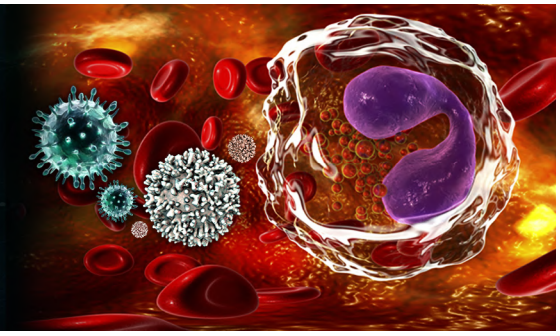
Immunology Research Review™



Making Education Easy

Issue 12 - 2025

In this issue:

Abbreviations used in this issue:

AR/C = with allergic rhinitis/rhinoconjunctivitis; **BiKE** = bispecific killer engager; **CTLA-4** = cytotoxic T-lymphocyte antigen; **HAE** = hereditary angioedema; **HDM** = house dust mite; **MAS** = macrophage activation syndrome; **MIS-C** = multisystem inflammatory syndrome in children; **PAD** = predominantly antibody deficiencies; **QoL** = quality of life; **SCIT** = subcutaneous allergen immunotherapy; **SLIT** = sublingual immunotherapy.

Welcome to the latest issue of Immunology Research Review.

This review begins with a phase III, randomised trial evaluating the efficacy and safety of SQ house dust mite sublingual immunotherapy, specifically in children aged 5-11 years with allergic rhinitis/rhinoconjunctivitis. Another notable study reviews three randomised phase III trials, which compared the effects of dupilumab versus placebo in patients with atopic dermatitis. The review concludes with an externally controlled study assessing the long-term effects of leniolisib compared to standard care, focusing on its impact on the annual rate of respiratory tract infections and IgM levels.

We hope you enjoy this update in immunology research, and we look forward to receiving comments and feedback.

Kind Regards,

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Efficacy and safety of SQ house dust mite sublingual immunotherapy-tablet (12 SQ-HDM) in children with allergic rhinitis/rhinoconjunctivitis with or without asthma (MT-12): a randomised, double-blind, placebo-controlled, phase III trial

Authors: Schuster A et al.

Summary: Within this phase III, randomised, placebo-controlled trial, researchers aimed to examine the efficacy and safety of SQ house dust mite (HDM) sublingual immunotherapy (SLIT). Patients aged 5-11 years with allergic rhinitis/rhinoconjunctivitis (AR/C), induced by HDMs, with or without asthma, were included for analysis. Each patient was randomised (1:1) to receive either placebo or the study treatment for approximately one year. Of the 1,460 patients included, 729 received the SQ HDM SLIT-tablet and 731 received placebo. Analysis revealed that total combined rhinitis scores were statistically significant for those who received the study treatment (n=693) compared to the control group (n=706), with an absolute difference of 1.0 (95% CI 0.5 to 1.4, p<0.0001) and a relative reduction of 22.0% (12.0 to 31.1). Additionally, patients who received the SQ HDM SLIT-tablet experienced a reduction in symptoms and medication use and showed improved disease-related quality of life (QoL) compared to those who received placebo. These findings support the use of SQ HDM SLIT-tablet for this patient population.

Comment: Although aeroallergen immunotherapy has been utilised for decades, few commercial products – particularly various extracts for subcutaneous immunotherapy – have ever been TGA approved, in part due to a lack of high-quality studies (particularly RCTs) demonstrating their efficacy. In recent years, however, the TGA has approved a number of sublingual immunotherapy products (which take the form of dissolvable tablets) following successful phase III trials. This multi-centre phase-III trial of an existing HDM SLIT product - already TGA approved for ages >12 - convincingly demonstrates its safety and efficacy in children aged 5-11 years both with and without asthma and is the largest study of its kind in this age group. Early introduction of allergen immunotherapy in sensitised individuals may prevent the onset of asthma, which makes the availability of therapies such as this for younger age groups particularly appealing.

Reference: Lancet Reg Health Eur. 2024;26:48:101136.
Abstract

Earn CPD

Nursing and Midwifery Board of Australia (NMBA) Journal reading and watching videos (including Research Reviews) may be considered a self-directed activity set out in the NMBA Registration Standard: Continuing Professional Development. One hour of active learning will equal one hour of CPD. Details at NMBA CPD page.

CRISPR-based therapy for hereditary angioedema

Authors: Cohn DM et al.

Summary: This phase II portion of a phase I-II trial examined the efficacy of NTLA-2002. Patients with hereditary angioedema (HAE), were randomly allocated (2:2:1) to receive either NTLA-2002 at 25 mg (n=10), NTLA-2002 at 50 mg (n=11), or placebo (n=6). A total of 27 patients were included, with those receiving 25 mg of NTLA-2002 having a monthly attack rate of 0.70 (95% CI 0.25 to 1.98), compared to 0.65 (0.24 to 1.76) for the 50 mg group and 2.82 (0.80 to 9.89) for placebo. Four of 10 patients receiving 25 mg and 8 of 11 patients receiving 50 mg were attack-free. The most frequently reported AEs were headache, fatigue, and nasopharyngitis. Overall, these findings suggest that dosages of 25 mg and 50 mg of NTLA-2002 may reduce angioedema attacks.

Comment: Rather than targeting the gene for C1 inhibitor (SERPING1), which is dysfunctional in HAE type I/II, NTLA-2002 targets kallikrein (KLBK1). Of note, both oral and injectable kallikrein inhibitors have been approved for management of HAE in recent years, so targeting of this downstream mediator is known to be effective. NTLA-2002 is administered as a one-time IV infusion and was demonstrated to be safe in phase I trials. This report on phase II included 27 patients with HAE: 10 received 25 mg, 11 received 50 mg and 6 received placebo. There was an overall reduction in attack rates compared with placebo for both treatment groups, with 4/10 patients in the 25mg group and 8/11 of the 50 mg group having 0 attacks. Of interest, the paper notes that 2 of the 3 patients that continued to have attacks following 50 mg NTLA-2002 had also experienced breakthrough attacks with trials of kallikrein inhibitors prior to entering the study. This suggests that some HAE patients may require other treatment modalities for effective prophylaxis, even if pending phase III trials prove NTLA-2002 to be a 'functional cure' for a majority.

Reference: N Engl J Med. 2025;30;392(5):458-467.
Abstract

Multi-centered clinical validation demonstrating superior precision in lupus diagnosis: T cell autoantibodies and TC4d outperform conventional lupus erythematosus biomarkers

Authors: Kyttaris V et al.

Summary: In this multi-centre clinical validation cohort, the characteristics of emergent T cell biomarkers were examined. A total of 400 patients were enrolled, deriving from 3 academic and 2 community-based autoimmune rheumatic centres. The cohort included 105 SLE patients, 173 patients with autoimmune rheumatic disease, 83 healthy volunteers, and 39 other disease controls for analysis. Each patient was tested for TC4d, TigG, and TIgM biomarkers, and an extensive autoantibody profile was collected. ROC analysis, which separated ANA-positive SLE (n=91) from autoimmune rheumatic diseases, showed AUC values for TigG, BC4d, and TC4d at 0.81, 0.80, and 0.79, respectively, outperforming anti-dsDNA (0.72), C3 (0.69), TIgM (0.67), C4 (0.66), and anti-Smith (0.61). Furthermore, researchers found that the sensitivity for SLE versus apparently healthy volunteers for TC4d, TigG, and TIgM was 58.1% (95% CI 48.1 to 67.7), 31.4% (22.7 to 41.2), and 29.5% (21.0 to 39.2), respectively. These results suggest that TC4d, TigG, and TIgM biomarkers may outperform conventional markers.

Comment: This study explores the clinical utility of recently described novel biomarkers for SLE – T cell autoantibodies (IgG and IgM) and T cell bound C4d, which are detected using a relatively straight-forward flow cytometric method – and demonstrates, via comparison of ROC curves, that they consistently outperformed traditional biomarkers (ANA, anti-dsDNA, C3/C4) in differentiating a heterogeneous outpatient SLE cohort (n=105) from cohorts of apparently healthy individuals and various disease controls. While the paper highlights that the apparently increased sensitivity of these biomarkers could lead to earlier diagnosis and improved patient outcomes, the SLE cohort studied were largely established cases that were well-controlled on therapy (mean SLEDAI-2K = 3.48). It would thus be interesting to see the utility of these biomarkers in the work-up of patients presenting with undifferentiated disease, as well as in the longitudinal assessment of disease activity/response to therapy. Given that the expertise needed to perform this testing would already exist within a typical diagnostic immunopathology laboratory, such real-world data could be near at hand.

Reference: Front. Immunol. 2025;16.
Abstract

NK cell and monocyte dysfunction in multisystem inflammatory syndrome in children

Authors: Dick JK et al.

Summary: Within this study, researchers aimed to better understand the immune response of multisystem inflammatory syndrome in children (MIS-C). Paediatric patients were prospectively enrolled between May 2020 and May 2021 from Children's Hospitals and Clinics of Minnesota, alongside adult subjects. After analysis, researchers found that monocytes were hyperfunctional in phagocytosis and cytokine production, whereas NK cells were hypofunctional for killing as well as cytokine production. Additionally, lower NK cell cytotoxicity was associated with an NK exhaustion marker signature and elevated systemic IL-6 levels. In summary, these findings suggest that Ab-mediated cellular responses of myeloid and NK cells may contribute to the development of MIS-C.

Comment: MIS-C is a rare but life-threatening complication of paediatric SARS-CoV-2 infection characterised by systemic inflammation resembling macrophage activation syndrome (MAS) and delayed viral clearance despite development of neutralising SARS-CoV-2 antibodies. Through various methods, including serum cytokine analysis, flow cytometric immunophenotyping and ex vivo functional assays, this fascinating paper compares children with MIS-C (n=14) with a number of control groups, including children and adults with a spectrum of SARS-CoV-2 infection severity and individuals not infected with SARS-CoV-2. Ultimately, there is compelling evidence that dysfunctional antibody-mediated cellular responses involving monocytes and NK cells play a key role in MIS-C pathogenesis. Broadly, subsets of monocytes display hyperfunctional phagocytosis and cytokine production, resulting in a cytokine storm. These cytokines, particularly IL-6, cause NK cells to become exhausted and hypofunctional, rendering them unable to effectively clear infected cells. Together, this results in persistent infection which promotes ongoing and excessive inflammation, a process that indeed has some similarities to MAS/HLH. Finally, the paper provides exciting in vitro evidence for a potential therapeutic mechanism to overcome the described NK cell exhaustion utilising a 'bispecific killer engager' (BiKE) – a bispecific nanobody which includes high affinity for CD16 (FcγRIIIA) that generates stronger signalling than the Fc portion of IgG.

Reference: J Immunol. 2024;15;213(10):1452-1466.
Abstract

Dupilumab reduces inflammatory biomarkers in pediatric patients with moderate-to-severe atopic dermatitis

Authors: Beck LA et al.

Summary: This study examined the effects of dupilumab compared to placebo in patients with atopic dermatitis. Researchers collected data from 3 randomised, double-blind, placebo-controlled, phase III trials that included patients with moderate to severe atopic dermatitis. Patients were randomly allocated to receive either dupilumab or placebo, with varying dosages for each age group: 6 months to 5 years (200/300 mg every 4 weeks), 6 to 11 years (100/200 mg every 2 weeks or 300 mg every 4 weeks), and 12 to 17 years (200/300 mg every 2 weeks or 300 mg every 4 weeks). Those in the two younger age groups also received additional topical corticosteroids. Post-analysis revealed that patients who received dupilumab, compared to placebo, had significantly greater median percent reductions by week 16 in thymus and activation-regulated chemokine/CC chemokine ligand 17 (−83.3% to −72.4% versus −14.9% to −1.8%), as well as total IgE (−71.2% to −58.4% versus −21.0% to +28.1%) and lactate dehydrogenase (−26.2% to −9.8% versus −1.5% to +1.5%). The differences between each dupilumab dosing group and placebo were all significant ($p<0.0001$). These findings indicate that dupilumab may reduce systemic type 2 and general inflammation in this patient population.

Comment: In adults with atopic dermatitis, dupilumab therapy has been shown to reduce several markers of type II inflammation (total IgE, eosinophil count, TARC/CCL17) which may also correlate with disease severity. This analysis of biomarker data from 3 RCTs explores these same markers in a paediatric population with moderate-to-severe atopic dermatitis, noting similar findings, although without significant changes in eosinophil levels. The changes to TACR/CCL17 were seen by week 2 of therapy, and total IgE by week 4.

Reference: J Allergy Clin Immunol. 2025;155(1):135-143.
Abstract

Subcutaneous immunotherapy for bee venom allergy induces epitope spreading and immunophenotypic changes in allergen-specific memory B cells

Authors: McKenzie CI et al.

Summary: The phenotype and antigen receptor sequences of Bmem, specifically Api m 1, both prior to and following ultra-rush subcutaneous allergen immunotherapy (SCIT) for bee venom allergy, were evaluated in this study. Researchers generated recombinant Api m 1 protein tetramers to assess basophil activation among participants with a bee venom allergy. A comprehensive flow cytometry analysis was also conducted, allowing researchers to evaluate and purify Api m 1-specific Bmem. Additionally, the immunoglobulin genes from a single Api m 1-specific Bmem were sequenced and structurally modelled onto Api m 1. After conducting the trial, it was found that SCIT led to class switching of Api m 1-specific Bmem, shifting to IgG2 and IgG, along with an increase in the expression of CD23 and CD29. The modelling of Api m 1-specific immunoglobulin from Bmem also revealed several new and diverse allergen epitopes on Api m 1, with certain epitopes preferentially binding immunoglobulin following SCIT. Overall, these findings suggest that allergen immunotherapy could induce shifting of epitope specificity and phenotypic changes.

Comment: This fascinating Australian study of 26 bee venom allergic patients neatly demonstrates the inhibitory capacity of immunotherapy-induced allergen specific IgG (particularly IgG4) by comparing BAT reactivity with both washed (no antibodies) and whole blood (contains antibodies) before and after commencement of VIT, demonstrating progressively increasing reactivity thresholds with whole blood but not washed. It then goes on to analyse Api m 1 (the major bee venom allergen) specific memory B cells in great detail, demonstrating a change in immunophenotype during VIT with increased surface expression of CD23 and CD29 via flow cytometry. As a similar change in immunophenotype was seen when assessing responses to immunotherapy in rye grass allergic patients, there are promising signs that these markers could prove to have utility in the assessment of response to allergen immunotherapy, something still highly sought after in clinical practice.

Reference: J Allergy Clin Immunol. 2024;154(6):1511-1522.
Abstract

Hematopoietic stem cell transplantation for CTLA-4 insufficiency across Europe: A European Society for Blood and Marrow Transplantation Inborn Errors Working Party study

Authors: Tsilifis C et al.

Summary: Within this retrospective study, the efficacy of HSCT for cytotoxic T-lymphocyte antigen 4 (CTLA-4) insufficiency, as well as the impact of pre-HSCT CTLA-4 fusion protein therapy and pre-HSCT immune dysregulation, were evaluated. Forty patients were included, with the primary endpoints of overall survival and disease- and chronic graft-versus-host disease-free survival. Among these patients, 58% received peripheral blood stem cells, and 43% received marrow from either a matched unrelated donor (75%), mismatched unrelated donor (12.5%), or matched family donor (12.5%). After a median follow-up of 3 years, patients achieved an overall survival of 76.7% and disease-free survival of 74.4%. These results indicate that HSCT is effective in preventing disease progression and morbidity in this patient population.

Comment: CTLA-4 insufficiency (like APDS, also discussed below) was previously considered as one of the few monogenic causes of CVID, although today is considered a distinct entity. As might be intuited, this condition can benefit from therapy with CTLA4-Ig (e.g. abatacept), so a confirmed genetic diagnosis can have significant implications for management. Nevertheless, a potentially curative HSCT may be required in refractory cases, as with other PIDs. This retrospective study includes 40 patients who underwent HSCT for CTLA4 insufficiency in Europe over a period of 25 years and demonstrates a 3-year overall survival of 76.7%, positioning HSCT as a viable cure. Higher levels of disease activity pre-HSCT were associated with an increased risk of poor outcomes, including mortality and GvHD. However, despite what might be expected, patients treated with abatacept pre-HSCT (60% of cohort) did not have significantly different rates of overall or disease-free survival (although the study may have been insufficiently powered). Irreversible organ damage due to previous disease activity is also posited as a potential confounder. The ongoing ABACHAI trial may provide further insight into the role of CTLA4-Ig in this condition.

Reference: J Allergy Clin Immunol. 2024;154(6):1534-1544.
Abstract

Independent commentary by Dr Matthew Krummenacher

Dr Matthew Krummenacher is a Consultant Clinical Immunologist and Immunopathologist with current appointments at PathWest, Sir Charles Gairdner Hospital and Royal Perth Hospital. He graduated from the University of Western Australia in 2012 and completed his Immunology advanced training in Perth, having also undertaken part of his training in Adelaide. He commenced work as a Consultant Immunologist in 2022, and in addition to his current roles, has previously held appointments at Clinipath and the WA Specialist Clinic."

Hereditary C1q deficiency is associated with type 1 interferon-pathway activation and a high risk of central nervous system inflammation

Authors: Triaille C et al.

Summary: In this paper, the activation of the type 1 interferon pathway, specifically among those with hereditary C1q deficiency, was evaluated. The study included 12 patients with genetically confirmed C1Q deficiency, and their clinical, biological, and radiological data was collected retrospectively. After analysis, researchers found that 10 patients had CNS involvement, 11 had mucocutaneous involvement, and 2 had renal involvement, with 2 out of 12 patients experiencing severe infections. All patients tested for elevated ISG expression were positive (10/10), as were all those tested for interferon alpha protein levels in cerebrospinal fluid (2/2). This study highlighted that individuals with C1Q deficiency exhibited several characteristics of known monogenic interferonopathies.

Comment: This is the largest review of genetically confirmed cases of hereditary C1q deficiency (n=77), including 11 patients not previously reported. It highlights the clinical phenotype, including prominent mucocutaneous manifestations (87.5%) and CNS involvement (36.2%). Although often considered as a monogenic cause of lupus, the paper points out notable differences to sporadic SLE, particularly the lower frequency of anti-dsDNA antibodies (18.6%) and renal disease (23.9%). Interestingly, while 37.5% had increased infections, there was a higher frequency in cases reported pre-2011 compared with afterwards (45.5% versus 24.4%); the paper suggests this may be due to increased rates of vaccination and/or antibiotic prophylaxis. The paper also demonstrates increased type I interferon signalling in C1q deficient cases, noting the physiologic role of C1q in suppressing type I interferon production by dendritic cells. Of the newly reported cases, 10/10 tested had increased expression of interferon stimulated genes in peripheral blood, and 2/2 tested had increased IFNalpha in serum and CSF. Based on this, the authors posit a potential therapeutic role for anifrolumab and other targets of type I interferon signalling, which remains to be explored.

Reference: J Clin Immunol. 2024;28;44(8):185.
Abstract

A cross-sectional study of health-related quality of life in patients with predominantly antibody deficiency

Authors: Elmoursi A et al.

Summary: Within this cross-sectional study, the effects of predominantly antibody deficiency (PAD) on health-related QoL were evaluated. Participants with PAD completed the Centres for Disease Control HRQoL-14 Health Days Measure questionnaire. Results from these questionnaires were then compared to data from the Centres for Disease Control-initiated Behavioural Risk Factor Surveillance System. In total, 83 patients completed the survey and were grouped based on their disease severity for PAD: mild (23.7%), moderate (35.5%), severe (40.8%), and secondary (8.4%). After analysing the results, it was found that the majority of patients (52.6%) reported a "fair or poor" health status, with 25% of patients experiencing 14 or more days per month of mental health challenges. Additionally, 44.7% of patients reported 14 or more days of physical health issues, and 80.3% stated they had activity limitations. Patients with autoimmune and inflammatory disease co-morbidities often reported more mental health challenges compared to those without (78% versus 54.3%, p=0.02). These findings suggest that patients with PAD have a reduced QoL, and further research is warranted to improve these outcomes.

Comment: This important study focussing on adults highlights the reduced health-related QoL that can be experienced by patients, even when the antibody deficiency seen in these conditions can typically be corrected by immunoglobulin replacement therapy. Indeed, there were no significant differences between groups classified as mild, moderate or severe PAD, indicating that there may be other aspects of the diagnosis (e.g. its chronicity and requirement for lifelong management) that are themselves detrimental to QoL. However, as highlighted by the papers discussed above focussing on APDS and CTLA-4 insufficiency, patients that might be classified as having a PID with predominantly antibody deficiency can also encounter additional issues relating to autoimmunity and/or lymphoproliferation, and these patients did show significantly worse mental health outcomes in particular (78% versus 54.29%, p=0.02).

Reference: J Clin Immunol. 2024;7;44(8):173.
Abstract

Comparative efficacy of leniolisib (CDZ173) versus standard of care on rates of respiratory tract infection and serum immunoglobulin M (IgM) levels among individuals with activated phosphoinositide 3-kinase delta (PI3Kδ) syndrome (APDS): an externally controlled study

Authors: Whalen J et al.

Summary: The long-term effects of leniolisib on the annual rate of respiratory tract infections and IgM levels, compared to the current standard of care, were evaluated in this externally controlled study. Thirty-seven patients were treated with leniolisib, while 62 patients were in the control group for respiratory tract infections and 49 in the serum IgM group, respectively. Post-analysis revealed that those receiving leniolisib had significant annual reductions in respiratory tract infections (RR 0.34, 95% CI 0.19 to 0.59) and serum IgM levels (treatment effect –1.09 g/L, 95% –1.78 to –0.39, p=0.002) compared to standard of care. This study illustrates the potential of leniolisib, suggesting it may offer long-term benefits, particularly in restoring immune system function and decreasing the rate of infection.

Comment: APDS is a rare PID caused by activating mutations of PI3Kd, and targeted therapy with the oral PI3kd inhibitor leniolisib has been shown to be effective, although previous studies have not directly compared leniolisib with standard of care (e.g. immunoglobulin replacement, antimicrobials, mTOR inhibition) over the longer-term. This retrospective study included 37 patients with APDS treated with leniolisib (recruited from previous leniolisib trials) and APDS controls identified from the ESID-APDS registry (who were considered to be receiving 'standard of care') and compared the endpoints of annualised rate of respiratory tract infections and change in serum IgM level, noting that APDS patients typically have elevated IgM levels due to impaired immunoglobulin class switching. Leniolisib treated patients showed significant improvement for both endpoints, further demonstrating the promise for this therapy in APDS. However, further studies are required to assess the long-term effect on other immunophenotypic abnormalities seen with APDS, such as increased proportions of transitional B cells and senescent T cells, and also whether there is benefit for other prominent clinical manifestations of APDS (e.g. autoimmunity, lymphoproliferation).

Reference: Clin Exp Immunol. 2025;21;219(1):uxae107.
Abstract