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## IL-1 receptor antagonist, MIS-C, and the peculiar autoimmunity of SARS-CoV-2



For years, rheumatologists have sought to make sense of autoantibodies that are identified in patients with inflammation following acute infections. Often, it is unclear whether these autoantibodies are directly triggered by infection, and furthermore whether they might be contributing to the patient's immunopathology.

Multisystem inflammatory syndrome in children (MIS-C, also known as paediatric inflammatory multisystem syndrome temporally associated with SARS-CoV-2), is a rare, enigmatic hyperinflammatory disorder triggered by antecedent SARS-CoV-2 infection. MIS-C develops 2–6 weeks after contracting SARS-CoV-2, often after asymptomatic infection, and presents with clinical features resembling Kawasaki disease but with several important distinctions, including predilection for older children (age <5 years in Kawasaki disease vs 8–11 years in MIS-C), presentation with intestinal symptoms, and involvement of the myocardium more often than coronary arteries. Particular observations appear consistent across patients with MIS-C, including innate immune activation, specific expansion of TRBV11-2 T cells, and possibly persistent or recurrent SARS-CoV-2 antigenaemia (all of which are most recently and comprehensively reported by Sacco and colleagues<sup>1</sup>). Several patho-aetiological hypotheses have been postulated, including occult intestinal SARS-CoV-2 persistence, virus-derived super-antigens, or the actions

of plasmablasts expressing the transcription factor T-bet<sup>2</sup> (a finding that might be associated with autoimmunity<sup>3</sup>).

Some pathogens (eg *Streptococcus pyogenes* or Epstein-Barr virus) are known to trigger autoimmune pathology, but the jury is still out on SARS-CoV-2. Indeed, up to 20% of severe COVID-19 cases might occur as a result of autoimmunity-turned-immunodeficiency due to pre-existing interferon-neutralising autoantibodies.<sup>4</sup> Although autoantibody arrays have detected the emergence of autoantibodies in adults with COVID-19,<sup>5</sup> a multinational study in children with MIS-C suggested high titres of autoantibodies were associated with having received intravenous immunoglobulin (IVIG).<sup>1</sup>

In a report in *The Lancet Rheumatology*, Jochen Pfeifer and colleagues identified high-titre autoantibodies against interleukin-1 receptor antagonist (IL-1Ra) in sera from 13 (62%) of 21 children with MIS-C (age 0–18 years; 19 sampled before receiving IVIG).<sup>6</sup> Anti-IL-1Ra autoantibodies were absent in an array of control participants (healthy children, children with suspected growth retardation [non-inflammatory group], children with mild or asymptomatic COVID-19, children with Kawasaki disease, and children with quiescent systemic juvenile idiopathic arthritis). An unrelated antibody (against *Clostridium tetanus* toxin) was not elevated in patients with MIS-C versus the control groups, suggesting their findings are not simply the result of non-specific polyclonal stimulation of plasmacytes. In a preprint paper,

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**Panel: Questions about interleukin-1 receptor antagonist (IL-1Ra)-specific autoantibodies in multisystem inflammatory syndrome in children (MIS-C)**

- In MIS-C, are there clinical differences at presentation in patients who have anti-IL-1Ra autoantibodies versus those who do not?
- What signals drive IL-1Ra hyperphosphorylation?
- Is IL-1Ra hyperphosphorylation unique to SARS-CoV-2 infections?
- When does IL-1Ra become hyperphosphorylated and when do neutralising autoantibodies develop?
- Can IL-1Ra hyperphosphorylation or anti-IL-1Ra autoantibody development be used as specific tests to support MIS-C diagnosis?
- What protects anti-IL-1Ra autoantibody-positive adults with COVID-19 from developing multisystem inflammatory syndrome?
- Is a parallel mechanism at work in the autoantibody-negative MIS-C patients, or in clinically similar diseases such as Kawasaki disease?
- What mechanisms give rise to the distinct clinical presentations of MIS-C and deficiency of IL-1Ra?<sup>10</sup>

the same researchers reported anti-IL-1Ra autoantibodies in about 50% of adults with severe or critical COVID-19.<sup>7</sup>

Given the increasing evidence of a link between excess IL-1 and Kawasaki disease-like phenotypes,<sup>8</sup> we are intrigued by the possibility that such autoantibodies could be contributing to MIS-C. Supporting this hypothesis, free IL-1Ra protein concentrations were lower in patients with MIS-C who were positive for anti-IL-1Ra autoantibodies, versus those who were negative for autoantibodies, or those with Kawasaki disease or quiescent systemic juvenile idiopathic arthritis. Western blots revealed antibody-IL-1Ra complexes, and reporter assays suggested neutralisation of IL-1Ra activity by autoantibody-containing plasma. Decreased autoantibody titres during longitudinal follow-up of two patients with MIS-C suggested that these autoantibodies were transient. The authors also offer a potential mechanism of IL-1Ra-specific autoimmunity: they identified a hyperphosphorylated form of IL-1Ra in the patients with MIS-C who were positive for anti-IL-1Ra autoantibodies, but not in the control groups or autoantibody-negative patients with MIS-C. Similarly, rises and falls in hyperphosphorylated IL-1Ra preceded corresponding rises and falls in anti-IL-1Ra autoantibodies in their adult COVID-19 cohort<sup>7</sup>, and in one of the patients with MIS-C.

These observations are provocative, placing IL-1 signalling downstream of SARS-CoV-2 infection but upstream of hyperinflammation in patients with MIS-C. Yet, this preliminary study has several limitations, including a small number of participants, few longitudinal samples, and incomplete mechanistic evaluation. As such, these findings should neither affect clinical decision making, nor favour an expanded front-line use of anakinra (recombinant IL-1Ra) in patients with MIS-C,<sup>9</sup> particularly given the complete response of most patients to IVIG and glucocorticoids.

However, if generalisable, these results inspire important questions (panel). The range and scope of such questions are a testament to the potential novelty and aetiological importance of this study. The apparently unique association of hyperphosphorylated IL-1Ra and neutralising autoantibodies after SARS-CoV-2 infection might launch a new line of study with great translational potential. In the interim, we can thank the unprecedented scientific response to SARS-CoV-2 and its related morbidities for another insight into the host-pathogen autoimmunity problem.

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## Humoral response following SARS-CoV-2 vaccination: not all immunosuppressants are created equal



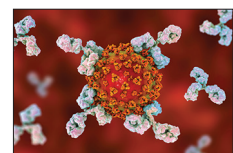
It is well established that many patients on immunosuppression have an attenuated humoral response to SARS-CoV-2 vaccination.<sup>1,2</sup> Indeed, people with immune dysregulation have a higher risk of SARS-CoV-2 breakthrough infection despite vaccination than do immunocompetent people.<sup>3</sup> As understanding of the SARS-CoV-2 vaccine response among immunosuppressed populations evolves, a hierarchy among agents is emerging, with recipients of lymphocyte-depleting therapies, such as rituximab and mycophenolate mofetil, at greatest risk of a reduced immune response.<sup>1,2</sup>

A study in *The Lancet Rheumatology* by Luuk Wieske and colleagues adds to existing evidence that humoral responses after standard vaccination (defined as two-dose ChAdOx1 nCoV-19 [Oxford–AstraZeneca], BNT162b2 [Pfizer–BioNtech], CX-024414 [Moderna], or single-dose Ad.26.COV2.S [Janssen]) are sub-optimal among patients with immune-mediated inflammatory diseases treated with anti-CD20 therapy, sphingosine 1-phosphate receptor (S1P) modulator, or mycophenolate mofetil combination therapies.<sup>4</sup> Similar rates of seroconversion were observed among patients treated with other immunosuppressants, although antibody titres were moderately reduced compared with controls. Given findings of a preserved recall response in these patients, the authors conclude that reduced antibody titres are unlikely to translate to loss of short-term protection. However, we believe that this conclusion might be premature in the absence of clinical outcome data, and more importantly, studies have demonstrated the correlation between antibody titres and breakthrough infections.<sup>5</sup> Moreover, recent data have highlighted that significantly higher antibody concentrations are required to overcome immune evasion induced by variants of concern,<sup>6</sup> further underlining the potential role of antibody titres in guiding strategies for infection prevention.

Although Wieske and colleagues did evaluate differential response between monotherapies and combination therapies, absence of dosing information limits additional insights into the role of immunosuppressive intensity in blunting humoral responses. In addition, the dose of both mycophenolate mofetil and glucocorticoid, as well as the degree of rituximab exposure, is important, particularly considering findings that glucocorticoids independently blunt antibody responses.<sup>1</sup> Moreover, two-dose vaccination with mRNA vaccines has been shown to elicit greater humoral responses compared with the Ad.26.COV2.S vaccine in patients with immune-mediated inflammatory diseases, whereas the CX-024414 vaccine induces greater humoral immunogenicity and is associated with lower rates of breakthrough infections than the BNT162b2 vaccine in immunocompetent people;<sup>7</sup> data pertaining to differential immunogenicity between vaccine platforms would be useful to inform clinical decision making.

Wieske and colleagues provide valuable insights into humoral responses following an additional mRNA vaccine dose; they report increased seroconversion among patients on mycophenolate mofetil combination therapy, but limited effects in those on anti-CD20 therapy and S1P modulators. A temporary hold of mycophenolate mofetil in the perivaccination period augments humoral responses in patients with immune-mediated inflammatory diseases and solid organ transplant recipients,<sup>8,9</sup> and it is unclear whether mycophenolate mofetil dosing was modulated in this study to facilitate increased seroconversion. In addition, heterologous boosting is associated with lower COVID-19 incidence rates than homologous boosting in immunocompetent people,<sup>10</sup> and assessment for different responses in these groups would be beneficial to guide the choice of optimal additional dose vaccine platform.

Wieske and colleagues suggest that antibody testing alone to determine additional vaccine doses is



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