Since January 2020 Elsevier has created a COVID-19 resource centre with free information in English and Mandarin on the novel coronavirus COVID-19. The COVID-19 resource centre is hosted on Elsevier Connect, the company's public news and information website.

and probably extremely fatigued after 2 years of the COVID-19 pandemic. Better evidence around which treatments are most effective in such conditions could also lead to better-defined recommended treatment pathways. Finally, system-wide issues around timely access to recommended care pathways, such as physiotherapy, need to be addressed.

We declare no competing interests.

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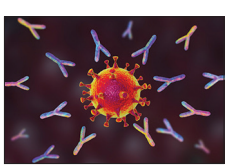
SARS-CoV-2 vaccine-induced antibody levels: what lies beneath

SARS-CoV-2 vaccine-induced antibodies are an immune correlate of protection against infection and are considered an appropriate metric to study susceptibility to infection.[1] To date, studies of SARS-CoV-2 vaccine-induced antibody responses in patients with immune-mediated inflammatory diseases have only examined a few diagnoses and treatments, or only monitored participants for a short duration after vaccination. Moreover, few studies have addressed factors that modulate inter-individual antibody levels such as age,[2] sex,[2] vaccine modality,[3] homologous or heterologous vaccination,[4,5] time interval between vaccinations,[4] infection before or after vaccination,[6] and the infecting variant.[7]

In *The Lancet Rheumatology*, David Simon and colleagues[8] define longitudinal SARS-CoV-2 vaccine-induced antibody responses relative to a broad range of immune-mediated inflammatory disease diagnoses and immunomodulatory treatments, considering the confounding variables of antibody responses. This thorough investigation contributes to the body of evidence that indicates that, irrespective of diagnosis or treatment, patients with immune-mediated inflammatory diseases have lower peak antibody responses compared with healthy controls. This study confirms that, compared with monotherapy, combination therapy further reduces peak responses or increases the rate of waning,[9] with the lowest antibody levels observed in patients receiving T-cell and B-cell inhibitors. Over the long term, antibody waning was most pronounced in patients receiving conventional immunomodulators and cytokine inhibitors.

Simon and colleagues identify target groups that, in general, might warrant being monitored for vaccine responsiveness, should be considered for additional or earlier booster vaccinations, or considered for pre-exposure prophylaxis. Undefined groups that require further study include firstly, patients with untreated immune-mediated inflammatory diseases, because immune dysfunction itself lowered antibody responses compared with healthy controls; and secondly, participants with immune-mediated inflammatory diseases who reported a worsening of their primary disease post-vaccination (4·7% in the present study). Defining the diagnoses represented within these groups, the treatments, and the longitudinal immune responses will give important insights into understanding vaccine-induced immunity or adverse events in these individuals.

In individuals who are immunocompetent, homologous mRNA-based vaccine regimens induce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Published **Online**
August 9, 2022
https://doi.org/10.1016/S2665-9913(22)00225-9

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higher antibody titres compared with homologous vector-based and inactivated vaccine regimens.[3] However, a heterologous combination of vector-based and mRNA-based vaccines induce immune responses similar to homologous mRNA vaccination titres;[5] this is understudied in people with immune-mediated inflammatory diseases. To this end, Simon and colleagues[8] categorised antibody responses according to vaccine type and homologous or heterologous vaccination. In all instances, participants with immune-mediated inflammatory diseases had reduced antibody responses compared with healthy controls. However, as expected, participants receiving homologous vector-based vaccines had the lowest antibody titres.

Notably, the authors show that heterologous vaccination increases antibody titres equivalent to homologous mRNA vaccination in people with immune-mediated inflammatory diseases, thus identifying that this strategy restores antibody responses in people with immune-mediated inflammatory diseases who only received vector-based vaccines. This finding also underscores the importance of studying vector-based or inactivated vaccines in homologous or heterologous regimens in people with immune-mediated inflammatory diseases, to inform policies in regions that extensively use these vaccine types (eg, Asia and Africa). Moreover, the Novavax protein-based vaccine recently approved by the US Food and Drug Administration offers new possibilities that require evaluation. Beyond heterologous vaccination, longer intervals between vaccine doses also increase antibody titres and cross-reaction with neutralisation-resistant variants in immunocompetent individuals.[4] Simon and colleagues[8] did not evaluate the effect of dose intervals in their cohort, which warrants consideration to inform policies regarding the timing of booster doses.

Infection in combination with vaccination increases antibody titres in a manner consistent with a third dose after a primary two-dose regimen.[6] In a sensitivity analysis, Simon and colleagues[8] excluded participants who had a PCR-positive test for COVID-19 and showed that it did not affect the conclusion that, overall, people with immune-mediated inflammatory diseases have reduced antibody responses. However, the authors did not perform a separate analysis for participants with a previous infection who are vaccinated. Such an analysis is essential, not only to define the confounding effect of previous infection, but also to understand infection-boosted immunity in people with immune-mediated inflammatory diseases, particularly at this stage of the pandemic with increased infection prevalence. Accordingly, future studies on SARS-CoV-2 vaccine protection should consider the combined effect of vaccination and infection, ideally defined by the presence of anti-SARS-CoV-2 nucleocapsid antibodies. Of note, considering infection in future studies will be complex, since different SARS-CoV-2 variants introduce specific antibody binding bias,[7] known as immune imprinting or previous antigenic sin.

The findings of Simon and colleagues[8] might extend to vaccine responses beyond SARS-CoV-2 in people with immune-mediated inflammatory diseases. However, for SARS-CoV-2 specifically, 30 months into the pandemic, assessing antibody responses against the vaccine strain will overestimate the potential protection of the vaccine against current and future strains. The emergence of highly mutated SARS-CoV-2 variants that differentially affect antibody binding and risk of infection, but not necessarily the risk of severe disease, brings into question the value of the continued use of antibody titres against the vaccine strain as a correlate of protection against infection and disease. Future studies might need to consider alternative biomarkers or at minimum, additionally study antibody responses against circulating variants. Accordingly, recommendations need to be responsive to the prevailing virus variants, which alter the immune balance and thus affect risk, in an ever-changing pandemic landscape.

We declare no competing interests.

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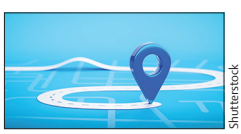
Healing structural damage in axial spondyloarthritis: are we there yet?

Under the overarching terminology of axial spondyloarthritis, two disease phenotypes are encompassed: non-radiographic axial spondyloarthritis, the earlier or milder form of the disease, which by definition does not fulfil the imaging part of the modified New York criteria, and radiographic axial spondyloarthritis, formerly known as ankylosing spondylitis, the more progressive form of the disease, in which unequivocal radiographic changes of the sacroiliac joint are evident, thus fulfilling the said criteria.[1] By contrast with other inflammatory rheumatic diseases, spondyloarthritides are characterised by the simultaneous presence of structural joint damage and new bone formation, both following active inflammation. In axial spondyloarthritis, several imaging lesions have been described, of which osteitis (inflammation), erosion (damage), ankylosis and backfill (new bone formation) are arguably the most important.[2] Backfill is an imaging phenomenon that can be seen in MRI images, in which characteristics of fatty tissue develop inside an erosion cavity when the inflammation diminishes; backfill is supposed to be the missing link between erosions and ankylosis.[3] In *The Lancet Rheumatology*, Walter Maksymowych and colleagues[4] present a post-hoc analysis from the COAST-X randomised controlled trial (RCT)[5] describing the effect of interleukin (IL)-17A inhibition with ixekizumab on structural lesions of the sacroiliac joints of patients with non-radiographic axial spondyloarthritis, as assessed by MRI after 16 weeks compared with placebo. The presented results are similar to those that have been described for the tumour necrosis factor (TNF) inhibitor etanercept in patients with non-radiographic axial spondyloarthritis: the imaging results suggest that erosions were subsequently filled with repair tissue, a process that could be considered as healing of structural damage, in patients treated with ixekizumab compared with placebo.[6] In parallel, development of fatty bone marrow lesions was more pronounced under therapy. Of note, a tendency towards progression of erosive changes was observed in the placebo group, by contrast with a decrease in erosion in the treatment groups (change from baseline to week 16 in mean Spondyloarthritis Research Consortium of Canada (SPARCC) sacroiliac joint structural score (SSS) for erosion was –0·39 for ixekizumab Q4W [p=0·003 *vs* placebo], –0·40 for ixekizumab Q2W [p=0·002], and 0·16 for placebo). However, erosion and backfill were scored in a mutually exclusive manner; thus, erosion at baseline infiltrated with backfill in the follow-up would have led to a reduced erosion score. Furthermore, the SPARCC SSS method assesses erosion per quadrant and backfill per sacroiliac joint half, such that scores and locations of both phenomena cannot be compared directly. Therefore, the Article by Maksymowych and colleagues leaves an important question unanswered: how many, if any, new bone erosions develop under treatment? In addition, we do not know whether the erosion load reduction was driven merely by an increase in backfill or by other factors. For their scorings, the readers only had access to T1 weighted sequences that might have been necessary to blind the raters to information about active inflammation. However, the use of semi-coronal T1 weighted sequences alone reduces the accuracy of lesion characterisation when other sequences, especially short tau inversion recovery or erosion specific sequences, are not available.

Nonetheless, it is crucial to understand that from what we understand today, the observed increase in structural lesions (ie, backfill and fatty marrow lesions) should be considered as damage repair and not as progression of the disease. Therefore, the study presents additional evidence that therapy with biological disease modifying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Published **Online** August 9, 2022 https://doi.org/10.1016/S2665-9913(22)00226-0

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