Biologics (Dermatology) Research Review™

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Issue 53 - 2022

In this issue:

Abbreviations used in this issue:

CD = cluster of differentiation
CI = confidence interval
DLQI = Dermatology Life Quality Index
DNAM = DNAX accessory molecule
EMA = European Medicines Agency
FDA = Food and Drug Administration
HiSCR = Hidradenitis Suppurativa Clinical Response
HR = hazard ratio
ICI = immune checkpoint inhibitor
IGA = Investigator's Global Assessment
IL = interleukin
JAK = Janus kinase
OR = odds ratio
PASI = Psoriasis Area Severity Index
PBS = Pharmaceutical Benefits Scheme
SF36 = Short Form-36
TEAE = treatment-emergent adverse event
TGA = Therapeutic Goods Administration
TIGIT = T cell immunoreceptor with immunoglobulin and immunoreceptor tyrosine-based inhibitory motif (ITIM) domain
TNF = tumour necrosis factor

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Welcome to Issue 53 of Biologics Research Review.

The findings of a recent cohort study suggest that the development of cutaneous immune-related adverse events is strongly associated with response to immune checkpoint inhibitor therapy and patient survival in those with malignant neoplasms. In a French study, mogamulizumab was shown to contribute to the restoration of an efficient immunity and reshape not only the malignant lymphocyte subset but also the benign subset in patients with Sézary syndrome. Other topics covered in this issue include the long-term use of risankizumab for moderate-to-severe plaque psoriasis, brodalumab for plaque psoriasis after failure of an IL-17A blocker, adalimumab therapy for hidradenitis suppurativa, and the patient's perspective on dupilumab for atopic dermatitis.

We hope you find our selection for Biologics Research Review stimulating reading and we welcome your feedback. Furthermore, if you have discovered or been involved with what you think is significant global research, please let us know and we will consider it for inclusion next time.

Kind Regards,

Clinical Professor Saxon D Smith AM
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Association of cutaneous immune-related adverse events with increased survival in patients treated with anti-programmed cell death 1 and anti–programmed cell death ligand 1 therapy

Authors: Tang K et al.

Summary: This retrospective cohort study analysed data from the US/EU TriNetX Diamond Network to determine the relationship between cutaneous immune-related adverse events during anti-programmed cell death 1 (PD-1) or anti-programmed cell death ligand 1 (PD-L1) treatment and patient survival. Among 7008 patients (43.3% women; mean age 68.2 years) and 7008 (43.4% women; mean age 68.3 years) matched controls with malignant neoplasms, mortality was lower in patients who experienced pruritus (HR 0.695; 95% CI 0.602-0.803; $p < 0.001$), drug eruption (HR 0.755; 95% CI 0.635-0.897; $p = 0.001$), xerosis (HR 0.626; 95% CI 0.469-0.834; $p = 0.001$), nonspecific rashes (HR 0.704; 95% CI 0.634-0.781; $p < 0.001$), or any cutaneous immune-related adverse events (HR 0.778; 95% CI 0.726-0.834; $p < 0.001$) and in those with psoriasis (HR 0.703; 95% CI 0.497-0.994; $p = 0.045$) and lichen planus/lichenoid dermatitis (HR 0.511; 95% CI 0.279-0.939; $p = 0.03$).

Comment: Immune checkpoint inhibitors (ICIs) have been transformative in the management of metastatic melanoma. With substantial improvement in survival rates and disease-free progression rates, this has helped many patients that only 10 years ago were looking down the barrel of a significantly poor prognosis. With the success in melanoma management, it is not surprising that trials in other cancers would proceed. At present, many of the advanced skin malignancies, such as squamous cell carcinoma and Merkel cell carcinoma, have shown similar positive responses seen in the melanoma population. There has also been improvement in some other solid organ malignancies such as lung cancers and is now in early phase for rarer soft tissue sarcomas. However, this success comes with a new batch of immune-mediated adverse drug reactions. The authors here indicate that having a cutaneous adverse drug eruption may be advantageous as a surrogate biomarker for response to therapy and potentially patient survival. Therefore, it will be important for clinicians to be aware of and manage these adverse reactions as they may continue for prolonged periods after the ICI has been ceased.

Reference: JAMA Dermatol. 2022;158(2):189-193
Abstract

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 Sydney Adventist Hospital Clinical School, Australian National University, Sydney, Australia. He has a special interest in biologics for the treatment of complex dermatologic conditions. He runs a large private practice which focuses on the management of inflammatory dermatosis (such as psoriasis, atopic dermatitis and chronic spontaneous urticaria); 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 and oncology on skin diseases in neurology including management of adverse reactions of treatment; and dermatology in renal transplant patients.

Mogamulizumab induces long term immune restoration and reshapes tumor heterogeneity in Sézary syndrome

Authors: Roelens M et al.

Summary: This study assessed the hypothesis that the anti-CCR4 monoclonal antibody mogamulizumab might reshape the immune tumour microenvironment as well as deplete Sézary cells in 26 patients with stage B2 disease. Before mogamulizumab initiation, the benign CD4+ T-cell subset displayed exhausted phenotypes, with an increased gradient in PD-1/TIGIT/DNAM/CD27/CD28 and CD70 expression compared to age-matched controls. All patients had Sézary cells with heterogeneous phenotypes with distinct malignant subsets exhibiting differential expression of individual markers. Early complete blood response in 17 patients was associated to higher baseline CCR4 expression. Benign T cells and activated Treg counts decreased during the first 4 weeks of treatment and long-term follow-up showed immune restoration involving CD8+, naive and stem-memory CD4+T cells, with near disappearance of exhausted lymphocytes. Mogamulizumab resistance/tumour escape was associated with emergence of CCR4 negative Sézary cells in blood and skin, with changes in heterogeneity patterns, and was not explained by mutations in CCR4 coding regions.

Comment: Cutaneous T-cell lymphoma (CTCL) is a rare type of cancer where the T-cells develop abnormalities that make them infiltrate and/or attack the skin without any extracutaneous disease at the time of diagnosis. Several types of CTCL exist and are largely defined by histopathological and immunohistochemical features. The most common type is mycosis fungoides, which tends to have a more indolent natural course of disease and may be localised or more widespread. On the other hand, Sézary syndrome is a less common type but tends to have a more aggressive disease course and causes erythroderma. The type of CTCL that a patient has often determines which treatments are best and can include topical corticosteroids, phototherapy, radiation therapy and systemic medications, such as chemotherapy. More recently an anti-CCR4 monoclonal antibody, mogamulizumab has started to transform the management of several CTCL subtypes.

Reference: Br J Dermatol. 2022;Jan 18 [Epub ahead of print]
Abstract

Secukinumab dosing every two weeks demonstrated superior efficacy compared with dosing every four weeks in patients with psoriasis weighing 90 kg or more: Results of a randomised controlled trial

Authors: Augustin M et al.

Summary: This multicentre, double-blind, parallel-group trial, examined use of secukinumab 300 mg every 2 weeks (Q2W; n = 165) versus secukinumab 300 mg every 4 weeks (Q4W; n = 166) in 331 patients with moderate-to-severe chronic plaque psoriasis with a body weight ≥90 kg. After 16 weeks of treatment, Q2W administration resulted in higher PASI 90 responses than Q4W administration (73.2% vs 55.5%, one-sided p = 0.0003; OR 2.3; 95% CI 1.4-3.8). After 52 weeks, greater efficacy was maintained in Q2W recipients (PASI 75 88.9% vs 74.8%; PASI 90 76.4% vs 52.4%, PASI 100 46.7% vs 27.3%; Investigator's Global Assessment [IGA] 0 or 1 75.9% vs 55.6% and Dermatology Life Quality Index [DLQI] 0 or 1 66.1% vs 48.8%). Q4W PASI 90 non-responders who up-titrated to Q2W (n = 31) had higher PASI 90 responses at 32 weeks (16 weeks after up-titration) than those who remained on Q4W administration (n = 40; 38.7% vs 16.5%).

Comment: Monoclonal antibodies targeting various points of the pathogenesis of psoriasis have transformed the management of psoriasis patients. These therapies when used in moderate-to-severe patients can reliably clear or almost clear at least 50% of patients depending on the cytokine targeted. Understandably this also leads to substantial improvements in the quality of life of these patients who often have been struggling with their psoriasis for many years. We know that there are key medical associations and co-morbidities with psoriasis as it is a systemic condition and not just simply a skin disease. A key medical association is obesity, with psoriasis patients much more likely to be obese. This association has even been shown in children with psoriasis who have higher weight to height ratios than the non-psoriasis age-matched population. At present there are only two monoclonal antibodies that allow for variation in dosing dependent on weight, infliximab and ustekinumab. However, the authors present an argument here that there is benefit to up-titrate patients over 90 kg on secukinumab from 300 mg Q2W to 300mg Q2W. Unfortunately, this is currently not supported by the PBS authority pathway.

Reference: Br J Dermatol. 2022;Jan 4 [Epub ahead of print]
Abstract

Long-term efficacy and safety of risankizumab for the treatment of moderate-to-severe plaque psoriasis: Interim analysis of the LIMMitless open-label extension trial beyond 3 years of follow-up

Authors: Papp KA et al.

Summary: The open-label phase III LIMMitless extension trial is examining the long-term use of isankizumab in 897 patients with psoriasis. After 172 weeks of treatment, 799 patients were still receiving treatment, of whom 85.5% had achieved PASI 90, 54.4% achieved PASI 100, 85.2% achieved static Physician's Global Assessment (sPGA) score of clear or almost clear (0/1), and 78.4% achieved a DLQI of 0/1. Rates of adverse events leading to discontinuation or of safety interest were low and similar to those identified previously.

Comment: Whilst monoclonal biologics have transformed the management of psoriasis, there always needs to be a balance with understanding the potential for adverse reactions. This balance is always most challenging in the early years, when clinicians have access to a new therapy. Clinical trials are structured to test the efficacy of the therapy on a disease state as well as monitor for any safety signals. They are essentially designed to satisfy the various countries, government medication authorities. In fact, the design of clinical trials has changed substantially over the last couple of decades in response to what the FDA or EMA require in order for these organisations to consider a therapeutic in their jurisdictions. Clinical trials provide some safety data but with patients in the trial often initially only on therapy for a few months to meet the primary endpoint, real-life longer-term exposure is needed to better understand safety. Therefore, it is always heartening to see open-label extension trials, such as presented by the authors here, help to reassure the longer-term safety profile of a medication such as rizankizumab.

Reference: Br J Dermatol. 2021;185(6):1135-1145
Abstract

Five-year maintenance of clinical response and health-related quality of life improvements in patients with moderate-to-severe psoriasis treated with guselkumab: Results from VOYAGE 1 and VOYAGE 2

Authors: Reich K et al.

Summary: This open-label extension trial examined the use of guselkumab 100 mg every 8 weeks for up to 252 weeks in 1829 patients with moderate-to-severe psoriasis. In VOYAGE 1 and VOYAGE 2, 84.1% and 82.0% of patients achieved a PASI 90, while 82.4% and 85.0% achieved an IGA 0/1, 54.7% and 55.5% achieved an IGA 0, and 52.7% and 53.0% achieved a PASI 100. The following Health-related quality of life endpoints were achieved; DLQI 0/1 72.7% and 71.1% of patients, Psoriasis Symptoms and Signs Diary [PSSD] symptom score 0 42.4% and 42.0%, and PSSD signs score 0 33.0% and 31.0%. Approximately 45% of patients in VOYAGE 2 achieved ≥5-point reduction in SF36 physical and mental component scores, and 80% had no anxiety or depression.

Comment: When new medications become available to clinicians for the management of conditions such as psoriasis, we are often preoccupied with safety and efficacy data. Obviously, these are two key datasets to help guide our individual comfort to prescribe a medication. We have been very fortunate that the explosion in the interest in therapeutics in dermatology has led to multiple new waves of therapeutics becoming available to help with the management of our patients. We now have a large armoury to manage psoriasis, a fledging armoury for the management of atopic dermatitis, as well as options in historically difficult to manage disease states such as hidradenitis suppurativa and chronic spontaneous urticaria. However, it is important for clinicians not to lose sight of the patient as the person who lived with their condition but also deals with any of the potential adverse reactions. Every patient is very different and their needs/wants should be factored into any management approach to personalise their therapy. Therefore, patient-reported outcomes are increasingly important to review as a third key dataset when critically appraising clinical trials.

Reference: Br J Dermatol. 2021;185(6):1146-1159
Abstract

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References: **1**. Papp KA *et al.* Efficacy and Safety of Continuous Risankizumab Every 12 Weeks Beyond 3 Years of Follow-Up: An Interim Analysis of the LIMMitless Open-Label Extension Trial. Poster presented at: American Academy of Dermatology (AAD) 2021 VMX Event, April 23–25, 2021. **2**. Papp KA *et al. Dermatol Ther (Heidelb)* 2021;11:487–497.

Changing within the same class: Efficacy of brodalumab in plaque psoriasis after treatment with an IL-17A blocker – a retrospective multicenter study

Authors: Kromer C et al.

Summary: This German retrospective multicentre chart review examined the effect of switching to brodalumab after failure of an IL-17-receptor A antagonist (ixekizumab or secukinumab) in 23 patients. PASI 75 was achieved by 11 (47.8%) patients at 12 and 24 weeks. Mild adverse events which did not lead to drug discontinuation occurred in three patients.

Comment: Selecting a monoclonal antibody biologic for a psoriasis patient has become somewhat more complicated with the addition of new therapeutic options and therapeutic classes. This opportunity to have an extend armoury of therapeutic agents is a double-edged sword because we lack sufficient clinically available biomarkers or pharmacogenetic screening to help us chose the best agent for each individual patient as part of a personalised medical management approach. Therefore, we are required to look for other surrogate markers to help inform the treatment decision, such as co-morbidities like psoriatic arthritis, or patient factors such as needle phobia, or side effect profiles. However, it is not uncommon that clinicians need to consider transitioning their patient to another agent when the initial selection either fails to achieve the desired efficacy or induces unwanted adverse reactions. This then raises the question about which agent to switch to. Do you stay in the same class? Or do you shift to a different class. It is important to remember that even within the same class there are different molecular targets (such as receptor binders), different binding affinities, as well as the unquantifiable genetic heterogeneity of each patient. Therefore, studies such as the authors present here can be used to help inform these decisions.

Reference: J Dermatolog Treat. 2021;32(8):878-882
Abstract

Seven years-experience of adalimumab therapy for hidradenitis suppurativa in a real-life dermatologic setting

Authors: Odorici G et al.

Summary: This Italian retrospective case review examined the real-life experiences of 76 patients (mean age 38.26 years) with hidradenitis suppurativa treated with adalimumab. Most treated patients had Hurley stage III disease (n = 58), the mean Sartorius score was 115.5 and the mean International Hidradenitis Suppurativa Severity Score System (IHS4) was 76.1. A correlation was found between cessation of adalimumab and hospitalisation, the loss of the achievement of the Hidradenitis Score (HiSCR) and surgery. No need for surgery was a protective factor against failure of adalimumab, suggesting that the most severe cases are more likely to fail biological therapy.

Comment: Hidradenitis suppurativa is a complex chronic waxing and waning inflammatory dermatosis. Its pathogenesis is increasingly being understood due to the upswing in research interest in this condition in the past 10 years. It appears that TNF and IL-17 play a significant role in the disease, which is why there is some crossover with psoriasis as a comorbidity. Importantly for patients, there has also been significant work to raise public and clinician awareness about this condition both in Australia and globally. However, the management of hidradenitis suppurativa has not substantially changed in recent years. Antibiotics and antibiotic combinations, which have anti-inflammatory effects, remain the first line of therapy as well as flare management. For patients who fail to respond to these and have Hurley stage II-III disease, adalimumab remains the only FDA/EMA/TGA approved monoclonal antibody therapeutic. Adalimumab has certainly been a large step forward in disease management for many sufferers. Furthermore, there is now up to 7 years of real-world data and experience in using adalimumab in this patient population. However, it will be exciting to have other therapeutic options in the near future in order to find the best jigsaw puzzle piece for each patient.

Reference: J Dermatolog Treat. 2021;32(8):878-882
Abstract

Janus kinase 1 inhibitor INCB054707 for patients with moderate-to-severe hidradenitis suppurativa: Results from two phase 2 studies

Authors: Alavi A et al.

Summary: This analysis of data from two multicentre phase II trials assessed the use of a JAK1 inhibitor (INCB054707 15 [1st trial; n = 10], 30, 60, or 90 [2nd trial] mg/day) in 45 patients with hidradenitis suppurativa. Overall, 70.0% of patients in the 1st trial and 80.8% in the 2nd trial experienced ≥1 TEAE. After 8 weeks, three patients in the 1st trial and 17 patients receiving INCB054707 (30 mg 55.6%; 60 mg 55.6%; 90 mg 87.5%) versus four patients receiving placebo in the 2nd trial achieved HiSCR.

Comment: Adalimumab has been the sole disease-modifying agent for patients with hidradenitis suppurativa Hurley stage II-III disease for many years. As demonstrated by the previously discussed paper, adalimumab has been successful for many patients to achieve a significant bandwidth of control of their disease. This has certainly transformed the lives of many sufferers. However, adalimumab is not a one size fits all medication in the setting of hidradenitis suppurativa because of the complex pathophysiology inflammatory cascade that drives the disease. Therefore, research into newer therapeutics and novel therapeutic pathways is needed to broaden the armoury available to these patients to better control this painful waxing and waning disease. There are phase III trials investigating IL-17 as a potential therapeutic target. Here the authors present the composite results of two phase II trials investigating a Janus kinase signalling inhibitor and its safety and efficacy. The results indicate this agent as a potential future therapy. However, the results of future phase III trials will be monitored with interest over the coming years.

Reference: Br J Dermatol. 2022;Jan 2 [Epub ahead of print]
Abstract

Efficacy of dupilumab in atopic dermatitis: The patient's perspective

Authors: de Bruin-Weller M et al.

Summary: This analysis of data from four placebo-controlled trials (CHRONOS, SOLO 1&2, and CAFÉ) was conducted to assess the use of dupilumab for atopic dermatitis from the patients' perspective using patient-reported outcome data (n = 1553). Across all four studies, more dupilumab-treated than placebo-treated patients ($p < 0.0001$) reported "Good", "Very Good" or "Excellent" disease status from week 2 to week 16 (SOLO 1&2 59.5% vs 24.6%; CAFÉ 16 weeks 84.1% vs 45.4%) or week 52 (CHRONOS 69.8% vs 25.1%), and more reported "Good", "Very Good", or "Excellent" treatment efficacy versus control (SOLO 1&2 65.0% vs 21.1%; CAFÉ 85.0% vs 36.1%; CHRONOS 72.6% vs 24.8%; all $p < 0.0001$).

Comment: It feels like we are on the crest of a wave to therapeutic opportunity for long suffering atopic dermatitis patients. There has been substantial research into the pathogenesis which has led to the identification of potential druggable targets such as directly inhibiting IL-4, IL-13, and IL-31, or inhibition via the JAK signalling pathway. Excitingly, we already have two TGA approved therapies with one in each of the monoclonal antibody biologics and JAK inhibitors. These have shown strong phase III study results in terms of efficacy and safety. However, it is also important to consider the patient perspectives which in the clinical trials is captured in the patient-reported outcomes data. However, we are now also starting to see real-world experience data which help to show the early impact of their disease-modifying drug on the quality of life of patients. Importantly the authors of this paper have demonstrated an early and sustained improved disease status as well as patient wellbeing out to 12 months.

Reference: Dermatol Ther (Heidelb). 2021;11(6):2123-2131
Abstract