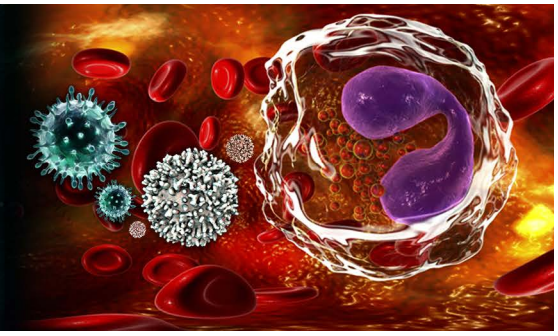
Immunology Research Review™



Making Education Easy

Issue 5 - 2022

In this issue:

Abbreviations used in this issue:

AERD = aspirin-exacerbated respiratory disease; **CI** = confidence interval; **CMV** = cytomegalovirus; **COVID-19** = coronavirus disease 2019; **CRSwNP** = chronic rhinosinusitis with nasal polyps; **CVID** = common variable immunodeficiency disorder; **HA** = hemagglutinin; **HAE** = hereditary angioedema; **HPV** = human papillomavirus; **ICS** = inhaled corticosteroid; **Ig** = immunoglobulin; **mRNA** = messenger RNA; **NCS** = nasal congestion score; **NPS** = nasal polyp score; **PCV13** = 13-valent pneumococcal conjugate vaccine; **PPV23** = 23-valent pneumococcal polysaccharide vaccine; **RR** = relative risk; **SARS-CoV-2** = severe acute respiratory syndrome coronavirus 2.

Welcome to the latest issue of Immunology Research Review.

The therapeutic arsenal to treat C1-esterase inhibitor-deficient hereditary angioedema (HAE) may soon be expanded with two investigational agents – donidalorsen and garadacimab – demonstrating efficacy in clinical trials when used prophylactically. Both agents also require a less frequent administration schedule comprised of monthly injection, as opposed to the two-weekly schedule of current therapies such as landelumab. The two agents have different mechanisms of action; donidalorsen is a second-generation ligand-conjugated antisense oligonucleotide prekallikrein inhibitor while garadacimab is a first-in-class anti-Factor XII monoclonal antibody. Donidalorsen was assessed in a phase 2 trial by Ionis Pharmaceuticals with results in *The New England Journal of Medicine* demonstrating significantly reduced disease burden after 12-weeks of treatment. CSL Behring evaluated garadacimab in a four-parallel-arm trial and reported almost complete amelioration of angioedema attacks with no adverse events in *The Lancet*. Results from phase 3/4 trials of both agents are eagerly awaited. In other research, anti-severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) vaccines elicit durable protection against the most severe outcomes of coronavirus disease 2019 (COVID-19) such as hospitalisation and death with effectiveness maintained at nine-months according to a real-world study from North Carolina in *The New England Journal of Medicine*, however waning immunity may allow breakthrough infections, supporting the use of booster vaccines. Finally, the emerging role of biologic agents for allergic respiratory disease continues to be elucidated with results from a long-term extension study including POLYP 1/2 trial participants confirming the efficacy of omalizumab for severe chronic rhinosinusitis with nasal polyps but finding it may not elicit durable remission and a real-world study of mepolizumab for severe eosinophilic asthma reporting clinical benefits as well as steroid-sparing activity.

We hope you find these and the other selected studies interesting, and look forward to receiving any feedback you may have.

Kind Regards,

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Inhibition of prekallikrein for hereditary angioedema

Authors: Fijen L et al.

Summary: Results from part A of this small phase 2a study published in *The New England Journal of Medicine* demonstrate preliminary efficacy of prophylactic donidalorsen therapy for hereditary angioedema (HAE) with C1 inhibitor deficiency. A total of 20 patients with a documented diagnosis of type 1 or 2 HAE with C1 inhibitor deficiency who experienced at least two HAE attacks during the eight-week screening period were accrued from seven sites across the US and Amsterdam UMC in the Netherlands, and enrolled in the Ionis Pharmaceuticals-sponsored trial. Patients underwent a 12-week treatment period consisting of four-weekly subcutaneous injections of 80 mg donidalorsen (n=14) or placebo (n=6). The trial met its primary outcome measure to show a significant improvement in angioedema attack rate with donidalorsen, eliciting a 90% mean reduction rate compared to placebo (mean angioedema attacks per month at week 17; 0.23 vs 2.21; $p<0.001$). Secondary endpoints were consistent in supporting this finding with benefits in angioedema-related quality of life (Mean improvement in Angioedema Quality of Life Questionnaire; 26.8 vs -6.2 points). The safety profile of donidalorsen was favourable with no serious adverse events or deaths and rates of mild-to-moderate adverse events lower than in the placebo arm (71% vs 83%). Results from part B of the study in patients with normal C1-inhibitor activity will be reported separately.

Comment: Donidalorsen inhibits prekallikrein production through antisense oligonucleotide messenger RNA (mRNA) silencing, enriched in target hepatic parenchymal cells through N-acetyl-galactosamine conjugation – a strategy that is being increasingly used to deliver small interfering RNA therapeutics in clinical practice. In this phase 2 study (n=20), four-weekly subcutaneous donidalorsen demonstrated significant clinical benefit for HAE from week five onwards, with 92% of treated patients remaining attack-free (12/13) compared to 0/6 receiving placebo up to week 17. There was a strong correlation between clinical activity and prekallikrein levels, suggesting an approach to monitoring that could be usefully employed. Interestingly, this study also enrolled three patients with normal C1 esterase inhibitor levels and function and a history of bradykinin-mediated angioedema (with elevated threshold-stimulated kallikrein activity), who also noted significant clinical improvement. There were no safety concerns identified. Donidalorsen, therefore shows promise as a well-tolerated and low-frequency treatment option for management of HAE syndromes, as well as offering new potential options for other bradykinin-mediated angioedema syndromes that can be identified through assessments of kallikrein activity.

Reference: N Engl J Med 2022;386(11):1026-33
Abstract

Prophylactic use of an anti-activated factor XII monoclonal antibody, garadacimab, for patients with C1-esterase inhibitor-deficient hereditary angioedema: a randomised, double-blind, placebo-controlled, phase 2 trial

Authors: Craig T et al.

Summary: CSL Behring conducted this phase 2, four-parallel-arm trial (ClinicalTrials.gov Identifier: NCT03712228) to assess the clinical efficacy of the first-in-class anti-activated Factor XII monoclonal antibody garadacimab for C1-esterase inhibitor-deficient HAE. Adult patients (n=32; median age 39.5 years; 56% female) with a history of at least four attacks in two consecutive months were enrolled from sites in Canada, Germany, Israel and the USA and randomised to 12 weeks of treatment in one of the four trial arms – garadacimab at a dose of 75 mg (n=9), 200 mg (n=8) or 600 mg (n=7) every four weeks, or placebo (n=8). Garadacimab treatment arms received an intravenous loading dose prior to commencement of four-weekly subcutaneous administration. The median number of attacks per month were significantly lower in the 200 mg and 600 mg garadacimab treatment arms compared to placebo, decreasing the rate of attacks by 100% and 93%, respectively (median attacks per month; 0 vs 0 vs 0.3; both $p \leq 0.0003$). No serious adverse events or deaths were reported. The study authors concluded that garadacimab warrants progression to phase 3 testing.

Comment: Garadacimab therapy for HAE (at this stage limited to those with C1 esterase inhibitor deficiency) involves targeted inhibition of activated factor XII with a fully humanised monoclonal antibody that can be administered four-weekly via subcutaneous injection after initial loading. This dose-ranging study involving 32 treated patients across multiple international centres demonstrated >90% reduction in angioedema episodes and requirement for rescue treatment across three doses (75 mg, 200 mg and 600 mg) with no significant adverse effects other than injection site reactions that appear to be dose-dependent. While response rates were similar across the three doses, the 200 mg four-weekly dose schedule appears to offer an optimised combination of therapeutic benefit (achieved with garadicimab concentrations > 10 µg/mL) and avoidance of complications including injection site reactions (1/8 at 200mg versus 4/7 at 600 mg/dose) as well as bleeding risk that could potentially be attributed to Factor XII inhibition (noting prolonged APTT results with 600 mg dosing). Garadacimab therefore shows promise as an effective management strategy for HAE that involves infrequent subcutaneous injections. Like donidalorsen, its mechanism of action offers a therapeutic approach that could extend beyond type 1 HAE, which in turn should broaden the spectrum of treatable bradykinin-mediated angioedema syndromes based on functional assessment of kallikrein activity.

Reference: Lancet 2022;399(10328):945-55
Abstract

Effectiveness of COVID-19 vaccines over a 9-month period in North Carolina

Authors: Lin D-Y M et al.

Summary: Researchers from the University of North Carolina at Chapel Hill in the US analysed linked data from the North Carolina COVID-19 Surveillance System and the COVID-19 Vaccine Management System to elucidate the durability of three COVID-19 vaccines in a real-world population. The study cohort was comprised of over 10.6 million (n= 10,600,823) residents of North Carolina, 57% of whom received a COVID-19 vaccine, most commonly the Pfizer–BioNTech (BNT162b2) messenger RNA vaccine (32%). Twenty-two percent of the cohort received the Moderna mRNA COVID vaccine (mRNA-1273) and 3% the Johnson & Johnson Ad26.COV2.S vaccine, generally a two-dose regimen administered at a 28-day interval and a single dose, respectively. Over a nine-month period between December 2020 and September 2021, 812,494 COVID-19 cases were recorded. Of cases with known outcomes the hospitalisation rate was 6.2% (20,232/324,997) and the mortality rate was 1.5% (7,461/487,496). Cox regression modelling revealed comparable short-term effectiveness for protection against COVID-related hospitalisation and death with a two-dose regimen of the Pfizer and Moderna vaccines with zeniths of 94.5% and 95.9% achieved, respectively, at two months after first dose. Effectiveness waned over time but still conferred significant reductions in the risk of death and hospitalisation at seven months (66.6% and 80.3%, respectively). The one-dose Johnson & Johnson vaccine had an effectiveness of 74.8% at one month and 59.4% at five-months. Subgroup analysis of early vaccine recipients indicated that emergency of the Delta COVID-19 variant reduced the effectiveness of the mRNA vaccines by between 10% to 15%. It was noted that vaccine protection against adverse outcomes was more durable than protection against infection.

Comment: This recent *NEJM* publication (March 10, 2022) provides a meaningful comparison of COVID-19 vaccine effectiveness in North Carolina (study population 10.6 million), therefore providing valuable clinical data while also reminding us of the speed of change that has characterised this epidemic, noting that the data collection period through mid-2021 preceded the current omicron wave and therefore has limited current application. Investigating two-dose vaccine regimens (a highly effective strategy for delta variant SARS-COV-2 as well as preceding variants), these surveillance data show durable benefit from mRNA vaccines (Pfizer 30 µg/dose; Moderna 100 µg/dose) with ≥90% protection from hospitalisation and death that was maintained between two–eight months following the first vaccine dose. The single-dose Johnson & Johnson Ad26.COV2.S vaccine showed lower effectiveness (peak 86% for both hospitalisation and death) and some evidence of waning benefit within the shorter six-month follow-up period (maintained at ~80%). While this evidence is somewhat reassuring with regard to the durability of vaccine-induced immunity, the emergence and subsequent dominance of omicron BA.1 and BA.2 variants has required a recalibration of vaccine effectiveness with strong evidence that three-dose vaccine regimens are required for protection from hospitalisation and death, while also acknowledging the reduced risk of severe COVID-19 illness associated with omicron versus delta infection (Nyberg T et al. *Lancet* 2022; 399 [10332]:1303-12).

Reference: N Engl J Med 2022;386(10):933-41
Abstract

A single residue in influenza virus H2 hemagglutinin enhances the breadth of the B cell response elicited by H2 vaccination

Authors: Andrews SF et al.

Summary: This study from a group at the National Institutes of Health in Bethesda, USA, adds to the growing knowledge base regarding the potential of a universal influenza vaccine to protect against influenza subtypes including H2, H5, H6 and H9 by targeting conserved epitopes on the viral hemagglutinin (HA) surface glycoprotein stem, rather than the head. The hypothesis under consideration is that the bulky phenylalanine residue at residue 45_{HA2} in HA ($Phe45_{HA2}$) found in the H2 subtype sterically prevents binding of cross-reactive anti-stem HA-antibodies from subtypes H1 and H5. The researchers performed a post-hoc analysis of data from two National Institute of Allergy and Infectious Diseases run phase 1 influenza vaccine trials (NCT03186781 & NCT01086657) to elucidate how the $Phe45_{HA2}$ residue in HA found in the H2N2 strain impacts HA-specific humoral immune responses. Both trials enrolled participants naïve to both H5 and H2 influenza subtypes and assessed vaccination with a H5N1 monovalent inactivated vaccine or an H2 HA ferritin nanoparticle. The researchers reported greater breadth of immunoglobulin binding and neutralisation in B cells after H2 versus H5 exposure without compromising the magnitude of response, suggesting that HA stem-based vaccination utilising H2 instead of H1 or H5 epitopes may provide a broader protection.

Comment: The rapid development of SARS-CoV-2 vaccines and antibody-based therapeutics, and the accompanying evolution of viral variants that evade immune recognition through diversification of the antigenic spike protein, has been a subject of much discussion. This study, and an accompanying clinical trial (Houser K et al Nat Med. 2022 ;28[2]:383-91) offer promising insights into the benefits of targeting the conserved stem region of influenza A HA to elicit broadly cross-reactive B cell responses capable of protecting against multiple H1, H2 and H5 influenza strains that have been associated with severe epidemic disease. The specific focus on a previously 'unattractive' stem region characterised by the presence of a bulky phenylalanine residue, derived from H2 influenza that last circulated more than 50 years ago, offers new insights into the creative approaches required to optimise vaccines (even down to a single amino acid residue) towards the goal of universal coverage.

Reference: Nat Med 2022;28(2):373-82
Abstract

Pre-existing maternal IgG antibodies as a protective factor against congenital cytomegalovirus infection

Authors: Huang Y et al.

Summary: A mother-child prospective cohort study conducted in China aimed to quantify the relationship between natural maternal immunity to cytomegalovirus (CMV) and protection against transplacental transmission leading to congenital CMV infection in the newborn. A total of 6,729 pregnant women were enrolled from three maternal and child health hospitals in the Henan Province of China and underwent serial serological testing utilising a well-validated enzyme-linked immunosorbent assay. Results showed that most of the cohort (98.11%) were seropositive at the first screening visit at a median of 13 weeks gestation. The incidence of congenital CMV infection in newborn babies was 0.77% (48/6,228 live babies born to 6,185 seropositive mothers including 43 sets of twins). A negative correlation was found between the risk of congenital CMV infection and maternal immunoglobulin (Ig) G antibody levels, restricted to the early gestation period. The optimal diagnostic threshold for anti-CMV antibodies was identified as 12.83 IU/mL with maternal anti-CMV IgG levels exceeding the threshold conferring a 50% reduced risk of intrauterine transmission (relative risk [RR] 0.50; 95% confidence interval [CI], 0.27-0.93; p=0.028).

Comment: Despite congenital CMV infection being the most common infectious cause of congenital malformation and sensorineural hearing loss in the developed world (Rawlinson W et al. *Lancet Infect Dis* 2017;17[6]:e177-88), risk factors for congenital CMV infection remain poorly characterised. Serological testing in pregnancy is not recommended in Australia given the lack of predictive value, noting that the rates of congenital CMV infection are estimated at 0.6%, with a risk of 30%-35% associated with primary maternal CMV infection in early pregnancy and 1%-2% associated with viral reactivation or reinfection. This study, conducted across three maternity hospitals in China, was undertaken after it was recognised that 98% of congenital CMV diagnoses in this region involved seropositive mothers without evidence of primary infection. Overall, congenital CMV infection was identified in 48/6228 newborns (0.77%), with no evidence of associated primary maternal CMV infection. Quantitative CMV (pp150) IgG testing identified an overall maternal seropositivity rate of 98%, with risk of congenital CMV infection associated with low-positive CMV IgG levels in early pregnancy (<12.8 IU/mL) compared to levels above this threshold (1.06% vs 0.48%; adjusted RR 0.50; p=0.012). There was no identified influence of socioeconomic factors or of rising titres through pregnancy that could indicate reinfection. This represents a small but useful step forward in understanding CMV serological status in the context of pregnancy, although not achieving predictive value that would warrant routine implementation. Recent Australian studies would suggest that there is more to be done in this area, given the significant mortality and morbidity burden of congenital CMV infection (Smithers-Sheedy H et al. *Eur J Paediatr Neurol* 2022;37:82-6).

Reference: EBioMedicine 2022;77:103885
Abstract

Independent commentary by Dr David Nolan

Dr David Nolan is a Consultant Physician and Head of Department in the Royal Perth Hospital Department of Immunology. After undergraduate training at the University of Melbourne and Austin Hospital (1990) and registrar appointment at Royal Darwin Hospital (1995-1996), David moved to Perth to work at Sir Charles Gairdner Hospital (1997-1998) before commencing work at Royal Perth Hospital in 1999 with a Clinical Research Fellow position from 2000-2006, followed by Consultant appointment that has been ongoing since that time. He also served as the Director Research at Royal Perth Hospital, and an adjunct Associate Professor at the Institute for Immunology and Infectious Diseases at Murdoch University.

Incidence and estimated vaccine effectiveness against hospitalisations for all-cause pneumonia among older US adults who were vaccinated and not vaccinated with 13-valent pneumococcal conjugate vaccine

Authors: Hsiao A et al.

Summary: This retrospective electronic medical record study, conducted by Pfizer, analysed data from a large US integrated healthcare system (Kaiser Permanente Northern California) to ascertain the real-world effectiveness of the 13-valent pneumococcal conjugate vaccine (PCV13) in older adults. Analysis was based on data from almost 200 thousand adults at least 65 years of age (n=192,061; median age 69 years; 56% female; 72% white) over the study period (2015-2018) with no history of prior pneumococcal vaccine (PCV13 or 23-valent pneumococcal polysaccharide vaccine [PPV23]). Routine use of the PCV13 vaccine was recommended in the US in this population in 2014 and coverage in this cohort reached over three-quarters (76.9%) by the end of the study period. A total of 3,488 individuals were hospitalised at least once for pneumonia and 3,846 for a lower respiratory tract infection (total hospitalisations, 3,766 and 4,173; respectively). Poisson regression analysis adjusted for sex, race, ethnicity, age and other confounding factors revealed a vaccine effectiveness of 10% for hospitalisation for pneumonia and 9.4% for hospitalisation for lower respiratory tract infection. These results were confirmed in secondary analyses restricted to first hospitalisation data only and in sensitivity analyses. The authors stated that PCV13 vaccination of older adults confers significant reductions in hospitalisations for respiratory infections even in a setting with a high paediatric coverage.

Comment: This study harnesses the considerable statistical power of the Kaiser Permanente Northern California cohort to demonstrate the effectiveness of PCV13 in preventing all-cause lower respiratory tract infection and pneumonia in adults ≥65 years. The study is typically well-designed, involving 192,061 adults who had not previously received pneumococcal vaccination, noting that the study period from 2014 – 2018 commenced when PCV13 (Prevenar) vaccines were first recommended so that initial coverage was 0%, rising to 77% by 2018. At the same time, PPV23 (Pneumovax) vaccination rates were 71% and 82%, respectively. In terms of the primary endpoints of the study, PCV13 vaccination was associated with ~9% reduction in all-cause hospitalised lower respiratory tract infection and pneumonia, which was not significantly influenced by adjustment for comorbidities or demographic factors. The adjusted multivariate analyses available in the supplementary material identified protective effects of PCV13 vaccination (RR 0.91) and influenza vaccination in the previous (but not current) season (RR 0.75). Interestingly, this did not demonstrate any significant benefit from PPV23 vaccination within the past five years (RR 1.08; p=0.14) and found increased risk among those who received PPV23 more than five years ago (RR 1.20; p<0.001). These analyses may have been limited by missing data regarding smoking and alcohol history but provided adjustment for diabetes and chronic respiratory disease diagnoses, which all remained significant risk factors. This level of protection from all-cause pneumonia suggests that the benefits of PCV13 vaccination may extend to a broad range of respiratory pathogens including viruses (potentially including COVID-19; Lewnard J et al. *J Infect Dis* 2021; Mar 9 Epub ahead of print), possibly because of interactions between viruses and pneumococci in the upper airway as noted by the authors. This does not argue against the effectiveness of PPV23 vaccination in reducing risk of pneumococcal pneumonia, estimated at ~24% in large cohort studies (Lawrence H et al. *PLoS Med* 2020;17[10]:e1003326), but certainly supports Australian recommendations for PCV13 vaccination for adults aged ≥ 70 years (≥ 50 years for Aboriginal and Torres Strait Islanders), with a prime-boost approach (PCV13 followed by PPV23) advocated for adults and children with risk factors for pneumococcal disease.

Reference: JAMA Netw Open 2022;5(3):e221111
Abstract

Efficacy, immunogenicity, and safety of a quadrivalent HPV vaccine in men

Authors: Goldstone S et al.

Summary: Results of an open-label, long-term extension of a randomised, placebo-controlled, phase 3 trial (V501-020; NCT00090285) published in *The Lancet Infectious Diseases* demonstrates the durable efficacy of the Gardasil™ quadrivalent human papillomavirus (HPV) vaccine for prevention of anogenital warts and malignancy in men. A total of 1,803 men of any sexual orientation who participated in the base study, either in the three-dose vaccine intervention arm (n=936; early vaccine group) or the placebo arm who subsequently received at least one dose of vaccine (n=867; catch-up group) were included in the extension study and followed for a mean of 9.5 years and 4.7 years, respectively. Three efficacy outcome measures were considered – the incidence of external genital warts related to HPV6 or 11, the incidence of external genital lesions related to HPV6, 11, 16, or 18 and the incidence of anal intraepithelial neoplasia or anal cancer related to HPV6, 11, 16, or 18 in homosexual males. In both the early vaccine and catch-up cohorts, the incidence of new onset genital warts due to HPV was completely eradicated after vaccination (early vaccine group: incidence per 10,000 patient-years in vaccinated vs placebo, 0 vs 137.3 and 0 vs 140.4; catch-up group: 0 vs 149.6 and 0 vs 155.1) and a significant reduction in anal intraepithelial neoplasms or anal cancers in homosexual males was seen (early vaccine cohort: 20.5 vs 906.2 per 10,000 patient-years; catch-up cohort: 101.3 vs 886 per 10,000 patient-years). There were no new safety concerns reported.

Comment: This study contributes further evidence of the extraordinary efficacy and safety of quadrivalent HPV vaccination, as well as its broad applicability in the prevention of HPV-associated genital lesions and neoplasia in men and women. Here, long-term follow-up of 1,803 males involved in an early vaccination study (n=936, 88% heterosexual, median follow-up 9.5 years) and in a catch-up vaccination study (n=867, 85% heterosexual, median follow-up 4.7 years), demonstrated virtually complete protection from new genital warts and other HPV-associated genital lesions, as well as a ~90% reduced incidence of anal intraepithelial neoplasia or anal cancer related to HPV 6,11, 16 or 18 (noting 886 cases/10,000 person-years in the control group). The safety and near-universal immunogenicity of the quadrivalent vaccine is well defined (Kamolratanakul S & Pitisuttithumand P. *Vaccines* (Basel). 2021;9[12]:1413) may be somewhat taken for granted even though only 20 years ago HPV vaccination was a promising innovation awaiting clinical proof (Frazer I. *Virus Res.* 2002;89[2]:271-4). In this respect, the use of novel viral-like particles (VLPs) created from self-assembling recombinant L1 capsid proteins that could induce immunogenicity without requiring adjuvants has proved to be a durably successful strategy. Current Australian guidelines now recommend the 9-valent HPV vaccination for adolescents 9-18 years (acknowledging the benefits of a gender-neutral approach to vaccination; Lehtinen M et al. *Expert Rev Vaccines* 2022;1-4) as well as for men who have sex with men, and those who are significantly immunocompromised. Routine HPV vaccination in adults is not recommended, although it will be interesting to see how guidelines evolve given new data highlighted here, as well as growing interest in potential roles of therapeutic HPV vaccination, as well as in preventing oropharyngeal cancer (Lu Y et al. *Cancer Epidemiol.* 2022;78:10214).

Reference: Lancet Infect Dis 2022;22(3):413-25
Abstract

Long-term efficacy and safety of omalizumab for nasal polyposis in an open-label extension study

Authors: Gevaert P et al.

Summary: Hoffmann-La Roche's 24-week phase 3 POLYP 1 and POLYP 2 trials (NCT03280550 & NCT03280537) demonstrated efficacy of omalizumab for adult patients with severe chronic rhinosinusitis with nasal polyps (CRSwNP) with inadequate response to intranasal corticosteroids, significantly improving both primary co-points compared to placebo (Gevaert P et al. *J Allergy Clin Immunol* 2020;146[3]:595-605). This publication in *The Journal of Allergy and Clinical Immunology* details results from the subsequent 28-week open-label extension study of omalizumab (NCT03478930) and 24-week off-treatment follow-up period. Base trial criteria restricted enrolment to patients with severe disease (Nasal Polyp Score [NPS] ≥5; Nasal Congestion Score [NCS] ≥ 2 and Sino-Nasal Outcome Test 22 ≥20). Omalizumab posology was determined by serum total IgE level and body weight (75-600 mg every two or four weeks) and was administered on a background of concomitant nasal mometasone furoate. Patients who completed the base trials (n=249) were enrolled in two cohorts – patients from the base omalizumab treatment arms received up to a total of 52 weeks of treatment, while patients crossing-over from placebo arms received up to 28-weeks. In patients continuing omalizumab therapy the extension phase elicited further clinical benefits with improvements in both NPS and NCS at week 52 compared to week 24 (mean change from baseline at week 24 vs week 52: NPS, -1.01 vs -1.31; NCS, -0.85 vs -1.12). Significant improvements in endoscopic, clinical and patient-reported outcomes were revealed in patients initiating omalizumab treatment after participation in placebo arms, comparable to that achieved in the base trials (mean change in NPS at week 52, -0.97; mean change in NCS at week 52, -0.99). Disease control was not durable after termination of omalizumab treatment with outcome measures deteriorating over the off-treatment follow-up period (mean change from baseline at week 76: NPS -0.54 and -0.48; NCS, -0.65 and -0.58).

Comment: CRSwNP is a common presentation affecting ~1%-2% of the population, which also often incorporates comorbid asthma with or without aspirin-exacerbated respiratory disease (AERD). Within this scheme, biologic agents are assuming a more prominent role, with emerging evidence to support the use of IgE-targeting omalizumab (PBS listed for severe allergic asthma or chronic spontaneous urticaria), as well as IL-5 inhibitors mepolizumab and benralizumab (PBS: uncontrolled severe asthma) and the IL-4 inhibitor dupilumab (PBS: uncontrolled severe asthma or severe atopic dermatitis). Clinical trial data (Borish L et al. *Ann Allergy Asthma Immunol* 2022; April 7 Epub online ahead of print) as well as early real-world studies (Tiotiu A et al. *Clin Rev Allergy Immunol* 2022; Apr 14 online ahead of print) suggest that each of these treatment options can provide significant clinical benefit, although a rational basis for choice of treatment has not yet been established and there is no evidence to date indicating prolonged post-treatment remission. This study provides 76-week follow-up data from 249 participants in the POLYP-1 and POLYP-2 trials of omalizumab therapy in CRSwNP, including 123 patients continuing treatment and 126 patients switching to open-label omalizumab after the initial 24-week trial. All patients completed a further 28 weeks of treatment and were then observed off-treatment for 24 weeks. Overall, there was evidence of continuing improvement in NPS and NCS as well as improved nasopharyngeal symptoms, along with improved asthma-related symptoms among the 142 participants with asthma (57%, including 27% with a diagnosis of AERD). Around 28% of patients met criteria for reduced need for surgery during the open-label treatment period, noting that 68% had already required surgery prior to trial enrolment. All indices worsened following treatment withdrawal, with no evidence of durable remission for any disease component although these outcomes had not returned to their pre-treatment baseline after 24 weeks of observation. Thus, this study provides further evidence of efficacy and safety of omalizumab therapy for CRSwNP, while also raising further questions regarding the duration of treatment that is likely to be required and whether long-term remission can be induced.

Reference: J Allergy Clin Immunol 2022;149(3):957-65.e3
Abstract

SARS-CoV-2 vaccine responses in individuals with antibody deficiency: Findings from the COV-AD study

Authors: Shields A et al., on behalf of the COV-AD consortium

Summary: This interim analysis from the UK COVID-19 in patients with antibody deficiency (COV-AD) study reports a diminished immunogenicity and efficacy of COVID vaccines in patients with antibody deficiency. A total of 320 adult patients with primary or secondary antibody deficiency (mean age 58.5 years; 40% male) undergoing immunoglobulin replacement therapy (93.8%) or who had a serum IgG concentration < 4 g/L and were receiving antibiotic prophylaxis were accrued from eight immunology centres. The cohort consisted mostly (71.3%) of patients with primary immunodeficiency such as common variable immunodeficiency disorder (CVID), specific polysaccharide antibody deficiency or X-linked agammaglobulinemia. Patients received a two-dose COVID vaccine regimen with either the Pfizer-BioNTech (42.1%) or AstraZeneca ChAdOx1 COVID-19 vaccine (55%). A cohort of healthy patients (n=205) from the COVID-19 convalescent (COCO) study who received two doses of the Pfizer COVID vaccine served as controls. Analysis of antibody response to vaccination at one-to-two months after both doses found seropositivity was only achieved in roughly half of patients with antibody deficiency but all control patients (54.8% vs 100%). Other responses in patients with antibody deficiency were blunted compared to controls with a significantly lower antibody response and reduced neutralising capacity. Analysis stratified by vaccine type found greater immunogenicity of the Pfizer vaccine versus the AstraZeneca in this population (seropositive; 65.7% vs 48%; p=0.03). There were 11 breakthrough infections over the study period, predominantly in recipients of the AstraZeneca vaccine (91%).

Comment: This study provides timely data at a time when many specialty services are grappling with COVID-19 vaccination and disease-modifying treatment recommendations for immunocompromised patients. The COV-AD UK cohort provides the largest longitudinal data collection to date involving a phenotypically diverse patient population of 320 participants. This report covers the period March – October 2021, just prior to the emergence of the omicron strain, so discussion around three-dose vaccination strategies has now been overtaken by clear evidence that the development of omicron-specific neutralising antibodies requires a booster vaccine dose in the majority of immunocompetent individuals (Wesemann D. Cell 2022;185[3]:411-13). Some key insights are provided that are in keeping with other observations. First, that vaccine-induced humoral immunity is variable but often inadequate, with an overall seroconversion rate of 55% based on binding assays, decreasing further to 37% of participants with CVID and 16% with primary antibody deficiency (compared to 100% of controls) when assessing neutralising antibody responses. The presence of 'positive' antibody responses on binding assay evaluation has also become far less reassuring in the context of omicron infection risk, noting that spike IgG antibody levels >1000 U/mL are required for correlation with omicron-specific neutralisation, an order of magnitude higher than equivalent thresholds for the delta variant (Garcia-Beltran W et al. *Cell* 2022;185(3):457-66.e4). Second, cellular immune deficiency including treatment-induced B cell deficiency serves as a particular risk factor for vaccine non-responsiveness as well as severe COVID-19 disease – now noted across many studies involving primary and secondary immune deficiency. In this context, the outcomes of COVID-19 infection in this cohort (18 pre-enrolment + 10 breakthrough infections under observation) were generally favourable with asymptomatic or mild illness in 27/28 cases. The one case requiring hospitalisation involved previous rituximab therapy with evidence of B-cell depletion. Recognition of the additional risk conferred by cellular immune depletion is reflected in guidelines for additional vaccine doses as well as prioritised access to early disease-modifying treatments.

Reference: J Clin Immunol 2022; Apr 14 [Epub ahead of print]
Abstract

A real-world study of inhaled corticosteroid use in patients with severe eosinophilic asthma treated with mepolizumab

Authors: Corren J et al.

Summary: Corren et al conducted a retrospective administrative claims study to assess the impact of mepolizumab treatment on inhaled corticosteroid (ICS) use in patients with severe eosinophilic asthma. Data on 351 patients who initiated mepolizumab treatment, on a background of concurrent high-dose ICS therapy, over an approximately two-and-a-half-year period spanning November 2015 to March 2018 were extracted from the IBM Watson Health MarketScan Database. In the year following commencement of mepolizumab therapy, the number of patients continuing inhaled high-dose ICS gradually decreased with 34.5% not on ICS therapy at 12-months and almost half of the cohort (49%) reducing or discontinuing ICS for at least three months. Reduced incidence of exacerbations and short-acting β2-agonist claims were noted in patients who discontinued versus continued concomitant ICS use.

Comment: This retrospective cohort study of mepolizumab therapy for severe eosinophilic asthma (n=351 followed up for 12 months, including 179 patients with 24-month follow-up data) provides further insights into the emerging role of biologic therapy for allergic respiratory disease, much of it in keeping with the study of omalizumab in CRSwNP also reviewed here. The main aim of this analysis was to assess the steroid-sparing activity of mepolizumab therapy, thus providing an evidence base for reduced long-term toxicity risk as well as improved clinical outcomes on combined treatment. Overall, there appeared to be an incremental reduction in the use of high-dose ICS therapy, with 100% at baseline; 79.8% at three months and 65.5% at 12 months. This remained relatively stable in the second year of follow-up, at ~57%. Asthma exacerbations and requirement for oral corticosteroid treatment also reduced over time within the 'responder' group who were able to reduce (14%) or cease (29%) their ICS therapy. Treatment benefits appear to become apparent between three and six months after initiating mepolizumab therapy, with further incremental benefit thereafter. Given the selection of severe asthma phenotypes in this cohort, these results certainly provide evidence of sustained benefit. Within the broader landscape of biologic treatments for asthma, it remains uncertain if there is a true 'non-responder' phenotype that can be identified early – noting that the use of oral corticosteroid therapy as well as short-acting bronchodilators remained static within the group that continued to require high-dose ICS in this study – or if longer treatment duration continues to produce incremental improvement in severe asthma.

Reference: Ann Allergy Asthma Immunol 2022;128(2):184-92.e1
Abstract