical trials including adults with moderate-to-severe atopic dermatitis, of up to 52 weeks' duration, showed tralokinumab was efficacious and well-tolerated. Importantly in this paper, the authors present the safety data for the initial treatment period of 16 weeks which show no new signals that differ substantially from dupilumab - which we use on a day-to-day basis already.

Reference: Br J Dermatol. 2022;187(6):888-99
Abstract

The effects of systemic immunomodulatory treatments on COVID-19 outcomes in patients with atopic dermatitis

Authors: Musters AH et al.

Summary: This paper outlines the results from the global SECURE-AD registry, which explored COVID-19 outcomes in patients with atopic dermatitis treated with systemic immunomodulatory treatments. A total of 442 individuals (mean age 35.9 years; 51.8% male) with atopic dermatitis and COVID-19 were identified from 27 countries, 297 (67.2%) of whom were treated with a single systemic therapy (mainly dupilumab n=216), while 131 patients (29.6%) were treated with topical therapy only. No deaths occurred, and 26 patients (5.9%) were admitted to hospital. Hospitalisation was more likely for patients treated with topical treatments than those treated with dupilumab monotherapy (aOR 4.99; 95% CI 1.4—20.84), and for patients treated with combination systemic therapy (not including systemic corticosteroids) than single-agent non-steroidal immunosuppressive treatment (aOR 37.57; 95% CI 1.05—871.11). The patients most likely to be hospitalised were those treated with combination systemic therapy including systemic corticosteroids (aOR 45.75; 95% CI 4.54—616.22). The authors concluded that the overall risk of COVID-19 complications is low among patients with atopic dermatitis, and that the lowest rate of hospitalisation occurred for patients on dupilumab monotherapy.

Comment: Despite the overall apathy of the general population and the glaring absence of stories around SARS-CoV-2 (COVID-19) from the media, we are still living in an age of a pandemic. I am not an epidemiologist, so I am not sure at what point in time we will move from being in a pandemic to SARS-CoV-2 being reduced to the level of a general endemic virus, like many we have lived with for decades, such as influenza. However, with death rates from SARS-CoV-2 still higher than at the peak of the pandemic isolations, it suggests that we have some way to go even if the wearing of masks (whilst recommended by the government health agencies) is not actually mandated nor followed by the vast majority of the population. As such, we must be very mindful of this when we are treating our dermatology patients with conventional oral systemics or advanced medical therapies. It has certainly become apparent over the last few years that it is not only the therapeutic agent but also the underlying medical condition for which it is being used that is perhaps the most important question. Therefore, it is reassuring to clinicians to see the data presented by these authors herewith about the SARS-CoV-2 infection and complication risk in the setting of patients with atopic dermatitis on these therapies. More importantly, it should be reassuring for the patients who are actually taking the agents.

Reference: J Eur Acad Dermatol Venereol. 2023;37(2):365-81
Abstract

Association of rituximab with risk of long-term cardiovascular and metabolic outcomes in patients with pemphigus

Authors: Kridin K et al.

Summary: The objective of this global, population-based, retrospective cohort study was to compare the risks of long-term cardiovascular and metabolic outcomes and all-cause mortality in patients with pemphigus managed with rituximab vs. first-line corticosteroid-sparing agents (azathioprine and mycophenolate mofetil). A total of 1,602 patients (53.4% female) were included in the analysis, 961 of whom were treated with rituximab (mean age 54.8 years) and 961 with azathioprine or mycophenolate mofetil (mean age 54.4 years). There was no significant between-group difference in all-cause mortality (HR 0.94; p=0.77), however patients in the rituximab cohort had lower risks of type 2 diabetes (RR 0.63; p<0.001), obesity (RR 0.49; p<0.001), hypertension (RR 0.48; p<0.001), peripheral vascular disease (RR 0.47; p=0.003), osteoporosis (RR 0.46; p<0.001), myocardial infarction (RR 0.45; p=0.01), hyperlipidaemia (RR 0.45; p<0.001) and stroke (RR 0.42; p<0.001), than those treated with azathioprine or mycophenolate mofetil. Researchers noted that rituximab may be the preferable treatment option for patients with cardiovascular and metabolic risk factors.

Comment: In many ways we have been fortunate to live in a golden age of dermatological disease management, especially with the advent of monoclonal antibody therapies. Many diseases which had been so difficult to treat reliably and reproducibly from patient-to-patient are now being treated with expectations of being clear, or almost clear. The balancing scales of therapeutics always has clinicians mindful to the known side effects as demonstrated in the clinical trials, as well as to the possibility of late signals of significant side effects, such as seen with efalizumab. But perhaps the next evolution in our understanding of the positive impacts of monoclonal antibody therapy is whether they can alter the natural disease course and its associations. The challenge to prove this is in the longer lead time in which associations may or may not develop, in particular the cardiovascular ones. However, if we are able to not only improve the immediate QoL of a patient, but also positively alter their underlying predisposition to significant associations (like cardiovascular disease in psoriasis and pemphigus), then this would open a new window to a second wave of transformative change in these patient populations.

Reference: JAMA Dermatol. 2023;159(1):56-61
Abstract

Efficacy and safety of mirikizumab in psoriasis

Authors: Blauvelt A et al.

Summary: The efficacy and safety of mirikizumab in patients with moderate-to-severe plaque psoriasis were explored in the 52-week, double-blind, placebo-controlled, randomised withdrawal, phase 3 trial, OASIS-1. Eligible patients (n=530; mean age 46.3 years; mean baseline PASI 22.6) were randomised 4:1 to receive either mirikizumab 250mg 4-weekly (n=423) or placebo (n=107) until week 16, before the mirikizumab cohort was randomised 1:1:1 to mirikizumab 250mg/125mg/placebo 8-weekly until week 52. With regard to the co-primary endpoints, a significantly greater proportion of patients in the mirikizumab arm achieved an sPGA score of 0 or 1 with ≥2-point improvement than the placebo arm at week 16 (69.3% vs. 6.5%; p<0.001), and a greater proportion achieved a ≥90% improvement in PASI score (PASI 90; 64.3% vs. 6.5%; p<0.001). Patients treated with mirikizumab also achieved higher rates of PASI 75 (82.5% vs. 9.3%; p<0.001) and PASI 100 (32.4% vs. 0.9%; p<0.001). The superiority of mirikizumab over placebo maintained efficacy through to week 52 across both 250mg (p<0.001) and 125mg doses (p<0.001). No deaths were recorded, and no novel safety concerns arose, with similar rates of serious AEs across all treatments.

Comment: It is important to have an array of therapeutic options in the management of disease states. For example, in psoriasis there are currently nine PBS-listed monoclonal antibody therapies. Even though these can be categorised into classes based on the target of action (such as IL23, IL17, IL12/23 and TNFa), we know that there is often substantial genetic mosaicism in the binding sites. Therefore, it can be a trial-and-error process to match the jigsaw piece of the active agent with the binding site, so having more treatment options is an advantage. Conversely, in disease states that have few, if any, advanced therapies, such as hidradenitis suppurativa which has one biologic, it highlights the need for more therapeutic options to help more patients find their best jigsaw piece. However, how do we make room for the next generation of therapies, such as mirikizumab? Will we see older therapies labelled as obsolete or simply removed from PBS over time? This is going to be a challenge for all health regulators for the foreseeable future. On the other hand, as a clinician, seeing other new potential agents coming though trial programmes is always of interest.

Reference: Br J Dermatol. 2022;187(6):866-77
Abstract

Predictors of time to relapse following ustekinumab withdrawal in patients with psoriasis who had responded to therapy

Authors: Chiu H-Y et al.

Summary: This 8-year multicentre study aimed to identify the predictors of relapse in patients with psoriasis who discontinue ustekinumab therapy in a real-world setting. A total of 202 eligible patients were included in the study, all of whom responded to therapy and were either withdrawn or discontinued ustekinumab treatment. Following cessation of treatment, the cumulative probabilities of being free from relapse were 49.3% at 6 months, 12.6% at 12 months, 5.3% at 24 months and 1.6% at 36 months. The significant predictors of time to relapse (after adjustments) included biologic-naïve status, maximum improvement in PASI during ustekinumab treatment, time to achieve a 50% improvement in baseline PASI score after commencing ustekinumab, family history of psoriasis, chronic kidney disease and immunosuppressant use while not receiving ustekinumab. The authors concluded that the discontinuation of ustekinumab in patients with well-controlled psoriasis should not be considered due to the high rates of relapse.

Comment: When a patient starts on their monoclonal antibody biologic, a common question that they ask is, "How long to I have to stay on it?" All of the phase 3 trials demonstrate the positive impact on the specific disease, with initial therapy for around 12-16 weeks and continuation therapy out to 52 weeks. This information is critical to have a drug registered and therefore accessible for patients. However, it does not specifically answer the patient's questions. Open-label extension trials and real-world evidence experience help to answer the long-term drug survival for patients as well as whether the real-world experience matches the phase 3 clinical trials. But again, it does not answer the patient's question. We are fortunate in Australia to have PBS support for many of the available monoclonal antibody therapies, especially in dermatology. However in other countries, particularly in Southeast Asia, patients are not as lucky. In Taiwan, patients can qualify for a period of government-supported biologic therapy (12-18 months depending on circumstances). Once this period is expired, and if the patient cannot afford to self-fund continuing treatment, then they are required to cease therapy and await a flare before being able to recommence. This is invaluable experience as it helps to categorise who is at risk of flaring, as well as the time to flare. The long and short of this type of experience demonstrates that the majority of patients will have flared by 6 months. Therefore, continuation of therapy for the indefinite future appears to remain the best cause of action, which answers the patient's question for now.

Reference: J Am Acad Dermatol. 2023;88(1):71-78
Abstract

Prevalence, risk and severity of SARS-CoV-2 infections in psoriasis patients receiving conventional systemic, biologic or topical treatment during the COVID-19 pandemic

Authors: Kwee KV et al.

Summary: This paper reports on the findings from the cross-sectional cohort study PsoCOVID, in which the objectives were to 1) estimate the prevalence of SARS-CoV-2 in psoriasis patients; 2) compare the rates of SARS-CoV-2 infection for biologic vs. systemic conventional vs. topical therapy treatment groups; and 3) outline the characteristics of patients with severe COVID-19 across treatment groups. Between April and October 2021, a total of 551 patients were included in the study (44.1% biologic therapy; 32.3% systemic therapy; 26.6% topical therapy), of whom 10.7% had suffered a SARS-CoV-2 infection. The infection risks for SARS-CoV-2 were comparable between biologic and non-biologic systemic therapy users, and patients receiving other treatment. Four patients (0.7%) were hospitalised, however none were admitted to ICU, and the mortality rate was 0.32% across all treatment groups. The authors concluded that the data further support the recommendation that a preventative cessation of systemic therapies to reduce the SARS-CoV-2 infection rate is not required in patients with psoriasis.

Comment: Following on the theme of being 'alert but not alarmed' for our biologics patients with respect to SARS-CoV-2, here the authors report on a psoriasis population. Again, it appears as though there is not a specific increased risk of catching SARS-CoV-2 for psoriasis patients on biologics and non-biologics systemics. This is interesting to compare against the previously-documented risk of patients with rheumatoid arthritis in earlier studies. This helps support the argument that the therapeutic and baseline disease states must be taken into consideration when consenting patients about their SARS-CoV-2 risk.

Reference: J Dermatolog Treat. 2023;34(1):2161297
Abstract

Treatment persistence of ixekizumab in adults with moderate-to-severe plaque psoriasis participating in the Canadian Patient Support Program

Authors: Gulliver W et al.

Summary: The impacts of the Canadian Patient Support Programme (PSP) on treatment adherence and persistence of ixekizumab among patients ≥18 years with moderate-to-severe plaque psoriasis were assessed in this retrospective, observational study. A total of 1,891 eligible patients were included in the analysis (mean age 52.3 years; 61.4% male; mean baseline PASI score 14.3; mean DLQI 16.5; mean BSA 17.4%). While participating in the PSP, adherence (≥80% of days covered) was high among patients treated with ixekizumab at 1 (92.0%) and 2 years (87.7%), and adherence was higher in biologic-naïve than in biologic-experienced patients at both 1 (94.6% vs. 87.3%) and 2 years (90.3% vs. 83.5%). Persistence was also high at 1 (90.4%) and 2 years (85.6%), and biologic-naïve demonstrated significantly higher persistence than biologic-experienced patients at both 1 ($p<0.01$) and 2 years ($p=0.010$).

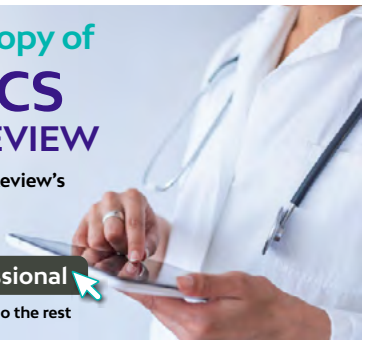
Comment: It is always important to consider the whole of the patient who is sitting in our consultation room with us. This is the fundamental of both patient-centric and personalised healthcare. In the setting of advanced therapies for cutaneous conditions, this clinical approach involves detailed consent as well as registering the patient for the company-supported PSP. PSPs are an invaluable adjunct to therapy. Their offerings are varied, but the central component is a nurse support program as well as appointment and injection reminders. Increasingly, I am seeing the value of the injection reminder component of these services. As we are reliably and reproducibly able to have more patients clear or almost clear of their underlying dermatosis, overtime it becomes more frequent that my patients start to forget their dosing schedule. This has been made worse since the various COVID-19 lockdowns where the 'taffy' nature of time really stretched, which made it easier for patients to forget the timing of their injections. On top of this there are dietician/diet supports and other useful services. The authors also present findings to suggest that PSPs contribute positively against treatment apathy, with patients more likely to remain on therapy if they are enrolled and engage with a PSP.

Reference: Dermatol Ther (Heidelb). 2023;13(1):235-44
Abstract

Biologics (Dermatology) Research Review™

Independent commentary by Clinical Professor Saxon D Smith AM

Clinical Professor Saxon D Smith AM is a consultant dermatologist in private practice in Gosford and St Leonards, Australia, and Clinical Professor at Sydney Adventist Hospital Clinical School, The Australian National University. He has a special interest in biologics for the treatment of complex dermatologic conditions. He previously ran public clinics at Royal North Shore Hospital in surgical cutaneous oncology; immune-oncology management and surveillance in advance melanoma; multi-disciplinary team with plastic surgery on the management of hidradenitis suppurativa; multi- disciplinary team with neurology on skin diseases in neurology including management of adverse reactions of treatment; and dermatology in renal transplant patients.



Australian Research Review subscribers can claim CPD/CME points for time spent reading our reviews from a wide range of local medical and nursing colleges. Find out more on our CPD page.