

Efficacy of inactivated vaccines in patients treated with immunosuppressive drug therapy

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Abstract

Inactivated vaccines are generally considered safe in immunocompromised patients but the ability of immunocompromised patients to generate an effective immune response to vaccines is uncertain. Although recent reviews have focused on the effects of vaccines in patients who are immunocompromised due to various disease states (primary immunodeficiency), the effects of immunosuppressive drug therapy (secondary immunodeficiency) has received relatively less attention. This review evaluates evidence regarding the efficacy of inactivated vaccines against influenza, COVID-19, and other diseases in patients treated with immunosuppressive oncologic agents, immunosuppressants used for transplant recipients, and immunosuppressants used for autoimmune disorders. Although evidence is mixed for many immunosuppressive agents and vaccines, most studies have found an attenuated immune response to inactivated vaccines, with the majority of data indicate anti-B-cell antibodies have a more severe and prolonged negative effect on vaccine efficacy.

KEYWORDS

antirheumatic agents, immunosuppressive agents, inactivated vaccine, vaccine

1 | INTRODUCTION

It is well known that immunosuppression impairs the ability of the immune system to effectively respond to vaccination. Although recent reviews have examined the response to vaccination in patients who are immunosuppressed due to a particular disease state,^{1,2} very few studies have examined the effect of immunosuppressive drug therapy on the response to inactivated vaccines. Though inactivated vaccines are generally considered safe in immunocompromised patients due to their inability to cause infection, questions regarding their efficacy, and whether all immunosuppressive drugs impact vaccine efficacy equally, remain.

Inactivated vaccines are those containing a killed pathogen, a protein component, or a polysaccharide component of a pathogen and are incapable of replicating or causing disease. Although generally safer than live attenuated vaccines due to a lower risk of vaccine-associated infection, inactivated vaccines are less immunogenetic and carry a higher risk of failing to induce a protective

immune response.³ Adjuvanted inactivated vaccines are those that contain an additional component to increase immunogenicity.

The objective of this review was to evaluate the available evidence surrounding the efficacy of inactivated vaccines in patients who are immunocompromised due to drug therapy and consider the differential impacts of particular immunosuppressive therapies. Although many individual drug therapies and classes are recognized as immunosuppressants, a consensus definition of what constitutes an immunosuppressive agent is lacking. For the purposes of this review, an agent was considered immunosuppressive if its labeling (i) contains a warning regarding the risk of serious infections or malignancies associated with its use, (ii) recommends testing for tuberculosis or hepatitis prior to initiating therapy due to the risk of viral reactivation, (iii) warns about a potential drug interaction with vaccines, or (iv) recommends dose adjustments for infectious complications, thrombocytopenia, neutropenia, or lymphopenia. In addition, systemic corticosteroids used for at least 2 weeks at immunosuppressive doses (≥ 2 mg/kg or 20 mg/day of prednisone [for persons

over 10 kg], as defined by the Advisory Committee on Immunization Practices [ACIP]), were considered to be immunosuppressive agents.⁴

2 | SEARCH STRATEGY

A PubMed search was conducted for each inactivated vaccine and all identified immunosuppressant drug therapies. Studies were included if they were conducted in humans and published in English and evaluated the safety and/or efficacy of inactivated vaccines administered to patients currently or previously treated with immunosuppressants.

3 | IMMUNOSUPPRESSIVE ONCOLOGIC AGENTS

Although oncologic diseases and patient age contribute to the potential for reduced immune response to vaccination, the immunosuppressive actions of drugs used to treat cancer also play a significant role. Despite concerns about the potential for reduced efficacy of inactivated vaccines, most data have demonstrated that administration of inactivated vaccines is likely safe in patients treated with oncologic agents.

3.1 | Influenza vaccines

Several clinical studies have shown decreased antibody titer response to influenza vaccine in cancer patients being treated with chemotherapy when compared with healthy controls or patients with cancer who are in remission or not undergoing treatment.⁵⁻⁷ A prospective study evaluated the response to trivalent inactivated influenza virus vaccine in 31 patients with ovarian cancer. Of the 31 patients included, 15 were treated with primary adjuvant chemotherapy or chemotherapy for recurrent disease consisting of cytotoxic chemotherapy (e.g., paclitaxel, carboplatin, liposomal doxorubicin), a VEGF inhibitor (e.g., bevacizumab, sorafenib), or a combination while 13 patients in remission received a dendritic cell vaccine with or without cyclophosphamide. In addition, three patients in remission received no cancer treatment. Fewer than 50% of patients achieved a 4-fold increase in hemagglutinin inhibition (HAI) titers for any of the three strains included in the influenza vaccine.⁵ The frequency of patients achieving a 4-fold increase in HAI titers did not vary according to the number of chemotherapy cycles received or patient age. A second study evaluated influenza vaccination in 38 patients with breast cancer undergoing chemotherapy with fluorouracil, epirubicin, and cyclophosphamide-containing chemotherapy regimens and found significantly lower vaccine response as measured by influenza virus-specific antibody titers among patients with breast cancer compared with healthy controls.⁶ Vaccine efficacy was not significantly different between breast cancer patients who were vaccinated early (day 4) or late (day 16) during their chemotherapy cycle, although titers were numerically higher

in the early vaccine group. Lastly, a study of 19 patients with chronic lymphocytic leukemia (CLL) treated with the irreversible Bruton tyrosine kinase inhibitor, ibrutinib, found that 26% of patients demonstrated seroconversion, as defined by an increase in HAI titers from <1:10 to ≥1:40 or a ≥4-fold increase in HAI titers, for at least one strain 3 months after influenza vaccination, and 37% of patients developed an influenza-like illness in the 6 months following vaccination.⁷ The influenza-like illness was of grade 1 to 2 severity in all but one patient. The available data suggest that patients undergoing cancer treatment with cytotoxic chemotherapy (e.g., paclitaxel, doxorubicin, epirubicin, fluorouracil, etc.), bevacizumab, sorafenib, and ibrutinib have a diminished response to influenza vaccination, whether measured by HAI titers or influenza virus-specific titers. Although data are not available, patients treated with other immunosuppressive oncologic therapies likely also have a diminished immune response. Failure to achieve HAI titers of at least 40 suggests patients have at least a 50% chance of contracting influenza.⁸ Although IDSA clinical practice guidelines recommend influenza vaccines for immunosuppressed patients, such as patients receiving cancer treatment, except those receiving intensive chemotherapy or B-cell-directed therapy, patients vaccinated during or within 14 days of initiating immunosuppressive therapy should be re-vaccinated 3 months after completing such treatment if immune competence has been restored.⁹

3.2 | COVID-19 Vaccines

Only one published study evaluated COVID-19 vaccination in patients treated with immunosuppressive oncologic agents. Among 195 patients with a hematologic malignancy or prior receipt of an allogeneic hematopoietic cell transplant (HCT) who received two doses of an mRNA COVID-19 vaccine, 47% developed IgG antibody levels consistent with an immune response to vaccination, compared with 87% in healthy controls.¹⁰ The majority (67%) of these patients were treated with B-cell-targeted therapies, although a small number were treated with other immunosuppressive oncologic agents such as cladribine, ibrutinib, and venetoclax. Despite the limited data available, patients with hematologic malignancies treated with immunosuppressive oncologic agents appear to have a diminished response to COVID mRNA vaccines. This diminished immune response likely occurs with other COVID-19 vaccines as well. Current CDC guidelines recommend a three-dose primary series of COVID mRNA vaccines, followed by a booster dose at least 5 months later, for patients treated with immunosuppressants.¹¹

3.3 | Other inactivated vaccines

Although data surrounding influenza vaccination has generally shown decreased immune response to vaccination in patients receiving immunosuppressive oncologic agents, data with other inactivated vaccines is mixed. The response to the adjuvanted 23-valent pneumococcal polysaccharide vaccine, as measured by IgM levels 4 weeks after vaccination, was reduced among patients with chronic phase

chronic myeloid leukemia treated with the tyrosine kinase inhibitors imatinib, dasatinib, or nilotinib when compared with that of healthy controls (40% vs 92% response rate in patients and controls, respectively).¹² Patients with breast cancer who received adjuvant chemotherapy with cyclophosphamide, methotrexate, and 5-fluorouracil and were vaccinated against tick-borne encephalitis (TBE) either during or 6 to 12 months after chemotherapy did not produce anti-TBE titers 2 to 4 weeks after the second of two vaccinations, although healthy controls did produce anti-TBE titers.¹³ Patients who were vaccinated prior to initiating chemotherapy did develop significant anti-TBE titers, which persisted throughout chemotherapy.

In contrast, not all chemotherapeutic agents impair response to inactivated vaccines. Among 122 patients with multiple myeloma who underwent autologous HCT and were re-vaccinated against pneumococcus with the adjuvanted 13-valent pneumococcal conjugate vaccine 12 months after transplant, the response rate to pneumococcal vaccination (as measured by a 2-fold increase in titers for 70% of pneumococcal serotypes) was 58%, regardless of whether patients were receiving lenalidomide maintenance therapy or not.¹⁴ In addition, the response rate to adjuvanted pertussis, diphtheria, tetanus, and *Haemophilus influenzae* (Hib) vaccinations administered beginning 1 year after transplant were 76%, 70%, 60%, and 71%, respectively.¹⁴ Among 24 children receiving maintenance chemotherapy for acute lymphoblastic leukemia with cytotoxic chemotherapy (e.g., vincristine, daunorubicin, cytosine arabinoside, carmustine, mercaptopurine, doxorubicin, hydroxyurea, and/or cyclophosphamide), methotrexate, and/or prednisone who received booster doses of tetanus-diphtheria toxoids, followed by Hib 1 month later, patients had protective titers against tetanus, diphtheria, and Hib at rates of 100%, 92%, and 84%, respectively.¹⁵ Vaccine response was defined as a pertussis toxin increase to >5 units/mL for pertussis, a 4-fold increase in protective antibody titers for diphtheria, >0.5 IU/ml for tetanus titers, and a non-protective to protective antibody level from <0.15 to ≥ 1 or 4-fold increase in antibodies for patients in the indeterminate range at baseline for Hib.

In summary, the available data suggest that patients undergoing treatment for cancer do not develop as robust immune response to inactivated vaccines as compared with healthy controls. However, patients who are vaccinated 1 year after HCT, and perhaps some pediatric oncology patients, do develop immune responses to inactivated vaccines. Adjuvanted vaccines, while generally associated with strong immune responses, do not ensure robust immune response in patients treated with immunosuppressive oncologic therapy. Importantly, how these immune responses correlate with protection from infection is not well defined.

4 | RITUXIMAB

4.1 | Influenza vaccines

A small study of seven patients with Non-Hodgkin's Lymphoma (NHL) treated with cyclophosphamide, doxorubicin, vincristine, prednisone, and rituximab (R-CHOP) demonstrated that influenza vaccination

produced a humoral response to recall antigens but not the primary antigen.¹⁶ Other studies have found decreased rates of seroconversion after influenza vaccination among patients treated with rituximab compared with healthy controls or patients treated with other immunosuppressants, such tumor necrosis factor (TNF) inhibitors, or non-immunosuppressive therapies, such as disease-modifying antirheumatic drugs (DMARDs).¹⁷⁻²⁰ Additionally, several studies found reduced immune response following influenza vaccine administration in rituximab-treated patients with rheumatoid arthritis (RA)²¹⁻²⁵; however, one study showed that the immune response to influenza vaccine seemed to return 6 to 10 months following rituximab administration.²⁴ Similar results were seen in rituximab-treated patients following influenza vaccination in other disease states including neuromyelitis optica spectrum disorder, other rheumatologic conditions, and NHL.²⁶⁻²⁹

Rituximab has been consistently shown to decrease the immune response to influenza vaccination across a wide range of disease states. This decreased immune response appears to persist for at least 6 months after rituximab treatment. Consistent with these findings, ACIP guidelines recommend vaccination with inactivated vaccines at least 14 days before initiating immunosuppressive therapy, and revaccination at least 6 months after rituximab discontinuation if vaccination occurs less than 14 days before or during rituximab therapy.⁴ Clinical practice guidelines from the Infectious Disease Society of America (IDSA) do not recommend influenza vaccination for patients currently treated with rituximab, or those who received rituximab in the previous 6 months.⁹

4.2 | COVID-19 Vaccines

The limited studies that have evaluated COVID-19 vaccination in patients treated with rituximab have consistently demonstrated decreased immune response to vaccination. One small prospective study evaluated five rituximab-treated patients and found only two patients had a detectable antibody response.³⁰ In a retrospective analysis of 89 patients with a rheumatologic disease who received at least one dose of the COVID-19 mRNA vaccine, 21 patients failed to achieve a serologic response and of those, 20 had received rituximab.³¹ A total of 30 patients had been treated with rituximab in this analysis, and those who did respond to COVID-19 vaccination had significantly more time elapsed since their last rituximab exposure than those who did not respond to vaccination (704 vs. 98 days, respectively). Among patients receiving rituximab for oncologic diagnoses, a study of 195 patients with a hematologic malignancy or prior receipt of an allogeneic HCT, 67% of whom were treated with B-cell-targeted therapies such as rituximab, evaluated the efficacy of two doses of an mRNA COVID-19 vaccine, and found that 47% of patients developed IgG antibody levels consistent with an immune response to vaccination, compared with 87% in healthy controls.¹⁰ Other studies have similarly found decreased response to the COVID-19 mRNA vaccine among patients treated with rituximab.^{32,33} Data evaluating the effect of rituximab on the adenovirus vector or inactivated COVID-19 vaccines are not currently available.

Although limited data are available, patients treated with immunosuppressive agents appear to have a diminished response to COVID mRNA vaccines. Current CDC guidelines recommend a three-dose primary series of COVID mRNA vaccines, followed by a booster dose at least 5 months later, for patients receiving immunosuppressants, such as rituximab.¹¹

4.3 | Other inactivated vaccines

The immune response to other inactivated vaccines is also impaired among rituximab-treated patients. In a study of 24 patients with immune thrombocytopenia treated with rituximab who received a pneumococcal polysaccharide vaccination, only 21% achieved a 4-fold increase in anti-pneumococcal antibodies, compared to 67% of placebo-treated patients achieving a 4-fold increase in anti-pneumococcal antibodies after vaccination.³⁴ The same study found that only 29% of rituximab-treated patients achieved a 4-fold increase in antibodies after Hib vaccination, compared with 83% of placebo-treated patients. Rituximab may impair vaccination response more than other immunosuppressive therapies. Among 103 patients with RA who received the 23-valent pneumococcal polysaccharide vaccine, the vaccination response rate, as defined by a 2-fold increase in titer response to ≥ 1 serotype, was lower among patients treated with rituximab and methotrexate ($n = 63$) compared with patients treated with methotrexate alone ($n = 28$) (57% and 82%, respectively).³⁵

Rituximab causes profound and prolonged B-cell depression, leading to severe immunosuppressive effects. In contrast to other immunosuppressive agents where data evaluating the efficacy of inactivated vaccines is mixed, studies of vaccine efficacy in rituximab-treated patients have consistently demonstrated diminished increases in antibody titers, suggesting impaired immune response to vaccination, which persists for at least 6 months after rituximab treatment.

5 | THERAPEUTIC IMMUNOSUPPRESSANTS USED FOR TRANSPLANT

Immunosuppression in the solid organ transplant (SOT) population occurs as a result of the immunosuppressive therapy patients require to prevent rejection of the organ. Post-transplant induction and maintenance immunosuppressive regimens can include corticosteroids, calcineurin inhibitors, antimetabolites, mammalian target of rapamycin (mTOR) inhibitors, or monoclonal antibodies in varying combinations depending on type of organ transplanted and degree of immunosuppression required, among other factors.

5.1 | Influenza vaccine

Research has consistently shown that SOT patients have lower antibody titer response following influenza vaccination compared with

healthy controls.³⁶⁻⁴² A study evaluating the incidence of influenza infection in renal transplant recipients found no difference in influenza infection rates between vaccinated versus unvaccinated renal transplant patients, suggesting vaccination did not provide protection against influenza in this patient population.³⁹ A study of liver transplant patients receiving a variety of immunosuppression regimens (e.g., cyclosporine with or without azathioprine and/or prednisone) showed that a second dose of influenza vaccine increased the proportion of patients having an antibody titer response of ≥ 40 from 68% to 80%.³⁸ Rates of seroconversion following influenza vaccination were lower in post-renal transplant patients receiving immunosuppression with tacrolimus or cyclosporine, mycophenolate mofetil, and methylprednisolone compared with dialysis patients (50% vs. 67%, respectively) but the rate did not seem to be impacted by dose of immunosuppressive therapy.⁴²

Some studies have shown the degree of response to influenza vaccine is impacted by type of immunosuppressive therapy. In studies of renal transplant recipients, immune response to influenza vaccination was better with azathioprine compared to cyclosporine- or mycophenolate-containing immunosuppressant regimens.^{43,44} In contrast, antibody titer increase following influenza vaccination did not differ significantly between kidney transplant recipients receiving sirolimus-based immunosuppressive therapy versus calcineurin inhibitor-based regimens.⁴⁵ A study of 61 adult islet transplant patients demonstrated that longer time from transplant resulted in increased likelihood of immune response to influenza vaccine while receipt of alemtuzumab was associated with lower seroconversion rates.⁴⁶

Overall, the available data suggest SOT recipients have an impaired response to influenza vaccination compared with healthy controls, and this diminished response may be greater in patients receiving sirolimus-based or alemtuzumab immunosuppression compared with those receiving calcineurin inhibitor-based immunosuppression.

5.2 | COVID Vaccines

Data available on efficacy and safety of COVID vaccine in the SOT population is limited to the mRNA COVID-19 vaccine. Thus far, use of the mRNA COVID-19 vaccine in the SOT population has not presented significant safety concerns but efficacy appears to depend on the number of vaccine doses and types of immunosuppressant used. In one study, antibody response to first dose of mRNA COVID-19 vaccine was detected in only 15% of 658 SOT patients.⁴⁷ However, following the second dose, rates of antibody response ranged from 22 to 54%.⁴⁸⁻⁵² Type of immunosuppressive agent did not seem to impact response rate to COVID-19 vaccine in SOT recipients in one study,⁴⁹ whereas several studies showed that mycophenolate use reduced immune response to COVID-19 vaccination.⁵⁰⁻⁵² In a study of 609 transplant recipients, no patients receiving belatacept had a positive antibody response following first dose of mRNA COVID-19 vaccine compared to 14% of non-belatacept patients.⁵³ After the

second dose of vaccine, 5% of belatacept patients had positive antibodies compared with 50% of the non-belatacept population. In a randomized trial, of 120 transplant recipients who had received 2 doses of mRNA COVID-19 vaccine antibody response occurred in 55% of transplant recipients receiving a third mRNA COVID-19 vaccine dose compared to 18% of patients receiving placebo.⁵⁴ Another study showed that the proportion of transplant patients with antibodies increased from 40% after the two-dose primary series of COVID-19 mRNA vaccine to 68% of patients 4 weeks after a 3rd supplemental dose.⁵⁵ Additionally, among the 59 patients who had been seronegative before the third dose, 44% were seropositive 4 weeks after the third dose.

Although limited data are available, SOT recipients seem to have a diminished response to COVID mRNA vaccines, the magnitude of which depends both on the type of immunosuppression used and the length of time elapsed since transplant. Current CDC guidelines recommend a three-dose primary series of COVID mRNA vaccines for patients receiving immunosuppressants, including solid organ or HCT recipients, followed by a booster dose at least 5 months later.¹¹

5.3 | Other inactivated vaccines

Efficacy of other inactivated vaccines in SOT patients has not been as thoroughly evaluated and evidence is largely limited to pneumococcal vaccine. A study of 49 kidney transplant patients demonstrated an acceptable antibody response in 53% of patients at 1 month and 45% of patients at 12 months following 13-valent pneumococcal (PCV13) vaccination, but an evaluation in matched healthy controls showed the response to be 5- to 10-fold higher in healthy age-matched controls than in the transplant population.⁵⁶ Treatment with mycophenolate and less than 12 months since initial transplant were both associated with lower antibody titer response in the transplant population. In a study of 32 renal or hepatic transplant patients, mean antibody response to all pneumococcal strains rose significantly following vaccination with pneumococcal polysaccharide (PPSV23) vaccine independent of the type of immunosuppressant (calcineurin inhibitor or sirolimus-based).⁴⁵

Also unknown regarding pneumococcal vaccine efficacy in the SOT population is the impact of pneumococcal vaccine type and the ideal vaccine schedule. A study comparing immune response to pneumococcal series (13-valent pneumococcal followed by pneumococcal polysaccharide vaccine 8 weeks later) in lung transplant recipients and lung transplant candidates failed to demonstrate a significant increase in antibody levels following the second vaccine in most serotypes studied.⁵⁷ Administration of three doses of conjugate pneumococcal vaccine (PCV7) at 8-week intervals followed by PPSV23 in 81 pediatric SOT recipients demonstrated that two doses of PCV7 were associated with appropriate increases in antibody titers in all organ groups with cardiac and lung transplant recipients receiving an additional increase with the third PCV7 dose and cardiac recipients showing the most benefit with the third dose.⁵⁸ Longer time from transplant was associated with increased

likelihood of vaccine response. Another study evaluating administration of two doses of PCV7 2 months apart followed by PPSV23 2 months later in 25 pediatric SOT patients showed that although antibody titers increased following the first PCV7 dose, it was a lower response than that seen in 23 age-matched healthy controls.⁵⁹ A significant antibody titer increase was not seen following the second PCV7 or PPSV23 doses in the SOT group. Immune response was worse among heart transplant recipients compared to liver transplant recipients.

The available data suggest that SOT patients treated with immunosuppressants have a diminished immune response to pneumococcal vaccination. Whether this diminished immune response is still sufficient to provide protection from pneumococcal infection is uncertain. The ideal pneumococcal vaccination schedule to maximize protection in SOT patients is also unknown.

6 | THERAPEUTIC IMMUNOSUPPRESSANTS USED FOR AUTOIMMUNE DISEASES

The impact of immunosuppressant use for autoimmune diseases on immune response to vaccines can be more difficult to predict as the dose and frequency of immunosuppressant use may be more individualized depending on the condition treated, individual therapy goals, and flare frequency.

6.1 | Influenza vaccines

Data on efficacy of influenza vaccination in patients with autoimmune diseases has been conflicting. Studies have shown that patients with various autoimmune diseases, including RA, systemic lupus erythematosus (SLE), inflammatory bowel disease, and multiple sclerosis on different immunosuppressive regimens had a lower antibody titer response following influenza vaccination compared to healthy controls.⁶⁰⁻⁶⁶ However, one study was not able to associate this reduced immune response to methotrexate- or prednisone-induced immunosuppression.⁶⁰ Another study in 24 patients with SLE found that those receiving azathioprine had a lower immune response to influenza vaccination, as measured by seroconversion and 4-fold increases in antibody titers, than patients receiving prednisone, hydroxychloroquine, or no treatment.⁶¹ Similarly, reduced immune response to influenza vaccination as measured by increases in antibody titers was demonstrated in patients with psoriatic arthritis or ankylosing spondylitis treated with rituximab but not in those treated with methotrexate, anti-tumor necrosis factor (anti-TNF) therapy, or biologics.⁶⁷ A study in autoimmune patients on anti-TNF agents also confirmed no reduced immune response to influenza vaccination.¹⁸

Several studies in patients with autoimmune diseases failed to show reduced immune response to influenza vaccination in

patients on immunosuppressive therapy with corticosteroids and/or DMARDs, TNF inhibitors, or IL-6 receptor antagonists compared with either healthy controls or patients not on immunotherapy.⁶⁸⁻⁷⁰

For patients with autoimmune diseases on immunosuppressant therapy, the ability of influenza vaccination to induce an immune response depends on the type of drug therapy used for treatment. Corticosteroids, DMARDs, TNF inhibitors, and perhaps azathioprine appear to present less risk of diminished immune response to influenza vaccine compared with other immunosuppressants.

6.2 | COVID vaccines

The majority of data on the use of COVID vaccines in patients with autoimmune diseases are limited to the mRNA COVID-19 vaccine. Most studies have shown safety and efficacy of the COVID-19 mRNA vaccine in this group but with the potential for reduced response depending on type of immunosuppressant therapy used.^{32,33,72,73} Two separate studies of patients with autoimmune diseases have shown that a higher proportion of patients not responding to the two-dose mRNA COVID-19 vaccine series were receiving mycophenolate.^{33,34} Another small case series in patients with RA and musculoskeletal diseases showed reduced immune response was associated with mycophenolate, corticosteroid, and rituximab use, whereas treatment with anti-TNF therapy was associated with a more favorable response.⁷¹

In a study of patients with RA on various immunosuppressive therapy, administration of two doses of the mRNA COVID-19 vaccine with interruption of immunosuppressive therapy per American College of Rheumatology (ACR) guidelines (1 week for methotrexate and JAK inhibitors after each vaccine dose; 1 week before and after first vaccine dose only for abatacept) was found to be safe (no increase in disease activity) and effective (defined as humoral and t-cell specific response) in the majority of patients.⁷² However, the degree of humoral and t-cell specific response was definitely influenced by type of immunosuppressive regimen with patients on IL-6 inhibitors or CLT4-inhibitors having a significantly lower titer response compared to a health care worker (HCW) control group.

A prospective cohort study examined the impact of the ACR recommendation for holding mycophenolate surrounding COVID-19 vaccination (either mRNA or adenovirus) and found a higher proportion of patients in the hold therapy group had a favorable immune response to vaccination compared to patients who did not hold mycophenolate therapy (92% vs 65%, respectively).⁷³ Two of 24 patients reported disease flare during the hold mycophenolate period requiring additional treatment with topical or oral corticosteroid therapy to control disease.

A small case series of 18 patients with autoimmune disease found that a booster dose of mRNA COVID-19 vaccine was associated with improved humoral response in almost all patients, with 80% of previous non-responders having a positive response.⁷⁴ Only two patients continued to fail to respond with one patient receiving mycophenolate and one receiving anti-CD20 therapy.

Finally, one observational study compared the response to adenovirus (n=45) versus mRNA (n=994) COVID-19 vaccines in patients with autoimmune disease and found that a higher proportion had a favorable immune response in the mRNA group versus the adenovirus group (92% and 80%, respectively).⁷⁵

Overall, although immunosuppressants used to treat autoimmune diseases appear to decrease the immune response to COVID-19 vaccination, the risk appears to be greatest with mycophenolate and inhibitors of IL-6 or CLT4. Guidance from the ACR recommends holding immunosuppressive therapies prior to COVID-19 vaccination; the duration of timing depends on the particular immunosuppressive agent used and level of disease activity.⁷⁶ As with other immunosuppressants, CDC guidelines recommend a three-dose primary series of COVID mRNA vaccines for patients receiving immunosuppressants, followed by a booster dose at least 5 months later.¹¹

6.3 | Other inactivated vaccines

Several studies have suggested that patients with autoimmune diseases on immunosuppressant therapy have a lower antibody response to pneumococcal vaccination when compared with controls.^{64,77-83} However, antibody functionality, as measured by a multiplexed opsonophagocytic killing assay, was similar among healthy controls and patients with RA treated with abatacept or methotrexate, in one study.⁷⁸ Similarly, other studies found that among patients with RA, those treated with anti-TNF agents,^{84,85} certolizumab pegol,⁸⁶ or tocilizumab^{81,87} had a similar immune response to pneumococcal vaccination as a control group.

In a study of 73 patients with SLE on various immunosuppressive therapy regimens, administration of three inactivated vaccines, pneumococcal, tetanus toxoid (TT), and *Haemophilus influenzae* type B (Hlib), was associated with a protective immune response in the majority of patients (90% and 88% for TT and HIB, respectively).⁸⁸ Protective immune response to pneumococcal vaccine was unable to be defined but 47% of patients had a 4-fold antibody titer response. Similarly, in a study of 43 autoimmune patients with inflammatory bowel disease who completed at least 24 weeks of therapy with azathioprine or 6-mercaptopurine, response to pneumococcal, TT, and HIB was similar to that of patients who were not treated with thiopurines.⁸⁹ Lastly, in a study of 68 patients with multiple sclerosis (MS), the proportion of patients responding to TT and PPSV23 vaccines was lower among those treated with ocrelizumab (23.9% and 71.6%, respectively) than those in the control group, who received interferon beta or non-disease-modifying therapy (54.5% and 100%, respectively).⁶⁴

Overall, while some data suggest that patients with autoimmune disorders treated with immunosuppressant therapy may have a decreased immune response to inactivated vaccines compared with that of healthy controls, the majority of data indicate that the efficacy of inactivated vaccines, particularly adjuvanted non-influenza vaccines, is not compromised in patients with autoimmune disorders treated with these agents.

7 | CONCLUSIONS

Although patients treated with immunosuppressant agents can safely receive inactivated vaccines, the efficacy of immunization is dependent on the specific immunosuppressant used. It is important to note that currently used measures of vaccine efficacy rely on the measurement of antibodies and, therefore, do not account for other measures of immune response (i.e., T-cell response) and are not necessarily fully representative of the ability of vaccination to prevent infection or severe disease. The majority of data indicate that patients treated with oncologic agents, including rituximab, will have a reduced immune response to influenza vaccines. This is most likely due to the fact that influenza vaccines are not adjuvanted and, therefore, induce a less robust response than other adjuvanted inactivated vaccines. The response to other inactivated vaccines among patients treated with rituximab can similarly be expected to be diminished, although the data evaluating vaccine response in patients taking other oncologic agents is inconclusive. Solid organ transplant and patients with autoimmune disorders treated with immunosuppressants can be expected to have a diminished immune response to inactivated vaccines, but the clinical relevance of this decrease in immune response is uncertain and likely depends on the specific agent used, as well as the time since transplant. In summary, although the antibody-mediated immune response to inactivated vaccines is likely decreased in patients treated with immunosuppressant therapies, the impact of these therapies on other immune-mediated responses, as well as the ability of inactivated vaccines to provide protection against infection or serious disease remains to be fully investigated.

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CONFLICT OF INTEREST

Nina M. Bemben reports her spouse owns stock shares in Moderna and BioNTech. Melody L. Berg reports no conflicts of interest.

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REFERENCES

- Kelly H, Sokola B, Abboud H. Safety and efficacy of COVID-19 vaccines in multiple sclerosis patients. *J Neuroimmunol*. 2021;356:577599.
- Shah BB, Goenka MK. A comprehensive review of vaccination in patients with inflammatory bowel diseases: an Indian perspective. *Indian J Gastroenterol*. 2020;39(4):321-330.
- Ghattas M, Dwivedi G, Lavertu M, Alameh M-G. Vaccine technologies and platforms for infectious diseases: current progress, challenges, and opportunities. *Vaccines*. 2021;9(12):1490.
- Centers for Disease Control and Prevention. *Vaccine Recommendations and Guidelines of the Advisory Committee on Immunization Practices (ACIP)* [Internet]. Centers for Disease Control and Prevention; 2013. Cited October 26, 2021. <https://www.cdc.gov/vaccines/hcp/acip-recs/general-recs/immunocompetence.html>
- Chu CS, Boyer JD, Jawad A, et al. Immunologic consequences of chemotherapy for ovarian cancer: impaired responses to the influenza vaccine. *Vaccine*. 2013;31(46):5435-5442.
- Meerveld-Eggink A, de Weerd O, van der Velden AMT, et al. Response to influenza virus vaccination during chemotherapy in patients with breast cancer. *Ann Oncol*. 2011;22(9):2031-2035.
- Sun C, Gao J, Couzens L, et al. Seasonal influenza vaccination in patients with chronic lymphocytic leukemia treated with ibrutinib. *JAMA Oncol*. 2016;2(12):1656-1657.
- Trombetta CM, Montomoli E. Influenza immunology evaluation and correlates of protection: a focus on vaccines. *Expert Rev Vaccines*. 2016;15(8):967-976.
- Rubin LG, Levin MJ, Ljungman P, et al. 2013 IDSA clinical practice guideline for vaccination of the immunocompromised host. *Clin Infect Dis*. 2014;58(3):309-318.
- Malard F, Gaugler B, Gozlan J, et al. Weak immunogenicity of SARS-CoV-2 vaccine in patients with hematologic malignancies. *Blood Cancer J*. 2021;11(8):142.
- Centers for Disease Control and Prevention. Interim clinical considerations for use of COVID-19 vaccines currently authorized in the United States. Accessed January 20, 2022. <https://www.cdc.gov/vaccines/covid-19/info-by-product/clinical-considerations.html>
- de Lavallade H, Khoder A, Hart M, et al. Tyrosine kinase inhibitors impair B-cell immune responses in CML through off-target inhibition of kinases important for cell signaling. *Blood*. 2013;122(2):227-238.
- Zielinski CC, Stuller I, Dorner F, Potzi P, Muller C, Eibl MM. Impaired primary, but not secondary, immune response in breast cancer patients under adjuvant chemotherapy. *Cancer*. 1986;58(8):1648-1652.
- Palazzo M, Shah GL, Copelan O, et al. Revaccination after autologous hematopoietic stem cell transplantation is safe and effective in patients with multiple myeloma receiving lenalidomide maintenance. *Biol Blood Marrow Transplant*. 2018;24(4):871-876.
- Ridgway D, Wolff LJ, Deforest A. Immunization response varies with intensity of acute lymphoblastic leukemia therapy. *Am J Dis Child*. 1991;145(8):887-891.
- Takata T, Suzumiya J, Ishikawa T, Takamatsu Y, Ikematsu H, Tamura K. Attenuated antibody reaction for the primary antigen but not for the recall antigen of influenza vaccination in patients with non-Hodgkin B-cell lymphoma after the administration of rituximab-CHOP. *J Clin Exp Hematop*. 2009;49(1):9-13.
- Adler S, Krivine A, Weix J, et al. Protective effect of A/H1N1 vaccination in immune-mediated disease—a prospectively controlled vaccination study. *Rheumatology*. 2012;51(4):695-700.
- Richi P, Martin MD, Navio MT, et al. Antibody responses to influenza vaccine in patients on biological therapy: results of RIER cohort study. *Med Clin*. 2019;153(10):380-386.
- Roll D, Ammer J, Holler B, et al. Vaccination against pandemic H1N1 (2009) in patients after allogeneic hematopoietic stem cell transplantation: a retrospective analysis. *Infection*. 2012;40(2):153-161.
- Oren S, Mandelboim M, Braun-Moscovici B, et al. Vaccination against influenza in patients with rheumatoid arthritis: the effect of rituximab on the humoral response. *Ann Rheum Dis*. 2008;67(7):937-941.
- Westra J, van Assen S, Wilting KR, et al. Rituximab impairs immunoglobulin (Ig)M and IgG (subclass) responses after influenza vaccination in rheumatoid arthritis patients. *Clin Exp Immunol*. 2014;178(1):40-47.
- Van Assen S, Holvast A, Benne CA, et al. Humoral responses after influenza vaccination are severely reduced in patients with rheumatoid arthritis treated with rituximab. *Arthritis Rheum*. 2010;62(1):75-81.

23. Arad U, Tzadok S, Amir S, et al. The cellular immune response to influenza vaccination is preserved in rheumatoid arthritis patients treated with rituximab. *Vaccine*. 2011;29(8):1643-1648.
24. Rehnberg M, Brisslert M, Amu S, Zendjanchi K, Hawi G, Bokarewa MI. Vaccination response to protein and carbohydrate antigens in patients with rheumatoid arthritis after rituximab treatment. *Arthritis Res Ther*. 2010;12(3):R111.
25. Gelinck LBS, Teng YKO, Rimmelzwaan GF, van den Bemt BJB, Kroon FP, van Laar JM. Poor serological responses upon influenza vaccination in patients with rheumatoid arthritis treated with rituximab. *Ann Rheum Dis*. 2007;66(10):1402-1403.
26. Kim W, Kim S-H, Huh S-Y, et al. Reduced antibody formation after influenza vaccination in patients with neuromyelitis optica spectrum disorder treated with rituximab. *Eur J Neurol*. 2013;20(6):975-980.
27. Eisenberg RA, Jawad AF, Boyer J, et al. Rituximab-treated patients have a poor response to influenza vaccination. *J Clin Immunol*. 2013;33:388.
28. Bedognetti D, Ansaldi F, Zanardi E, et al. Seasonal and pandemic (A/H1N1 2009) MG-59-adjuvanted influenza vaccines in complete remission non-Hodgkin lymphoma patients previously treated with rituximab containing regimens. *Blood*. 2012;120(9):1941-1957.
29. Yri OE, Torfoss D, Hungnes O, et al. Rituximab blocks protective serologic response to influenza A (H1N1) 2009 vaccination in lymphoma patients during or within 6 months after treatment. *Blood*. 2011;118(26):6769-6771.
30. Bonelli MM, Mrak D, Perkmann T, Haslachner H, Aletaha D. SARS-CoV-2 vaccination in rituximab-treated patients: evidence for impaired humoral but inducible cellular immune response. *Ann Rheum Dis*. 2021;80(10):1355-1356.
31. Spiera R, Jinich S, Jannat-Khah D. Rituximab, but not other anti-rheumatic therapies, is associated with impaired serological response to SARS-CoV-2 vaccination in patients with rheumatic diseases. *Ann Rheum Dis*. 2021;80(10):1357-1359.
32. Boyarsky BJ, Ruddy JA, Connolly CM, et al. Antibody response to a single dose of SARS-CoV-2 mRNA vaccine in patients with rheumatic and musculoskeletal diseases. *Ann Rheum Dis*. 2021;80(8):1098-1099.
33. Connolly CM, Boyarsky BJ, Ruddy JA, et al. Absence of humoral response after two-dose SARS-CoV-2 messenger RNA vaccination in patients with rheumatic and musculoskeletal diseases: a case series. *Ann Intern Med*. 2021;174(9):1332-1334.
34. Nazi I, Kelton JG, Larche M, et al. The effects of rituximab on vaccine responses in patients with immune thrombocytopenia. *Blood*. 2013;122(11):1946-1953.
35. Bingham CO 3rd, Looney RJ, Deodhar A, et al. Immunization responses in rheumatoid arthritis patients treated with rituximab: results from a controlled clinical trial. *Arthritis Rheum*. 2010;62(1):64-74.
36. Huang KL, Armstrong MA, Ho M. Antibody response after influenza immunization in renal transplant patients receiving cyclosporin A or azathioprine. *Infect Immun*. 1983;40(1):421-424.
37. Gangappa S, Wrammert J, Wang D, et al. Kinetics of antibody response to influenza vaccination in renal transplant recipients. *Transpl Immunol*. 2019;53:51-60.
38. Soesman NM, Rimmelzwaan GF, Nieuwkoop NJ, et al. Efficacy of influenza vaccination in adult liver transplant recipients. *J Med Virol*. 2000;61(1):85-93.
39. Blumberg EA, Albano C, Pruett T, et al. The immunogenicity of influenza virus vaccine in solid organ transplant recipients. *Clin Infect Dis*. 1996;22(2):295-302.
40. Versluis DJ, Beyer WE, Masurel N, Wenting GJ, Weimar W. Impairment of the immune response to influenza vaccination in renal transplant recipients by cyclosporine, but not azathioprine. *Transplantation*. 1986;42(4):376-379.
41. Versluis DJ, Beyer WE, Masurel N, Weimar W. Influenza vaccination in dialysis and transplant patients. *Antiviral Res*. 1985;1:289-292.
42. Tsujimura S, Ota M, Chinen K, et al. Effect of influenza vaccine in patients with kidney transplant. *Transplant Proc*. 2018;50(8):2443-2446.
43. Keshtkar-Jahromi M, Argani H, Rahnavardi M, et al. Antibody response to influenza immunization in kidney transplant recipients receiving either azathioprine or mycophenolate: a controlled trial. *Am J Nephrol*. 2008;28(4):654-660.
44. Salles MJC, Sens YAS, Boas LSV, Machado CM. Influenza virus vaccination in kidney transplant recipients: serum antibody response to different immunosuppressive drugs. *Clin Transplant*. 2010;24(1):E17-E23.
45. Willcocks LC, Chaundhry AN, Smith JC, et al. The effect of sirolimus therapy on vaccine responses in transplant recipients. *Am J Transplant*. 2007;7(8):2006-2011.
46. Silva M, Humar A, Shapiro AMJ, et al. Humoral immune response following seasonal influenza vaccine in islet transplant recipients. *Cell Transplant*. 2013;22(3):469-476.
47. Boyarsky BJ, Werbel WA, Avery RK, et al. Antibody response to 2-dose SARS-CoV-2 mRNA vaccine series in solid organ transplant recipients. *JAMA*. 2021;325(21):2204-2206.
48. Boyarsky BJ, Werbel WA, Avery RK, et al. Immunogenicity of a single dose of SARS-CoV-2 messenger RNA vaccine in solid organ transplant recipients. *JAMA*. 2021;325(17):1784-1786.
49. Korth J, Jahn M, Dorsch O, et al. Impaired humoral response in renal transplant recipients to SARS-CoV-2 vaccination with BNT162b2 (Pfizer-BioNTech). *Viruses*. 2021;13(5):756.
50. Rabinowich L, Grupper A, Baruch R, et al. Low immunogenicity to SARS-CoV-2 vaccination among liver transplant recipients. *J Hepatol*. 2021;75(2):435-438.
51. Zadok OIB, Shaul AA, Ben-Avraham B, et al. Immunogenicity of the BNT162b2 mRNA vaccine in heart transplant recipients- a prospective cohort study. *Eur J Heart Fail*. 2021;23(9):1555-1559.
52. Grupper A, Rabinowich L, Schwartz D, et al. Reduced humoral response to mRNA SARS-CoV-2 BNT162b2 vaccine in kidney transplant recipients without prior exposure to the virus. *Am J Transplant*. 2021;21(8):2719-2726.
53. Ou MT, Boyarsky BJ, Chian TPY, et al. Immunogenicity and reactogenicity after SARS-CoV-2 mRNA vaccination in kidney transplant recipients taking belatacept. *Transplantation*. 2021;105(9):2119-2123.
54. Hall VG, Ferreira VH, Ku T, et al. Randomized trial of a third dose of mRNA-1273 vaccine in transplant recipients. *N Engl J Med*. 2021;385(13):1244-1246.
55. Kamar N, Abravanel F, Marion O, Couat C, Izopet J, Del Bello A. Three doses of an mRNA Covid-19 vaccine in solid-organ transplant recipients. *N Engl J Med*. 2021;385(7):661-662.
56. Oesterreich S, Lindemann M, Goldblatt D, Horn PA, Wilde B, Witzke O. Humoral response to a 13-valent pneumococcal conjugate vaccine in kidney transplant recipients. *Vaccine*. 2020;38(17):3339-3350.
57. Hoffman TW, Meek B, Rijkers GT, Grutters JC, van Kessel DA. Pneumococcal conjugate vaccination followed by pneumococcal polysaccharide vaccination in lung transplant candidates and recipients. *Transplant Direct*. 2020;6(6):e555.
58. Barton M, Wasfy S, Dipchand AI, et al. Seven-valent pneumococcal conjugate vaccine in pediatric solid organ transplant recipients: a prospective study of safety and immunogenicity. *Pediatr Infect Dis J*. 2009;28(8):688-692.
59. Lin PL, Michaels MG, Green M, et al. Safety and immunogenicity of the American Academy of Pediatrics- recommended sequential pneumococcal conjugate and polysaccharide vaccine schedule in pediatric solid organ transplant recipients. *Pediatrics*. 2005;116(1):160-167.
60. Fomin I, Caspi D, Levy V, et al. Vaccination against influenza in rheumatoid arthritis: the effect of disease modifying drugs, including TNF alpha blockers. *Ann Rheum Dis*. 2006;65(2):191-194.

61. Abu-Shakra M, Press J, Varsano N, et al. Specific antibody response after influenza immunization in systemic lupus erythematosus. *J Rheumatol*. 2002;29(12):2555-2557.
62. Hagihara Y, Ohfugi S, Watanabe K, et al. Infliximab and/or immunomodulators inhibit immune responses to trivalent influenza vaccination in adults with inflammatory bowel disease. *J Crohns Colitis*. 2014;8(3):223-233.
63. Mamula P, Markowitz JE, Piccoli DA, Klimov A, Cohen L, Baldassano RN. Immune response to influenza vaccine in pediatric patients with inflammatory bowel disease. *Clin Gastroenterol Hepatol*. 2007;5(7):851-856.
64. Bar-Or A, Calkwood JC, Chognot C, et al. Effect of ocrelizumab on vaccine responses in patients with multiple sclerosis: the VELOCE study. *Neurology*. 2020;95(14):e1999-e2008.
65. Williams GW, Steinberg AD, Reinertsen JL, Klassen LW, Decker JL, Dolin R. Influenza immunization in systemic lupus erythematosus. A double-blind trial. *Ann Intern Med*. 1978;88(6):729-734.
66. Holvast A, Huckriede A, Wilschut J, et al. Safety and efficacy of influenza vaccination in systemic lupus erythematosus patients with quiescent disease. *Ann Rheum Dis*. 2006;65(7):913-918.
67. Richi P, Martin MD, de Ory F, et al. Secukinumab does not impair the immunogenic response to the influenza vaccine in patients. *RMD Open*. 2019;5(2):e001018.
68. Kanakoudi-Tsakalidou F, Trachana M, Pratsidou-Gertsis P, Tsitsami E, Kyriazopoulou-Dalaina V. Influenza vaccination in children with chronic rheumatic diseases and long-term immunosuppressive therapy. *Clin Exp Rheumatol*. 2001;19(5):589-594.
69. Lakota K, Perdan-Pirkmajer K, Sodin-Semrl S, et al. The immunogenicity of seasonal and pandemic influenza vaccination in auto-immune inflammatory rheumatic patients—a 6-month follow-up prospective study. *Clin Rheumatol*. 2019;38(5):1277-1292.
70. Chalmers A, Scheifele D, Patterson C, et al. Immunization of patients with rheumatoid arthritis against influenza: a study of vaccine safety and immunogenicity. *J Rheumatol*. 1994;21(7):1203-1206.
71. Ruddy JA, Connolly CM, Boyarsky BJ, et al. High antibody response to two-dose SARS-CoV-2 messenger RNA vaccination in patients with rheumatic and musculoskeletal diseases. *Ann Rheum Dis*. 2021;80(10):1351-1352.
72. Picchianti-Diamanti A, Aiello A, Lagana B, et al. Immunosuppressive therapies differently modulate humoral- and T-cell-specific responses to COVID-19 mRNA vaccine in rheumatoid arthritis patients. *Front Immunol*. 2021;12:740249.
73. Connolly CM, Chiang TP, Boyarsky BJ, et al. Temporary hold of mycophenolate augments humoral response to SARS-CoV-2 vaccination in patients with rheumatic and musculoskeletal diseases: a case series. *Ann Rheum Dis*. 2022;81(2):293-295.
74. Connolly CM, Teles M, Frey S, et al. Booster-dose SARS-CoV-2 vaccination in patients with autoimmune disease: a case series. *Ann Rheum Dis*. 2022;81(2):291-293.
75. Chiang TP, Connolly CM, Ruddy JA, et al. Antibody response to the Janssen/Johnson & Johnson SARS-CoV-2 vaccine in patients with rheumatic and musculoskeletal diseases. *Ann Rheum Dis*. 2021;80(10):1365-1366.
76. American College of Rheumatology. COVID-19 vaccine clinical guidance summary for patients with rheumatic and musculoskeletal diseases. 2021. <https://www.rheumatology.org/Portals/0/Files/COVID-19-Vaccine-Clinical-Guidance-Rheumatic-Diseases-Summary.pdf>. Accessed January 20, 2022.
77. Pittet LF, Veroleto CM, Michetti P, et al. High immunogenicity of the pneumococcal conjugated vaccine in immunocompromised adults with inflammatory bowel disease. *Am J Gastroenterol*. 2019;114(7):1130-1141.
78. Migita K, Akeda Y, Akazawa M, et al. Effect of abatacept on the immunogenicity of 23-valent pneumococcal polysaccharide vaccination (PPSV23) in rheumatoid arthritis patients. *Arthritis Res Ther*. 2015;17:357.
79. Winthrop KL, Silverfield J, Racewicz A, et al. The effect of tofacitinib on pneumococcal and influenza vaccine responses in rheumatoid arthritis. *Ann Rheum Dis*. 2016;75(4):687-695.
80. Kapetanovic MC, Saxne T, Sjöholm A, Truedsson L, Jonsson G, Geborek P. Influence of methotrexate, TNF blockers and prednisolone on antibody responses to pneumococcal polysaccharide vaccine in patients with rheumatoid arthritis. *Rheumatology*. 2006;45(1):106-111.
81. Kapetanovic MC, Saxne T, Jonsson G, Truedsson L, Geborek P. Rituximab and abatacept but not tocilizumab impair antibody response to pneumococcal conjugate vaccine in patients with rheumatoid arthritis. *Arthritis Res Ther*. 2013;15(5):R171.
82. Visvanathan S, Keenan GF, Baker DG, Levinson AI, Wanger CL. Response to pneumococcal vaccine in patients with early rheumatoid arthritis receiving infliximab plus methotrexate or methotrexate alone. *J Rheumatol*. 2007;34(5):952-957.
83. Migita K, Akeda Y, Akazawa M, et al. Pneumococcal polysaccharide vaccination in rheumatoid arthritis patients receiving tacrolimus. *Arthritis Res Ther*. 2015;17(1):149.
84. Kapetanovic MC, Roseman C, Jonsson G, Truedsson L, Saxne T, Geborek P. Antibody response is reduced following vaccination with 7-valent conjugate pneumococcal vaccine in adult methotrexate-treated patients with established arthritis, but not those treated with tumor necrosis factor inhibitors. *Arthritis Rheum*. 2011;63(12):3723-3732.
85. Mease PJ, Ritchlin CT, Martin RW, et al. Pneumococcal vaccine response in psoriatic arthritis patients during treatment with etanercept. *J Rheumatol*. 2004;31(7):1356-1361.
86. Kivitz AJ, Schechtman J, Texter M, et al. Vaccine responses in patients with rheumatoid arthritis treated with certolizumab pegol: results from a single-blind randomized phase IV trial. *J Rheumatol*. 2014;41(4):648-657.
87. Mori S, Ueki Y, Akeda Y, et al. Pneumococcal polysaccharide vaccination in rheumatoid arthritis patients receiving tocilizumab therapy. *Ann Rheum Dis*. 2013;72(8):1362-1366.
88. Battafarano DF, Battafarano NJ, Larsen L, et al. Antigen-specific antibody responses in lupus patients following immunization. *Arthritis Rheum*. 1998;41(10):1828-1834.
89. Dotan I, Werner L, Vigodman S, et al. Normal response to vaccines in inflammatory bowel disease patients treated with thiopurines. *Inflamm Bowel Dis*. 2012;18(2):261-268.

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