



Immunogenicity, breakthrough infection, and underlying disease flare after SARS-CoV-2 vaccination among individuals with systemic autoimmune rheumatic diseases

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Abstract

Many patients with systemic autoimmune rheumatic diseases (SARDs) require immunosuppression to reduce disease activity, but this also has important possible detrimental impacts on immune responses following vaccination. The phase III clinical trials for severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) vaccines did not include those who are immunosuppressed. Fortunately, we now have a clearer idea of how immune responses following SARS-CoV-2 vaccination has for the immunosuppressed, with much of the data being within a year of its introduction. Here, we summarize what is known in this rapidly evolving field about the impact immunosuppression has on humoral immunogenicity including waning immunity and additional doses, breakthrough infection rates and severity, disease flare rates, along with additional considerations and remaining unanswered questions.

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Introduction

Immunosuppressed individuals with systemic autoimmune rheumatic diseases (SARDs) may be vulnerable to both severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection and severe coronavirus disease 2019 (COVID-19) outcomes [1–4]. Therefore, SARS-CoV-2 vaccination may be especially crucial for

individuals with SARDs. However, the SARS-CoV-2 vaccine clinical trials did not include SARDs or other immunosuppressive conditions. Immunosuppressive medications and underlying altered immunity may impact vaccine immunogenicity and result in lower effectiveness, resulting in breakthrough infection after vaccination. Specific immunosuppressive medications may particularly impact SARS-CoV-2 vaccine response and also affect the immune response to SARS-CoV-2 infection [5]. Temporary discontinuation around SARS-CoV-2 vaccine doses has been proposed to optimize immune response [6]. However, immunosuppressive medication disruption and immune activation after vaccination could also lead to underlying SARD flares and increased disease activity. Also, it is possible that the immune response may wane more quickly in immunosuppressed individuals than the general population, necessitating the need for additional vaccine doses. Finally, immunosuppressed patients may have prolonged viral shedding that may introduce new variants [7,8]. Thus, there are a myriad of considerations patients and providers with SARDs must balance related to SARS-CoV-2 vaccination (see Table 1).

In this narrative review, we will provide an overview of the current evidence related to humoral immunogenicity from SARS-CoV-2 vaccination, focusing on specific immunosuppressive drugs, waning immunity, medication discontinuation around vaccination, and additional doses. We will also discuss the studies investigating clinical cases of breakthrough infection after vaccination. Finally, we will detail studies investigating disease flare or increased disease activity after SARS-CoV-2 vaccination.

Humoral immunogenicity

Humoral response in immunosuppressed patients with rheumatic and musculoskeletal diseases have been reported to be diminished [9–12]. It is now well appreciated that depending on the type of immunosuppressive therapy, such as B cell depleting agents and mycophenolate mofetil, the antibody response can be dampened significantly. It is not surprising then that rheumatic patients treated with such

Table 1

Selected studies evaluating breakthrough infection after COVID-19 vaccination among patients with systemic autoimmune rheumatic diseases.

First author ^{Ref}	Study design	Location Calendar time n of COVID-19 after vaccination	Key findings/immunosuppressive medications implicated	Comments
Cook et al. [30]	Case series	Boston, MA, USA 30-Jan-2021 to 31-Jul-2021 n = 16 breakthrough cases	<ul style="list-style-type: none"> - 5/16 on rituximab - 4/16 on mycophenolate mofetil - 3/15 on methotrexate - 6/16 hospitalized - 2/16 died (both on rituximab for ILD) 	<ul style="list-style-type: none"> - Systemic case identification at Mass General Brigham - First study reporting breakthrough infection among SARDs - All breakthrough cases were at least 14 days after 2nd mRNA dose or first J&J dose
Lawson-Tovey et al. [31]	Case series	Europe 19-Jan-2021 to 27-Jul-2021 n = 38 after any vaccine dose; n = 10 breakthrough cases	<ul style="list-style-type: none"> - 2 deaths in breakthrough cases (glucocorticoids, rituximab) 	<ul style="list-style-type: none"> - Cases identified from EULAR COVID-19 and COVAX voluntary physician registries - Limited data presented about breakthrough cases
Liew et al. [32]	Case series	International 5-Jan-2021 to 30-Sep-2021 n = 197 after any vaccine dose; n = 87 breakthrough cases	<ul style="list-style-type: none"> - 22 breakthrough cases hospitalized - 9/22 hospitalized breakthrough cases on B cell depleting therapy - 3/22 hospitalized breakthrough cases on mycophenolate mofetil - 5 deaths 	<ul style="list-style-type: none"> - Cases identified from the Global Rheumatology Alliance voluntary physician registry
Sun et al. [33]	Retrospective cohort study	United States 10-Dec-2020 to 16-Sep-2021 n = 664,722 after any does with either RA (n = 13,445), other immune dysfunction condition, or healthy comparator; n = 22,917 breakthrough cases (n = 511 among RA)	<ul style="list-style-type: none"> - Overall incidence rate of breakthrough infection was 5.0 per 1000 person-months - RA had adjusted hazard ratio of 1.20 (95% CI 1.09–1.32) for breakthrough infection compared to healthy comparators - Lower proportion of severe COVID-19 for breakthrough cases compared to pre-vaccination 	<ul style="list-style-type: none"> - Analyzed data from the National COVID Cohort Collaborative (N3C), a consortium of EHR data from 65 study sites across US - Largest study; included a contemporary control group - Immunosuppressive medications not analyzed - Analyses stratified by before or after 20-Jun-2021 due to Delta variant emergence
Papagoras et al. [34]	Case series	Greece 1-Mar-2020 to 31-Aug-2021 n = 48 after any vaccine dose; n = 29 breakthrough cases	<ul style="list-style-type: none"> - 10/29 breakthrough cases on TNF inhibitors - 4/28 breakthrough cases on mycophenolate mofetil - 2/28 breakthrough cases on rituximab - Lower proportion of severe COVID-19 for vaccinated vs. unvaccinated - No deaths among breakthrough cases 	<ul style="list-style-type: none"> - Cases identified from the Greek Rheumatology Society voluntary physician registry
Ahmed et al. [35]	Prospective cohort study	India Mar-2021 to Oct-2021 n = 630 who provided blood 4–6 weeks after second vaccine dose (n = 47 breakthrough cases)	<ul style="list-style-type: none"> - Non-response to COVID-19 vaccine had HR of 3.6 (95% CI 1.58–8.0) for breakthrough infection compared to good response - Mycophenolate mofetil, rituximab, and glucocorticoids associated with breakthrough infection in univariate analyses 	<ul style="list-style-type: none"> - Categorized patients based on humoral vaccine response to anti-RBD antibodies into good response, inadequate response, no response
Vanni et al. [36]	Case series	Boston, MA, USA 13-Aug-2021 to 25-Oct-2021 n = 2	<ul style="list-style-type: none"> - Both cases were mild - Both cases occurred in patients with RA on TNF inhibitor monotherapy 	<ul style="list-style-type: none"> - Systemic case identification at Mass General Brigham - First study reporting breakthrough infection after 3 mRNA vaccine doses

Calabrese <i>et al.</i> [37]	Case series	Cleveland, OH, USA Dec-2020 to 15-Dec-2021 n = 74 after any vaccine dose on B cell depleting therapy for immune-mediated inflammatory diseases; n = 68 breakthrough cases	<ul style="list-style-type: none"> -15 breakthrough cases after "booster" vaccine dose -26/74 hospitalized -6/74 died -No association between most recent infusion of B cell depleting therapy and infection -Monoclonal antibody receipt was strongly associated with mild COVID-19 	<ul style="list-style-type: none"> -Currently in preprint form (not yet peer-reviewed) -Largest study that included breakthrough infection after 3 mRNA doses
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CI, confidence interval; EHR, electronic health record; EULAR, European Alliance of Associations for Rheumatology; HR, hazard ratio; ILD, interstitial lung disease; RA, rheumatoid arthritis; RBD, receptor binding domain; SAPD, systemic autoimmune rheumatic disease; TNF, tumor necrosis factor.

agents would be more vulnerable to severe COVID-19 infection despite vaccination. This section will review the body of evidence that supports how different immunosuppressive therapies can blunt the humoral response (see [Figure 1](#)).

B-cell depleting agents

B cell-depleting agents, such as rituximab, have been reported to be the most significant offender in reducing humoral response after SARS-CoV-2 vaccination [12–16]. In fact, some studies have demonstrated that patients who receive rituximab do not mount any antibody response which in particular can be concerning for those on maintenance therapy. Duration since rituximab exposure may be an important contributor to improved humoral response [17]. In a retrospective study of 56 patients treated with rituximab, the longer the period between the patient’s last exposure of rituximab and SARS-CoV-2 vaccination was associated with a positive serologic response, with those who had exposure > 12 months had the best response [18]. Additionally, B cell reconstitution has been reported to be a reliable marker of seroresponse in those with vasculitis or rheumatoid arthritis [14,17,18].

Antimetabolites

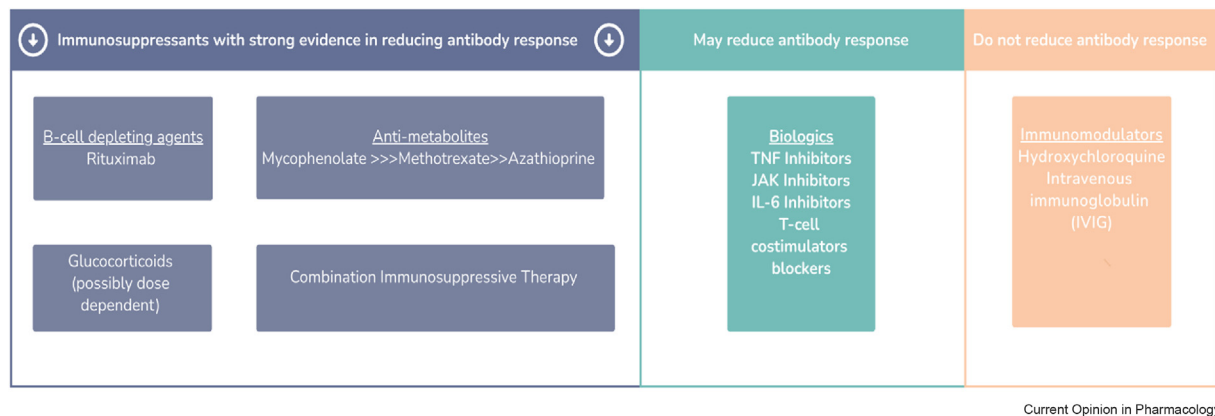
Mycophenolate mofetil and mycophenolic acid have been reported in multiple studies to blunt the humoral response [12,19]. In the rheumatic arm of the national vaccine response study at Johns Hopkins, patients taking mycophenolate reported rates of seroconversion as low as 27% after the first dose of the SARS-CoV-2 mRNA vaccine, with improvement to 73% after the second dose [9,12]. Even more reduced response has been reported in patients on anti-metabolite regimens containing MMF in single organ transplant recipients [11,19]. Interestingly, azathioprine has not been reported to have a significant impact on the humoral response [12].

Methotrexate has been reported to have lower rates of seroconversion, but reports have not been consistent [9,10,16,19]. For example, in the Johns Hopkins cohort, there was no significant impact of methotrexate on humoral response. However, in other cohort studies that included a US based cohort at New York University Langone with a European validation cohort, humoral immune response was diminished. Only 62.2% of patients on background methotrexate demonstrated an adequate response after two-dose vaccination [20].

Glucocorticoids

The dose of glucocorticoids and its direct effects on humoral response after SARS-CoV-2 vaccination still needs further study. However, since most people with SARDs are on combination therapy with other

Figure 1



Key immunosuppressants associated with reducing antibody response after SARS-CoV-2 vaccination. Those with the strongest evidence are highlighted in the left panel (purple), while those that may reduce antibody response are in the middle panel (green), and those that do not reduce antibody response are in the right panel (orange).

immunosuppressants, it may be difficult to isolate the sole effects of steroids alone. Nonetheless, a well characterized US cohort study, the COVARI PAD study, demonstrated that antibody titers were lower in patients who receive low dose prednisone (< 7.5mg/daily) [10].

Other Biologics/DMARDs

In one of the largest observational studies of 686 patients with rheumatic diseases, seroconversion was lower for those on immunosuppression, such as abatacept (71% seroconverted), JAK inhibitors (90% seroconverted), while other immunosuppressants (leflunomide, hydroxychloroquine, TNF inhibitors, IL-6 inhibitors, and IL-17 inhibitors) did not significantly impact seroconversion [21]. In contrast, in a prospective cohort of 133 patients, JAK inhibitors and other biologics such as TNF inhibitors, IL-12/IL-23 had a modest impact on antibody formation [10].

Combination therapy

Combination therapy with multiple agents, in particular with B-cell depleting therapies, can contribute to a poor humoral response. Connolly and colleagues reported on 20 patients who did not have detectable anti-RBD antibodies at a median of 30 days after the second dose of SARS-CoV-2 mRNA vaccine and found that 90% of the patients were on multiple immunosuppressive agents, and maintenance corticosteroids were a part of 16 (80%) participant regimens [13].

Waning immunity

While antibody responses are detectable for a minimum of 6 months following the initial series of SARS-CoV-2 mRNA vaccination in immunocompetent individuals [22,23], titers do tend to wane during this period

potentially leading to loss of protective responses. Due to attenuated humoral responses associated with immunosuppression, the impact immunosuppression has on antibody decay kinetics is critical to inform providers about the need for additional boosting or administration of pre-exposure prophylaxis.

Data is starting to emerge suggesting that most individuals with SARDs on immunosuppression likely maintain antibody titers that are protective. Data from the Johns Hopkins cohort revealed that while anti-RBD titers reduced by 2.8-fold between the 1-month to 6-month post-vaccination period, 96% of the study participants remained seropositive (96%) and 80% continued to maintain predicted protective neutralizing antibody titers [24,25]. Those on monotherapy had the high rates of high antibody titers compared to participants on combination therapy, and similar to antibody responses immediately post-vaccination those on therapies that B cell modulating therapies and T cell costimulation blockade were seronegative at the 6-month timepoint [24]. These early findings should be encouraging for immunosuppressed patients with SARDs, as initial antibody responses appear to be predictive of durable responses.

Additional vaccine doses and peri-vaccination hold

An additional 3rd SARS-CoV-2 vaccine dose in those who had a poor antibody response have found that up to 80% seroconvert in a case series of 18 patients [26]. Similarly, a fourth dose has also been reported to improve humoral response in a case report of a patient with rheumatoid arthritis even without pausing immunosuppression [27]. Interestingly, another case series of 18 patients from the Johns Hopkins cohort also

demonstrated that a 4th additional dose augmented humoral response [28]. However, there was a subset of patients who did not hold immunosuppression who remained persistently negative.

Beyond additional vaccine doses, peri-vaccination hold of immunosuppressants can be a complementary strategy to improve humoral response in rheumatic patients on immunosuppression. Peri-vaccination hold of mycophenolate mofetil has been reported to augment humoral response in rheumatic patients [29]. In a case series of 24 patients who withheld mycophenolate, 22/24 (92%) had detectable antibodies compared with 112/171 (65%) who continued therapy. There were two participants who reported flares of their underlying disease requiring treatment in the peri-vaccination period, therefore careful assessment of disease activity should be done when optimizing vaccination strategies.

Breakthrough infection/severity

Several studies have investigated clinical outcomes among SARDs from COVID-19 breakthrough infection, defined by the US Centers for Disease Control and Prevention as a positive COVID-19 test 14 days or longer after completion of the initial vaccine series. Infections occurring between initial vaccination and that time point are considered partially vaccinated. The initial case series reporting breakthrough infections among SARDs was from Mass General Brigham in Boston, MA, USA [30]. This study identified 16 breakthrough infections among SARD patients [30]. Many of the medications also implicated with impaired humoral immunity after COVID-19 were over-represented (e.g., rituximab, mycophenolate mofetil, methotrexate) [30]. Some of the patients had severe outcomes and there were 2 deaths (both in patients with interstitial lung disease treated with rituximab) [30]. Other investigators analyzed European Alliance of Associations for Rheumatology to identify 38 COVID-19 cases after vaccination (10 breakthrough and 26 partially vaccinated infections)³¹. That study also reported two deaths among those with breakthrough infection (one with RA and Sjogren's syndrome treated with rituximab, 1 with RA treated with glucocorticoids) [31]. Finally, the Global Rheumatology Alliance reported a large case series of 197 COVID-19 cases occurring after vaccination, 87 of which qualified as breakthrough infections [32]. Among those with breakthrough infection, 22 were hospitalized (9 on rituximab, 3 on mycophenolate mofetil; 8 had pre-existing lung disease) and 5 died [32]. Overall, these case series show that some SARD patients are susceptible to severe clinical outcomes even after vaccination, particularly those with pre-existing lung disease and those treated with B cell depleting therapy or mycophenolate mofetil. However, firm conclusions are limited due to lack of denominator and small size of studies.

A large retrospective cohort study investigated breakthrough infection in conditions characterized by immune dysfunction using the National COVID Cohort Collaborative (N3C). This study compared COVID-19 risk after vaccination among patients with HIV infection, multiple sclerosis, rheumatoid arthritis, solid organ transplant, or bone marrow transplant to the general population (n = 664,722) [33]. The overall rate of COVID-19 after vaccination was 5.0 per 1000 person-months. Full vaccination was associated with 28% lower risk of COVID-19 compared to partial vaccination [33]. Compared to the general population, solid organ transplant (HR 2.16, 95% CI 1.96–2.38), HIV infection (HR 1.33, 95% CI 1.18–1.49), and rheumatoid arthritis (HR 1.20, 95% CI 1.09–1.32) were each associated with higher COVID-19 risk [33]. While some patients were hospitalized for COVID-19 after vaccination, the proportion was much lower compared to pre-vaccination cases [33]. A small study analyzing the Greek Rheumatology registry (n = 195) also reported improvement in the proportion of COVID-19 cases requiring hospitalization after vaccination among SARDs [34].

A large prospective cohort study in India linked humoral vaccine response to clinical outcomes for breakthrough infections among SARDs [35]. This prospective cohort study enrolled 630 patients with SARDs and measured anti-RBD antibodies 4–6 weeks after the 2nd vaccine dose [35]. They categorized patients based on the anti-RBD level as having a good response, inadequate response, or no response [35]. They contacted each patient every two months to identify COVID-19 cases. Their study coincided with the Delta wave in India [35]. Overall, there were 47 breakthrough infections (7.4% of patients) [35]. Those with no response to vaccination had nearly 4-fold increased risk of breakthrough infection (HR 3.6, 95%CI 1.6–8.0) compared to those with good response [35]. Thus, the humoral vaccine response may be a marker for risk of COVID-19.

All of these previous studies investigated breakthrough infection after 2 doses of mRNA vaccine (or one of J&J), but the US CDC now recommends an additional dose to complete the initial series for immunocompromised patients. The Mass General Brigham group reported their first 2 cases of breakthrough infection occurring in patients with rheumatoid arthritis on TNF inhibitor monotherapy [36]. A recent preprint investigated breakthrough infection after CD20 inhibitor use for immune-mediated inflammatory diseases at a single center and detailed 74 COVID-19 cases after vaccination (45 occurring after 2 vaccine doses and 23 occurring after 3 doses) [37]. More work is needed to investigate breakthrough infection after 3 or 4 vaccine doses and current variants.

Disease flares after SARS-CoV-2 vaccine series

In one of the largest physician-reported registries of inflammatory/autoimmune rheumatic musculoskeletal diseases (n = 5121 participants from 30 countries), it was found that flares were reported in 4.4% of cases, with 1.5% resulting in medication changes [38]. Results from the COVID-19 Global Rheumatology Alliance Vaccine Survey (n = 2860 participants) also found that flares that required medication changes occurred in only 4.6% of patients [39]. In a smaller study of the Johns Hopkins cohort (n = 1377 patients with RMD), 11% reported flares that required treatment [40]. There were no reports of severe flares in this group. The most common reactions were local reactions such as injection site pain and fatigue which did not interfere with daily activity. Of note, flares were associated with a flare in the 6 months preceding vaccination, prior COVID-19, and use of combination immunomodulatory therapy potentially highlighting patients who may have had more refractory disease at baseline.

Since SARDs represent a heterogeneous group of many autoimmune diseases, there have now also been reports on the risk of disease flare in specific autoimmune diseases such as systemic lupus erythematosus (SLE). In the VACOLUP study, 696 participants from 30 countries were included to determine the risk of flare after COVID vaccine administration. 21 (3%) of 696 patients reported a medically confirmed SLE flare [41]. 15 of 21 (71%) of the cases required a change in SLE treatment and 4 patients were admitted to the hospital [41]. Similar to the Johns Hopkins cohort [40], having a flare during the past year before vaccination was associated with an increased risk for SLE flare after vaccination [41]. A more recent study of 90 SLE patients in a multiethnic/multi-racial cohort also demonstrated that postvaccination flares occurred in 11.4% of patients, and only 1.3% of these were severe [42]. Another small single-center prospective study of 71 RA patients receiving an additional dose of COVID-19 vaccine showed no pre/post vaccine differences in patient-reported disease activity or in cellular markers of immune activation in a subset [43]. A study performed in Hong Kong using administrative data among 5493 RA patients showed no association between vaccine receipt and RA flare as well as no difference in RA drug prescriptions after vaccination [44]. However, a randomized trial of holding vs. continuing methotrexate in RA patients after COVID-19 vaccine did show higher disease activity in those who held methotrexate [45]. This suggests that immunosuppressive medication changes around vaccination, rather than vaccine-specific effects, could explain at least some RMD flares after vaccination.

Overall, risk of severe flare after COVID vaccination was relatively uncommon in multiple studies and may be

similar to the baseline rate of SARDs. These findings emphasize the safety of SARS-CoV-2 vaccines for immunosuppressed patients with SARDs.

Additional considerations

In the immunocompetent population, germinal center (GC) responses in draining lymph nodes last for a minimum of 6 months [46] which are critical for optimizing antibody diversity, affinity, and function. The duration of GC responses likely has major implications for the immunosuppressed: if immunosuppression is held perivaccination, restarting these medications likely are occurring early in the GC response. Blunting GC responses will theoretically attenuate cross-variant neutralization responses, as observed in the setting of MMF or TNFi. GCs are absent in patients who underwent kidney transplantation, partially due to the use of MMF [47]. In the setting of SARS-CoV-2 vaccination, TNFi monotherapy users possessed greatly reduced cross-variant neutralization titers to both B.1.351 (Beta) and B.1.617.2 (Delta) variants [48], possibly through the loss of GC structures as observed in the tonsils of patients with RA on TNFi [49]. Fortunately, a third dose restored these titers to predicted protective levels suggesting highlighting the critical importance of these additional doses [48].

The question about the sufficiency of T cell responses in vaccine-induced protective immunity continues to be debated. While a clear correlate of protection is neutralizing antibodies, SARS-CoV-2 vaccination in immunocompetent individuals generates robust and broadly reactive T cell responses, including the generation of memory T cells [50,51]. It has been suggested that neutralizing antibodies mediate protection from infection, while cellular responses influence severity of disease and infection resolution [52]. T cell responses may be particularly important in the setting of B cell depletion, which confers the greatest risk of poor or absent humoral responses as discussed above. Patients with multiple sclerosis on BCDT mounted modestly reduced follicular T cell responses in the blood [53], a cell necessary to generate effective GC responses. While CD8⁺ T cell frequencies are elevated, the increased incidence of breakthrough infections in these patients (as discussed above) likely suggests that T cells are not protective in this setting. This may be due to T cell dysfunction, as reductions in cytokine production by S-specific CD4⁺ T cells have been observed in patients on BCDT [15].

Finally, vaccine hesitancy remains an important issue among people with SARDs related to potential for disease flare, timing of vaccine receipt related to high disease activity and immunosuppressive medication use, and the novelty of SARS-CoV-2 [54–56] vaccines. More research is needed to show that SARS-CoV-2 vaccines

are safe and effective and to develop specific interventions to increase vaccine uptake.

Future research

Within a year of the introduction of SARS-CoV-2 vaccines, we impressively have a solid idea of how various classes of immunosuppressive influence antibody titers. But these data have open additional questions regarding the relationship between immunogenicity, protection, and the complete impact of immunosuppression has on both. For example, all studies have found large variation in antibody titers among study participants for any given immunosuppressive class. Whether this is due to concomitant medication use, disease state or activity, sleep quality (as has been observed with hepatitis A vaccination [57]), or host genetics will require additional efforts to deconvolute.

Furthermore, these responses assessed immediately after SARS-CoV-2 vaccination do not fully represent the mature humoral response. As discussed above, germinal center responses linger for months after vaccination in the immunocompetent, which serves to improve antibody quality by diversifying antibody repertoire. We only have a limited idea of the impact of immunosuppression on antibody quality, which is limited to TNFi. This has implications on whether to hold medications, as they will be restarted when germinal center responses are clearly ongoing. The NIH/NIAID-sponsored ACV01 clinical trial, which seeks to examine the impact of additional doses of SARS-CoV-2 vaccine and holding either methotrexate or mycophenolate on antibody and cellular responses [58].

Finally, questions remain about the robustness and importance of T cell responses particularly for non-B cell depletion therapies. Also, the generation of mucosal immunity vis-a-vis S-specific IgA remains unclear, with little data published thus far [59]. As these and other questions are answered over the following months and years, this will provide the most comprehensive collective dataset that will certainly inform about how to improve the outcomes with other vaccines these patients require.

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Credit author statement

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Conflict of interest statement

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- * of special interest
- ** of outstanding interest

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