Biologics (Dermatology) Research Review™

Making Education Easy

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In this issue:

Abbreviations used in this issue:

CI = confidence interval; **COVID-19** = coronavirus disease 2019; **CRP** = C-reactive protein; **HR** = hazard ratio; **Ig** = immunoglobulin; **IL** = interleukin; **PBS** = Pharmaceutical Benefits Scheme; **PD-1** = programmed cell death protein 1; **RFS** = recurrence-free survival; **RR** = relative risk; **SARS-CoV-2** = severe acute respiratory syndrome coronavirus; **SII** = systemic immune-inflammation index; **Th** = T helper; **TNF** = tumour necrosis factor.

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Welcome to Issue 96 of Biologics Research Review.

First up we take a look at a retrospective study investigating novel inflammatory biomarkers in patients with hidradenitis suppurativa receiving adalimumab and learn that while this agent significantly reduced a number of inflammatory markers, response and non-response to adalimumab was not predicted by biomarker changes. In a systematic review and meta-analysis of 45 studies, the risk of *de novo* heart failure nor worsening of heart failure in patients with immune-mediated inflammatory diseases was not increased by the use of TNF inhibitors. We conclude this issue with a study investigating prognostic biomarkers for anti-PD-1 monoclonal antibodies in the first-line treatment of advanced melanoma.

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,

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Novel inflammatory biomarkers in hidradenitis suppurativa receiving adalimumab

Authors: Esen M et al.

Summary: This retrospective study evaluated the effect of adalimumab on novel inflammatory biomarkers like the systemic immune-inflammation index (SII), systemic inflammation response index (SIRI), and pan-immune-inflammation value (PIV) and their association with hidradenitis suppurativa (HS) severity in 97 patients with Hurley stage 2/3 HS. Adalimumab reduced clinical (fistula, abscess), haematologic (neutrophils, monocytes, platelets, mean platelet volume [MPV]), and inflammatory markers (neutrophil-to-lymphocyte ratio [NLR], platelet-to-lymphocyte ratio [PLR], monocyte-to-lymphocyte ratio [MLR], SIRI, SII, PIV) ($p < 0.001$), while lymphocytes increased ($p < 0.001$). Only MLR predicted severe disease ($p = 0.019$) and no baseline biomarkers predicted treatment response. MLR reductions were correlated with decreases in abscess and total lesion counts, while reductions in PLR and PIV correlated with a reduction in abscess count. Response and non-response to adalimumab was not predicted by biomarker changes.

Comment: Biomarker is a common buzzword; however, the identification and validation of biomarkers in inflammatory skin disease required adherence to a standardised protocol of identification, replication and clinical validation in the setting of randomised controlled trials. This retrospective cohort study aimed to correlate serum measures of inflammation previously utilised in other inflammatory disorders such as inflammatory bowel disease and arthritis, to HS. A number of markers such as the neutrophil:lymphocyte ratio have previously been reported in HS; however their longitudinal validation beyond a single timepoint has been rarely associated with clinically significant change. This study presents data that a number of static markers such as CRP and full blood count results correlate with objective disease severity; however, it is important to note that a number of the negative results from this study highlight the difficulties in validation of longitudinal biomarkers in disease. No differences in the various markers were seen between clinical responders and non-responders to adalimumab suggesting that these markers are not responsive to clinical disease status and hence may only be valid for single timepoint assessment of disease state. Additionally, given the large number of variables examined, one must critique the paper for not adjusting for multiple comparisons, which brings into question the validity of the one marker they report as "significant".

Reference: Arch Derm Res. 2025:317:905

Abstract

Evaluation of the risk of heart failure with tumour necrosis factor inhibitors: A large-scale meta-analysis in immune-mediated inflammatory diseases

Authors: Galajda N Á et al.

Summary: This systematic review and meta-analysis of 45 studies examined the risk of heart failure in TNF inhibitor-treated patients versus untreated controls in patients with immune-mediated inflammatory diseases (IMIDs). Pooled analysis of non-randomised observational studies showed no effect of TNF inhibitors on risk of worsening heart failure (RR 1.18; 95% CI 0.69-2.00). There was no change in risk of *de novo* heart failure with TNF inhibitors versus controls in randomised controlled trials (RR 0.87; 95% CI 0.60-1.25) or non-randomised observational studies (RR 0.86; 95% CI 0.64-1.14). There was also no change in risk in composite (worsening and *de novo*) heart failure.

Comment: Many of the safety concerns from early TNF inhibitors have made their way across to various TNF inhibitors within the class, even with a low level of evidence and lack of validation across different disease states. Whilst the evidence for heart failure exacerbation in the setting of infliximab therapy was identified in rheumatology, there have been various contraindicating studies suggesting that the risk may be much lower than reported. This systematic review and meta-analyses examined the extant literature for the risk of *de novo* heart failure as well as exacerbation of existing heart failure. No significant association was found across examination of 45 studies in pooled analysis. This certainly brings into question the level of contraindication of TNF inhibitors in heart failure, particularly in the setting where a risk-benefit analysis is required for individual patient safety. The evidence suggests that the use of TNF inhibitors may only be a relative contraindication given the lack of significant association with *de novo* and exacerbation of disease, with the final decision resting on the proposed benefit versus risk to the individual patient.

Reference: J Eur Acad Dermatol Venereol. 2025;39(10):1760-1772
Abstract

Omalizumab dosing patterns and drug survival in adult patients with chronic spontaneous urticaria

Authors: Zhang DG et al.

Summary: This Danish, single-centre, retrospective, observational, real-world study examined omalizumab treatment patterns, dosing modifications and discontinuation in 430 patients with chronic spontaneous urticaria. Overall, 32.4% of patients escalated treatment, 37.5% reduced treatment, and 21.0% discontinued treatment from the standard dose. Median time to dose escalation was 2 years (95% CI 1.17-3.55), with the strongest predictor of dose escalation being a positive basophil histamine release assay (HR 2.79; 95% CI 1.69-4.61). Risk of dose escalation was reduced by faster treatment response (HR 0.50; 95% CI 0.33-0.75) and higher baseline Urticaria Control Test (UCT) scores (HR 0.89; 95% CI 0.82-0.97). Median survival time before dose reduction was 1.2 years (95% CI 0.98-1.49) with a higher likelihood in males (HR 1.68; 95% CI 1.13-2.50) and those with a faster treatment response (HR 1.66; 95% CI 1.12-2.48). Median time to discontinuation for any reason was 3 years (95% CI 2.35-3.64).

Comment: Omalizumab is a highly safe and effective therapy for chronic spontaneous urticaria; however, the flexibility in dosing is something often utilised by dermatologists. Real-world evidence as to the proportion of patients undergoing flexible dosing (either up or down titration) is useful data in order to quantify cost benefit, as well as understand options for patients with less-than-optimal response to standard therapy. This real-world Danish evidence suggests that roughly one-third of individuals require dose escalation, and another third having dose reduction. Omalizumab demonstrated a significant longevity in response, even in the setting of dose escalation, with median survival of greater than 2 years. Differences between gender were identified with males more likely to undergo treatment reduction than females. Overall, these real-world data help support the need for dose escalation in around one-third of individuals with chronic spontaneous urticaria, which is accessible and covered under Australian prescribing through the PBS.

Reference: J Eur Acad Dermatol Venereol. 2025;39(10):1796-1805
Abstract

Early termination does not negatively impact the outcome of adjuvant immunotherapy in melanoma

Authors: Tomsitz D et al.

Summary: This analysis of data from the prospective, multicentre, real-world skin cancer ADOREG registry (German Dermatologic Cooperative Oncology Group) assessed survival outcome as a function of duration of adjuvant anti-PD-1 therapy (nivolumab or pembrolizumab) in 620 patients with stage III/IV resected melanoma. Median follow-up was 26.0 months in 229 patients with normal treatment duration (median 51.3 weeks) and no disease recurrence during therapy, and 19.0 months in 214 patients with a premature end of treatment (median 22.2 weeks). Early discontinuation was due to treatment-related adverse events in 45.3% of patients and reasons other than toxicity in 54.7%. The 2-year recurrence-free survival (RFS) rate was 72.4% (95% CI 68.5-76.3) for early discontinuation patients and 51.5% (95% CI 48.8-54.2) for patients who had received, or were intended to receive, a normal duration of treatment. A higher RFS rate of 84.1% (95% CI 81.5-86.7) was observed in patients who did not relapse during adjuvant treatment. A trend towards better RFS in those receiving the regular treatment duration.

Comment: There is a push towards adjuvant PD-1 therapy for resected metastatic melanoma given its positive effects on disease-free survival. However, given the challenging adverse events which may occur, premature treatment cessation may occur in some patients. Despite this, periods of disease-free remission are significant even in the setting of premature discontinuation. This manuscript formally analyses data from 620 patients treated with PD-1 inhibitors comparing those with a full 12 months of therapy, and those completing less than 48 weeks of therapy. There were no significant differences in disease-free survival for the first 2 years after therapy between groups; however, the authors did indicate that longer-term data are needed given the trend to higher levels of recurrence in those with a shorter treatment duration approaching 24 months of monitoring. Therefore, although short-term data does not indicate significant differences in the first 1-2 years of follow-up, longer-term data are needed to quantify the risk of recurrence beyond 2 years in this patient population.

Reference: J Eur Acad Dermatol Venereol. 2025;39(11):1975-1986
Abstract

References: 1. Pharmaceutical Benefits Scheme. Available at https://www.pbs.gov.au/pbs/search?term=dupixent. Accessed on 01 September 2025. **2.** Australian Approved Product Information for DUPIXENT (dupilumab).

Dupilumab in papuloerythroderma of Ofuji: Therapeutic efficacy and paradoxical flares in a case-based review

Authors: Liu T et al.

Summary: This case-based review explored the clinical manifestations, treatments, and prognosis of papuloerythroderma of Ofuji and the efficacy and paradoxical flares associated with dupilumab. Overall, 52 patients were identified with onset most often occurring in patients aged over 70 years. Systemic treatments were dupilumab, cyclosporine, glucocorticoids, acitretin, methotrexate, and apremilast. In seven patients receiving dupilumab, skin lesion improvement occurred within a short period. There were no adverse events in three patients, and elevated eosinophil counts accompanied by worsened lesions in one patient.

Comment: Papuloerythroderma of Ofuji is a relative rare condition; however, in the roughly half of individuals with an idiopathic variant, symptomatic treatment is the main course of action. This case series describes the use of dupilumab in this condition which, given the recent concerns regarding cutaneous lymphoma with the use of dupilumab, needs further clarification and discussion. One of the main issues with the diagnosis of papuloerythroderma of Ofuji is the exclusion of early-stage mycosis fungoides. This is a similar situation which has been proposed in the setting of atopic dermatitis treated with dupilumab which may then manifest as mycosis fungoides at a later time. In both cases, it is arguable whether the initial diagnosis the whole time was mycosis fungoides. Therefore, this case report and literature review needs to be read and analysed with great care. Given the overlap in clinical manifestations between cutaneous T-cell lymphoma and papuloerythroderma of Ofuji, repeated clinical and histological assessment should be undertaken prior to consideration of dupilumab therapy for this condition. Not only because of the unclear association of dupilumab with cutaneous T-cell lymphoma, but also due to the risk of misdiagnosis.

Reference: J Dermatolog Treat. 2025;36(1):2562300
Abstract

Long-term effectiveness and safety of bimekizumab in patients with moderate to severe hidradenitis suppurativa under real clinical practice conditions: The importance of combined treatment in Hurley III patients and potential factors associated with complete response

Authors: Mansilla-Polo M et al.

Summary: This multicentre, retrospective observational study assessed the long-term effectiveness and safety of bimekizumab in 78 adult patients (mean age 48.5 years) with moderate-to-severe hidradenitis suppurativa (60.3% Hurley stage III) receiving bimekizumab. After 24 weeks, International Hidradenitis Suppurativa Severity Score System (IHS4)-55 score was achieved by 67.9%, IHS4-75 by 30.7%, and IHS4-90 by 2.5% of patients; at week 48, these proportions were 82.1%, 62.5%, and 32.1%, and 23.2% had achieved a complete response (IHS4-100). Combination therapy was more frequent in Hurley III patients, who had similar IHS4-55 efficacy as Hurley II patients at week 48. Adverse events occurred in 43.6% of patients, most commonly mild to moderate fungal infections (26.9%) and eczematous reactions (9%). In total, 10.3% of patients discontinued treatment, mostly because of lack of efficacy (6.4%).

Comment: The results of phase III clinical trials of bimekizumab for moderate-to-severe hidradenitis suppurativa have emphasised the important role of IL-17A and IL-17F in disease pathophysiology. However, it is well established that for many therapies in hidradenitis suppurativa, secondary loss of response is a common occurrence, and it remains unpredictable which patients will likely maintain good clinical disease control. The difficulty with open-label extension studies from phase III clinical programs is the exclusion of the most severe patients, which in the real-world would be the first to trial a new therapy. Additionally, they often preclude surgical interventions, which are the mainstay of combination therapy in hidradenitis suppurativa. This real-world analysis examines the utility and long-term efficacy (up to 48 weeks) of bimekizumab. In line with what has been previously published, improvement in clinical outcomes continued well up until the 48-week timepoint. No evidence of increased risks of infections or wound dehiscence were seen with medical surgical combination therapy, and adverse event profile and discontinuation were consistent with previously published data. Overall, this important real-world experience adds to the evidence for the utility of bimekizumab as a new therapy for hidradenitis suppurativa.

Reference: Dermatol Ther. (Heidelb) 2025;15(11):3267-3283
Abstract

Long-term dupilumab efficacy and safety in pediatric patients: A real-world experience over 2 years

Authors: Traini DO et al.

Summary: This exploratory retrospective, single-centre observational study assessed the long-term use of dupilumab in 42 paediatric patients with moderate-to-severe atopic dermatitis and the effect of seasonal dosage modulation with extended dupilumab dosing intervals in summer months. After 24 months, mean Eczema Area and Severity Index (EASI) scores were reduced from 21.2 to 1.6 ($p < 0.0001$), with improvements in Pruritus Numerical Rating Scale (P-NRS) and sleep quality; by week 16, 95% of patients had achieved ≥50% improvement. In all patients, summer dosage modulation retained disease control, but 50% of patients required a return to standard dosing in autumn. Dupilumab was well-tolerated, with conjunctivitis being the sole adverse event (9.5% of patients).

Comment: Dupilumab has found many uses for atopic dermatitis, especially in cases of genodermatosis in which dermatitis is a prominent symptom. This retrospective series examines the long-term efficacy and safety in this rare genodermatosis population including conditions such as Costello syndrome and Down syndrome. This case series highlights the efficacy in atopic dermatitis manifestations in these individuals with dermatitis driven by genodermatoses and highlights the longer-term safety and efficacy in this paediatric population. Although presenting as small numbers, these case reports highlight the utility of treating atopic dermatitis symptoms even in situations where the underlying driver of disease is a unique genetic variant or condition. This highlights the commonalities in inflammatory and cutaneous dysfunction that manifest in dermatitis, which are amenable to modulation with dupilumab.

Reference: Dermatol Ther. 2025:2025(1);4857510
Abstract

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Independent commentary by Associate Professor John Frew

Associate Professor John Frew is a fellow of the Australasian College of Dermatologists and researcher in the field of inflammatory skin diseases with a focus on hidradenitis suppurativa. He holds a staff specialist position at Liverpool Hospital and is a conjoint lecturer at the University of New South Wales supervising dermatology trainees and postgraduate research students. He completed his post-doctoral fellowship at the Rockefeller University in New York City identifying immunological pathways and novel therapies for the treatment of hidradenitis suppurativa. He has over 100 peer-reviewed publications and contributions to international dermatology and immunology textbooks in the field of inflammatory skin disease.

Eczematous eruption on hands and feet after treatment with biological agents for psoriasis

Authors: Peng F et al.

Summary: This Chinese, single-centre, case study and review examined the clinical diagnosis and management of immune drift in psoriasis induced by biological therapy. In total, 57 patients were described in the literature, and three patients were identified in hospital cases who developed eczema on hands and feet after biological treatment. Medications identified included adalimumab, ustekinumab, ixekizumab, secukinumab, infliximab, etanercept, and guselkumab; eight patients experienced immune drift reactions to >1 biological agent. Time from treatment initiation to the onset of eczematous rash varied from 4 days to 22 months and included erythema and papules with exudation or scales; affected areas included scalp, face, neck, trunk, and limbs. In the literature, laboratory indicators included elevated eosinophils (48.9%) and elevated IgE levels (19.1%); biopsy results were consistent with eczema. Overall, 23 cases stopped original biologics and switched to other biologics or small-molecule drugs, or systemic glucocorticoids, cyclosporine, and methotrexate; 11 cases continued previous biologics, of whom eight improved with topical glucocorticoids and three cases received no treatment and improved. Among the three hospital cases, two had elevated serum total IgE and one elevated eosinophils. All three patients stopped previous biologics and improved after switching to other biologics or systemic glucocorticoids and immunosuppressants.

Comment: Since the widespread use of biologic agents for atopic dermatitis and psoriasis there have been several reports of somewhat paradoxical reactions with eczematous eruptions after use of psoriasis-specific biologics and psoriatic eruptions in the setting of eczema biologic therapies. This review identifies a large number of cases and discusses the concept of immune drift. This drift can explain the emergence of eczematous reactions in psoriasis biologics by acknowledging that blockade of IL-17 and IL-23 particularly, can lead to an upregulation of Th2 immunity by blocking Th17 immunity. Whilst there may be more complex explanations in individual patients contributed to by background genetic variants and coexistence of psoriasis and atopic dermatitis, the concept of immune drift is useful to explain the broad mechanisms of this phenomenon. As expected, the clinical progress of these reactions ceased upon switching to alternative agents, whether another class of biologic or traditional systemic immunosuppressant therapies. This highlights the need to acknowledge that the immune dysregulation in inflammatory skin disease is not static, and that long-term immune drift can occur, contributing both to more common events like secondary loss of efficacy, but also adverse events.

Reference: Dermatol Ther. 2025;1:1668153
Abstract

Dupilumab as a therapeutic option in autoimmune bullous diseases following SARS-CoV-2 infection and COVID-19 vaccination: A comprehensive case series analysis

Authors: Svara F et al.

Summary: This case series analysed four patients diagnosed with autoimmune bullous diseases, with generalised bullous eruptions after COVID-19 disease and vaccination. Dupilumab was administered as a 600 mg loading dose followed by 300 mg biweekly. Three of the patients achieved remission and discontinued corticosteroids while maintaining long-term disease control. The fourth patient, who had pemphigus vulgaris, did not respond to dupilumab and was subsequently treated with rituximab.

Comment: Dupilumab has recently reported a positive read out for top line results in phase III clinical trials for bullous pemphigoid. Given the role of IL-4 and Il-13 in B-cell activity and Th2 driven blistering, it stands to reason to enquire whether other forms of autoimmune blistering disorders may respond to dupilumab therapy. Reports of COVID-19 vaccine-induced bullous pemphigoid have emerged in the literature, but given the ubiquity of the vaccine, and the background rate of bullous pemphigoid in an ageing population, causation is difficult to establish. Regardless, this case series identified two individuals with an excellent response to dupilumab as a steroid-sparing agent after onset of bullous pemphigoid after vaccination. A third patient with pemphigus did not have a similar response, which is in line with the more complex cellular-related immunity pathogenesis of pemphigus as opposed to pemphigoid. Hence, as more evidence emerges, including greater information and data regarding the positive phase III clinical studies in dupilumab for bullous pemphigoid, we will hopefully have the potential to use dupilumab as a steroid-sparing agent for autoimmune bullous diseases such as bullous pemphigoid.

Reference: Dermatol Ther. 2025;1:2257832
Abstract

Prognostic biomarkers for anti-PD-1 monoclonal antibodies in the first line treatment of advanced melanoma

Authors: Pásek M et al.

Summary: This single-centre retrospective analysis assessed possible prognostic biomarkers for objective response, progression-free survival (PFS), or overall survival (OS) after treatment with anti-PD-1 monoclonal antibodies in 138 patients with advanced melanoma. Over a median 44.1-month (95% CI 40.4-49.4) follow-up, elevated pretreatment lactate dehydrogenase (LDH) level and SII were negative prognostic factors for PFS, but in multivariate analysis, only LDH was prognostic (HR 1.72; 95% CI 1.09-2.70; p = 0.019). In multivariate analysis, elevated pre-treatment LDH (HR 2.25; 95% CI 1.35-3.75; p = 0.002) and SII (HR 2.37; 95% CI 1.29-4.37; p = 0.006) were both negative prognostic factors for OS.

Comment: Targeted therapies for melanoma have dramatically increased survival rates and periods of disease-free remission in metastatic melanoma. However, given only 50% of individuals with first-line PD-1 therapy have a significant response, baseline prognostic biomarkers would be of great utility for counselling of patients. This small retrospective analysis only included 138 patients; however, it did identify baseline LDH as a significant variable associated with a decreased length of time of disease-free remission and OS in the first 24 months of treatment. Critiques of this study would include the small samples size and the median age of the participants at over 65 years, which implies it may not be as relevant to the Australian context. Additionally, 42% of the melanomas examined were nodular melanomas, therefore, larger cohorts more representative of the Australian population would be required prior to these findings having a clinical impact upon practice.

Reference: Int J Dermatol. 2025;64(10):1839-1854
Abstract