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Impact of disease modifying anti-rheumatic drugs on vaccine immunogenicity in patients with inflammatory rheumatic and musculoskeletal diseases

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Abstract

Patients with rheumatic diseases are at increased risk of infectious complications; vaccinations are a critical component of their care. Disease modifying anti-rheumatic drugs (DMARDs) may reduce the immunogenicity of common vaccines. We will review here available data regarding the effect of these medications on influenza, pneumococcal, herpes zoster, SARS-CoV-2, hepatitis B, human papilloma virus and yellow fever vaccines. Rituximab has the most substantial impact on vaccine immunogenicity, which is most profound when vaccinations are given at shorter intervals after rituximab dosing. Methotrexate has less substantial effect but appears to adversely impact most vaccine immunogenicity. Abatacept likely decrease vaccine immunogenicity, although these studies are limited by the lack of adequate control groups. Janus kinase and tumor necrosis factor inhibitors decrease absolute antibody titers for many vaccines, but do not seem to significantly impact the proportions of patients achieving seroprotection. Other biologics (IL-6R, IL-12/23 and IL-17 inhibitors) have little observed impact on vaccine immunogenicity. Data regarding the effect of these medications on the SARS-CoV-2 vaccine immunogenicity is just now emerging, and early glimpses appear similar to our experience with other vaccines. In this review, we summarize the most recent data regarding vaccine response and efficacy in this setting, particularly in light of current vaccination recommendations for immunocompromised patients.

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DMARDs; Biologics; Vaccination; SARS-CoV-2 Vaccine; Influenza vaccine; Pneumococcal vaccine; Zoster vaccine

Introduction:

Patients with inflammatory rheumatic diseases are at increased risk of vaccine-preventable infectious diseases.[1–6] Vaccinations reduce the risks of infectious complications in rheumatic disease patients[7,8], yet are under-utilized.[9,10] While vaccinations are critically important, the drugs used to treat inflammatory diseases may impair responses to vaccines. This review addresses available data regarding the effect of disease modifying anti-rheumatic drugs (DMARDs) on vaccine immunogenicity (Table 1) and summarizes vaccination recommendations made for this population (Table 2).

Vaccine immunogenicity is typically measured as a surrogate for clinical vaccine efficacy. Interpreting and harmonizing results from studies of vaccine immunogenicity are complicated by several factors. First, the arsenal of DMARD therapy is rapidly expanding with new drug classes and more drugs within each class, and these may have subtle yet important differences (for example, differences in janus kinase [JAK]-inhibitor targets and JAK selectivity.) Secondly, recommended vaccines continue to change; pneumococcal and influenza vaccines frequently change, and we now have multiple critically important SARS-CoV-2 vaccines. Lastly, outcome measures (timing of response measurement, how response is measure, definitions of response[11]) and study design (control groups, concomitant methotrexate [MTX] or low dose glucocorticoid therapy) are inconsistent across studies, making it difficult to parse out the true impact of the drug on vaccine immunogenicity or efficacy.

We will summarize here the available data evaluating the effect of DMARDs on vaccine immunogenicity, as well as to summarize current recommendations for how and when to vaccinate rheumatic disease patients on DMARD therapy. While all vaccines are potentially important, we will focus on influenza, pneumococcus, herpes zoster, hepatitis B virus (HBV), tetanus, human papilloma virus (HPV), and yellow fever (YF) vaccines, as well as the newly emerging data for the SARS-CoV-2 vaccines (Table 1). We will additionally review safety data regarding live vaccines (herpes zoster and YF) and newer highly immunogenic recombinant herpes zoster and SARS-CoV-2 vaccines.

Influenza Vaccination:

Background:

Intramuscular influenza vaccines are available as trivalent vaccines containing two strains of influenza A and one strain of influenza B, and quadrivalent vaccines, which contain an additional B strain.[12,13] Two quadrivalent vaccines are currently recommended for adults age ≥65—a high dose quadrivalent vaccine (Fluzone High-Dose) and an adjuvanted quadrivalent vaccine (Fluad Quadrivalent).[12,13] The live attenuated intranasal influenza vaccine is contraindicated in patients taking biologics or other immunomodulatory therapies (e.g.

JAK inhibitors). Influenza vaccine efficacy is estimated using a surrogate of hemagglutinin inhibition titers. A titer of 1:40 is considered “seroprotected” (as defined as 50% vaccine efficacy.)

Effect of DMARD therapy of vaccine efficacy:

Rituximab[14–21] and MTX[142223] reduce influenza vaccine immunogenicity. Abatacept likely impairs immunogenicity though data is limited.[24–26] Post-vaccination antibody titers are lower in patients on TNF[142027–29] and JAK inhibitors[30], although the proportion of patients achieving seroprotection is similar to rheumatic disease patients not treated with these medications. Interleukin (IL)-6, IL-12/23, and IL-17 inhibitors do not appear to impact the influenza vaccine.[31–35] (Table 1)

Influenza vaccination responses may be improved for rituximab[1621] and MTX[2223] treated patients by optimally timing the drug and vaccine. Timing the influenza vaccine 6–10 months after rituximab yielded modestly better results than 4–8 weeks after rituximab (5/12 versus 1/11 patients achieved seroprotection p =0.108).[21] In a randomized, controlled trial, 316 patients with RA were randomized to take continuous MTX or to hold MTX for 2 weeks after influenza vaccine. Those who held MTX had higher rates of satisfactory vaccine response (75.5% vs 54.5%, p<0.001); however, lower doses of MTX ≤7.5 mg/week did not show a significant improvement with MTX dose interruption. [23] Post-hoc analyses found that MTX reduced vaccine response only in patients with high B cell activating factor (BAFF) levels, raising questions about whether these results are generalizable to all patients or only a subset with elevated BAFF (which is not routinely evaluated).[36]

Abatacept likely impairs influenza vaccine immunogenicity, though data are limited.[24–26] Two studies of the pandemic 2009 influenza A/H1N1 vaccine found that patients on abatacept had a substantially lower rate of seroconversion; in one study this rate was as low as 9% compared to 69% of controls (p=0.001).[2426] However, an uncontrolled study of the trivalent 2011–2012 seasonal influenza vaccine found that 81.2% of patients on subcutaneous abatacept were able to mount protective antibody titers,[25] which is only modestly reduced compared to general populations rates (89–97% for each flu strain).[37]

Low-dose glucocorticoid use has not been shown to impact influenza vaccine response when added to other DMARD thearpy. In a study of infliximab and influenza vaccine response, concomitant low dose glucocorticoids (mean doses 5–10 mg/day) were not found to impact influenza vaccine response. [38] Similarly, low dose prednisone (mean 8 mg/day) in RA did not adversely affect influenza vaccine response in a multivariant regression analysis when evaluated alongside other DMARD therapy. [27]

Recommendations:

Routine yearly influenza vaccines are recommended for all people aged 6 months or older. [1239] The European League Against Rheumatism (EULAR) and American College of Rheumatology (ACR) both recommend yearly intramuscular influenza vaccinations for all RA patients. [4041]

High-dose influenza vaccines may be more effective in rheumatic disease patients[42–44], although at this time the high-dose vaccine is recommended only for adults age ≥65. [12] A randomized study of 279 patients with RA found that those receiving the high-dose influenza vaccine were more likely to seroconvert (odds ratio (OR) 2.99, 95% CI 1.46–6.11); this effect was similar in patients on synthetic and biologic DMARDs.[42]

Rituximab-treated patients should ideally receive the influenza vaccine before initiating rituximab, or as long after the last dose of rituximab and 2–4 weeks before the next dose[41], as compatible with the influenza season. However, when this timing is not compatible with the influenza season, patients on rituximab may still be able to mount a T cell response to the vaccination (although it is not known whether T cell responses correlate with influenza protection.)[17] Patients on MTX can improve influenza vaccination responses by holding MTX for two weeks after vaccination, particularly for those on ≥ 15 mg/week; holding methotrexate did not appear to increase disease activity measures, although this group had a small increase in the rate of flares (5.1% vs. 10.6%, p =0.07).[2223]

Pneumococcal Vaccination:

Background:

Two pneumococcal vaccines are commonly used, pneumococcal conjugate vaccine 13-valent (PCV13) and pneumococcal polysaccharide vaccine 23-valent (PPSV23). PCV-13 is conjugated to a diphtheria protein and is more immunogenic than the polysaccharide vaccine. Both PCV-13 and PPSV-23 vaccine immunogenicity is typically measured by post-vaccination antibody titers against serotypes found in each vaccine, although the titer level chosen as “protective” can be variable and is arbitrary, as no level of “seroprotection” against most pneumococcal disease has been established.[11]

Effect of DMARD therapy on vaccine efficacy:

As with most vaccines in the rheumatologic setting, studies have not been large enough to evaluate changes in efficacy related to DMARD usage. Immunogenicity outcomes are achievable in such studies, and it is clear that Rituximab[141845–47] and MTX[111448–51] reduce pneumococcal vaccine immunogenicity. JAK-inhibitors[305253] and abatacept[254546] appear to modestly reduce immunogenicity, while other biologics (TNF, IL-6, IL-12/23, and IL-17 inhibitors) do not impair vaccine immunogenicity.[143154–56]

A meta-analysis reported that rituximab-treated patients had a pooled OR for non-seroconversion (inability to mount a 2-fold increase in antibody concentrations post-vaccination) ranging from 4.91 (95% CI 2.32–10.40) to 13.06 (95% CI 2.39–71.34) depending on the pneumococcal serotype.[11] The effect of MTX is less than that of rituximab; pooled ORs for non-seroconversion ranged from 2.0 (95% CI 1.06–3.77) to 5.41 (95% CI 2.09–13.98) depending on the serotype.[11]

Interpretation of data from abatacept studies is complicated by concomitant MTX and/or a lack of controls. In one uncontrolled study of patients on subcutaneous abatacept (most of whom were also on MTX) vaccinated with PPSV23, 34/46 (74%) of patients developed protective antibody titers, consistent with expected response.[25] However, another study of 17

patients on IV abatacept vaccinated with PCV7 (13 of whom were receiving concomitant MTX) found a lower likelihood of a ≥2-fold increase in post-vaccination antibody titer compared to patients on tocilizumab or controls.[45] Lastly, in a pneumococcal booster study, the booster strategy improved antibody response in 23 abatacept-treated patients (half of whom were on MTX); however the antibody response was lower than in healthy controls.[46]

JAK-inhibitors appear to have a modest impact on the rate of satisfactory responses to pneumococcal vaccinations (defined as a ≥2-fold increase in antibody concentrations in ≥6 serotypes), at least to PPSV-23 where there is comparative data published.[3053] A placebo-controlled study of RA patients vaccinated after 4 weeks of tofacitinib or placebo found that those on tofacitinib were less likely to develop a satisfactory antibody response compared to placebo (45.1% vs. 68.4%, −23% difference [95% CI −36.6% to −9.6%]), particularly if they were also on MTX (31.6%).[30] Temporary interruption in tofacitinib for 1 week pre-vaccination and 1 week post-vaccination modestly improved PPSV23 response when compared to continuous tofacitinib, but this did not reach significance (84.6% vs. 75.0%, −9.6% difference [95% CI −24.0 to 4.7]).[30] A final uncontrolled study of 106 baricitinib-treated patients (89% of whom were also on MTX) vaccinated with PCV13 found that approximately 2/3 of patients received a satisfactory antibody response;[53] these proportions were similar to another study evaluating PCV-13 responses in healthy controls and RA patients not using DMARDs.[50]

Low-dose glucocorticoids taken concomitantly with other DMARD therapy have not been found to impact pneumococcal vaccine responses, [535758] while high dose-glucocorticoids may adversely impact pneumococcal vaccine immunogenicity.[59] Among patients with inflammatory diseases vaccinated with the PPV23, 57% of non-responders were taking prednisone >20 mg/day compared with 22% of vaccine responders (p =0.07).[59] In an uncontrolled baricitinib study where approximately 30% of particpants were taking concomitant low-dose corticosteroids (mean dose 6.2 mg/day), PCV-13 response rates were similar in those taking corticosteroids versus those not taking corticosteroids (71% [95% CI 53.4–83.9] vs 67% [95% CI 55.2–76.5]). [53] Similarly, in a study of patients on methotrexate with or without infliximab, concomitant low-dose glucocorticoids (prednisone equivalent <10 mg/day) did not adversely impact vaccine response.[58]

Recommendations:

The EULAR, ACR, and center for disease control (CDC)) all recommend pneumococcal vaccinations for patients with rheumatic disease taking DMARD therapy.[406061] Patients should receive a dose of PCV13 followed by a dose of PPSV23 at least 8 weeks later. A second PPSV23 vaccine should be given 5 years after the first one. PCV13 followed by a booster of PPSV23 improves pneumococcal antibody responses for patients on conventional synthetic DMARDs and partially improves responses for patients on abatacept but may not improve vaccine response for those on rituximab.[46]

Patients should be given their first dose of a pneumococcal vaccine ideally before starting DMARD therapy. Patients on rituximab should receive the required vaccine dose at least 2 weeks before their next dose of rituximab is due. Although extrapolating from influenza

studies and observational data raises the idea that holding methotrexate at the time of vaccination could improve pneumococcal vaccine response, this idea has yet to be studied.

Herpes Zoster Vaccination

Background:

There are two approved herpes zoster vaccines—the recombinant zoster vaccine (RZV) (Shingrix) and the live zoster vaccine (ZVL) (Zostavax). In non-head-to-head studies in the general population, the RZV appears more effective such that the ZVL is no longer marketed in the United States although it is still used in many parts of the world.[62] Response to zoster vaccine is measured by a humoral varicella zoster virus IgG and/or cell-mediated VZV-specific T cell enumeration. Although both measures correlated with vaccine efficacy, cell-mediated responses correlate more strongly with the risk of future shingles.[63]

Effect of DMARD therapy on vaccine efficacy:

Few studies have evaluated the immunogenicity of zoster vaccines in rheumatic disease patients.

112 RA patients on MTX were vaccinated with the ZVL and then randomized to start tofacitinib or placebo 2–3 weeks post-vaccination. Patients in both groups had similar post-vaccine responses.[52] In this study, approximately 40% of placebo patients and 47% of tofacitinib patients were taking concomitant glucocorticoids (mean dose 7.1 and 5.9 mg/day prednisone or equivalent respectively). ZVL vaccine responses were similar in those taking glucocorticoids and those not taking glucocorticoids.[52] TNF-inhibitor treated patients vaccinated with the ZVL developed 30% increases in humoral and cell-mediated responses relative to a placebo vaccine, which are about half the response observed in initial pivotal trials among healthy subjects.[64] Zoster vaccines have not been studied in rheumatic disease patients on rituximab, however, among patients with hematologic malignancies on anti-CD20 therapies (alone or in combination with other chemotherapies) the RZV produced significant T-cell responses.[65] Zoster vaccine immunogenicity data for patients currently taking JAK-inhibitors, abatacept, and other biologics have not been reported.

Safety in patients with rheumatic diseases:

While the ZVL vaccine is contraindicated in immunocompromised patients, given the theoretical concern of potential local or disseminated vaccine-strain varicella with vaccination, available data suggest it is safer than initially thought. In the study of MTX and tofacitinib above, there was 1 case of cutaneous vaccine dissemination in a patient on MTX randomized to start tofacitinib, however, this patient lacked primary immunity to varicella (i.e. they did not have chickenpox as a child) and were not a candidate for the live vaccine.[52] Among 633 United States Medicare patients inadvertently vaccinated while on biologics, no cases of shingles occurred in the 6 weeks post-vaccination.[10] 600 patients on TNF-inhibitors (with or without MTX and prednisone) randomized 1:1 to receive the ZVL vs placebo and found no cases of varicella infection or zoster within the subsequent 42 day risk period of highest interest.[64] These data suggest that the ZVL may be given safely to those using TNF-inhibitors with/without MTX and/or prednisone if the RZV is not available.

The recombinant vaccine is not live and is likely safe in patients with rheumatic diseases, however, phase 3 clinical trials excluded patients on immunosuppressive therapy. There has been theoretical concern that the adjuvant in the RZV may cause a flare of underlying inflammatory disease. The first retrospective review of 403 rheumatic disease patients vaccinated with the RZV found a 7% incidence of disease flare within 12 weeks of receiving a vaccine dose; this incidence was considered to be similar to expected rates from clinical trials.[66] However, a second retrospective review of 359 patients with rheumatic diseases found that 16% had a flare of their disease within 12 weeks of receiving a vaccine dose.[67] The differences in these results may be related to a difference in flare definition, however neither was prospective or controlled. A post-hoc analysis of clinical trials (NCT01165177 and NCT01165229) pooled data from nearly 2,000 patients (approximately half received vaccine) with self-reported inflammatory disease who were not treated with DMARDs. This analysis found similar high rates of vaccine efficacy and no new safety concerns, however, it is likely that these self-reported individuals had either mild or no disease given their lack of DMARD therapy.[68] Future prospective, controlled studies are necessary to adequately evaluate safety and efficacy of this vaccine in the rheumatology setting.

Recommendations:

The CDC recommends the RZV for all patients aged 50 and above.[12] The European Medicines Agency recently approved the RZV for adults over age 18 with immunocompromising conditions[69], however, very little data exist in this age group and guidelines are not yet available for the use of this vaccine in patients with rheumatic diseases. The ACR recommends use of the ZVL for patients with RA over age 50[40], and EULAR recommends zoster vaccination in high-risk patients[41], however, neither of these guidelines address the newer RZV. Given that immunocompromised patients with rheumatic diseases are at increased risk of zoster[670], future guidelines may be expanded to recommend the RZV for high-risk patients at a younger age (e.g. 18 and older).

SARS-CoV-2 Vaccination

Background:

A growing number of SARS-CoV-2 vaccines are in use world-wide, including mRNA, adenoviral vector, protein subunit, and inactivated virus vaccines.[71] We will focus our discussion on 2 mRNA vaccines and 2 adenoviral vector vaccines, which have been most widely studied in patients with rheumatic diseases. In phase III trials, the BNT162b2 (Pfizer/BioNTech) mRNA vaccine was 95% effective (95% CI 90.3–97.6)[72] and the mRNA01273 (Moderna) vaccine was 94.1% effective (95% CI 89.3–96.8)[73] in preventing symptomatic COVID-19 infection following the second dose. Phase III trials found the Ad26.COV2.S (Janssen/Johnson & Johnson) vaccine single dose vaccine to be 66.9% effective (95% CI 59.0–73.4) [74] and the ChAdOx1 nCoV-19/AZD1222 (University of Oxford/AstraZeneca/Serum Institute of India) vaccine to be 70.4% effective (95% CI 54.8–80.6) following the second dose.[75]

SARS-CoV-2 vaccine immunogenicity can be measured by humoral IgG to spike protein (not nucleocapsid protein) or cellular T-cell reactivity via interferon (IFN)-γ response to

SARS-CoV-2 peptide. Antibody responses are reported as “seroconversion” (newly positive anti-spike protein IgG), or by post-vaccination antibody titers. The role of T cell responses to SARS-CoV-2 vaccines are not fully understood, however emerging evidence suggest that T cell responses may confer protection [7677] even in the absence of humoral response.[7879] However, we do not yet know how immunogenicity cutoffs correlate with efficacy, whether reduced absolute titers may still be adequate titers, or whether immune responses wane over time, making SARS-CoV-2 immunogenicity studies difficult to fully interpret.

Effect of DMARD therapy on SARS CoV-2 vaccine efficacy:

Early data in this setting is largely consistent with that from other vaccine studies. Data suggest that rituximab[80–84], glucocorticoids[8284], MTX[828485], abatacept[84], mycophenolate mofetil[84] and JAK-inhibitors[82] impair SARS-CoV-2 vaccine responses in many patients. The mRNA vaccine mechanism and potential impact of DMARD therapy is described in Figure 1.

The largest observational study to date evaluated the BNT162b2 (Pfizer/BioNTech) mRNA vaccine in 686 patients with rheumatic diseases. Compared to controls where 100% seroconverted to vaccination (i.e. newly positive anti-spike IgG), seroconversion rates were significantly lower for patients on rituximab (39% seroconverted, $p<0.0001$), mycophenolate mofetil (64% seroconverted, $p<0.0001$), abatacept (71% seroconverted, $p<0.0001$), JAK-inhibitors (90% seroconverted, $p=0.02$), MTX (92% seroconverted, $p=0.02$), and glucocorticoids (mean dose 6.7 mg/day, 77% seroconverted, $p <0.0001$), while other DMARDs (leflunomide, hydroxychloroquine, TNF, IL-6 and IL-17-inhibitors) did not significantly impact seroconversion.[84] A logistic regression further identified anti-CD20 therapy (adjusted OR 0.13, $p<0.001$), glucocorticoids (adjusted OR 0.48, $p=0.02$), abatacept (adjusted OR 0.14, $p<0.001$), and mycophenolate mofetil (adjusted OR 0.1, $p=0.0013$) as independent predictors of a poor vaccine response. [84] Another prospective study of 133 patients with immune mediated inflammatory diseases on various DMARD therapies and 53 controls vaccinated with mRNA vaccines found that rituximab significantly reduced mRNA vaccine immunogenicity, JAK-inhibitors and MTX moderately reduced antibody titers, and other therapies (TNF, IL-12/23, and integrin inhibitors) had a modest impact on antibody formation.[82]

Risk factors for a poor humoral response on rituximab include a shorter duration between rituximab dose and vaccine, and lack of B-cell reconstitution.[8186] Rituximab-treated patients vaccinated 6 months after their last rituximab dose had a seropositivity rate around 20%, and those vaccinated 1 year after the last rituximab dose had rates around 50%.[84] Despite a reduced humoral response, early data suggests that rituximab-treated patients may still mount a normal cellular vaccine response, such that the net impact on clinical protection is not clear. [86]

MTX appears to reduce some aspects of the SARS-CoV-2 vaccine response.[828485] In a New York cohort of patients with immune mediated inflammatory disease, 72% of MTX-treated patients had adequate humoral antibody titers (defined as IgG to spike protein >5,000 units) compared to 92.3% of patient with rheumatic disease not on MTX and 96.1% of healthy controls ($p=0.023$).[85] Patients on MTX also had reduced activated CD8+ T cells response

but a preserved CD4+ T cell response.[85] In the Furer et al. cohort of 176 MTX-treated patients, 84% of all MTX-treated patients and 92% of patients on MTX-monotherapy seroconverted, compared to 100% of controls ($p<0.05$).[84]

TNF-inhibitors appear to reduce SARS-CoV-2 post-vaccination titers[82878788], but do not seem to substantially impact rates of seroconversion[83878884]—although antibody cutoffs for seroprotection are not defined. Among 865 infliximab-treated inflammatory bowel disease patients given a single vaccine dose of the BNT162b2 mRNA vaccine or the ChAdOx1 nCoV-19 adenoviral vaccine had lower antibody concentrations and seroconversion rates compared to those on vedolizumab.[88] However, in the 27 patients who were studied after a second vaccine dose of the mRNA vaccine, there was no difference in the rate of seroconversion (85% vs. 86%, $p=0.68$).[88] Similarly, in the Furer et al. cohort, 172 patients on TNF-inhibitors fully vaccinated with BNT162b2 mRNA vaccine showed no significant difference in seroconversion rates compared to healthy controls[84] Whether reductions in quantitative humoral responses is of clinical significance is unknown.

JAK inhibitors likely reduce antibody titers and have a mild effect on seroconversion, although the clinical important of these observations is unknown and data are scant. The 10 patients on JAK-inhibitors in the Deepak et al. cohort had a >6-fold reduction in titers compared to controls (95% CI 2.9–15.3, $p<0.05$.)[82] However, in the Furer et al. study, among 21 patients on JAK-inhibitor monotherapy and 24 on combination therapy, 19 (90%) and 22 (92%) respectively seroconverted, neither of which were significantly different from controls.[84]

Safety in patients with rheumatic diseases:

Because of its substantial immunogenicity, there is concern that the SARS-CoV-2 vaccine may induce flares in patients with inflammatory diseases. This concern is supported by reports of thrombocytopenic purpura[89–92] and myocarditis/pericarditis[93–95] after vaccination. There have additionally been observational reports of new onset immune-mediated disease[96] and/or disease flares after SARS-CoV-2 vaccination[9697], which must be balanced against the risk of immune-mediated disease resulting from SARS-CoV-2 infection itself.[98–100]

The Furer et al. cohort of rheumatic disease patients documented two fatalities post-vaccination; one ANCA-vasculitis patient developed cutaneous vasculitis with subsequent fatal sepsis three weeks after the second vaccine dose and the second had a history of cardiovascular disease and died of a myocardial infarction 2 months after the second vaccine dose. Other adverse events of note were two cases of uveitis, one case of pericarditis, six cases of herpes zoster, and one case of herpes labialis, while risks of typical side effects were similar to the controls.[84] Small prospective studies thus far have not found an increased in underlying inflammatory disease activity measures after SARS-CoV-2 vaccination,[8487] however, more prospective data are needed to understand the safety of these vaccines and risk of disease flare in patients with rheumatic diseases.

Recommendations:

The ACR has provided detailed recommendations for management of DMARD therapy in the setting of the SARS-CoV-2 vaccine (Table 2).[101] EULAR is also developing guidelines for SARS-CoV-2 vaccines in patients with rheumatic diseases, which should be available in the near future. All patients with rheumatic diseases should receive the SARS-CoV-2 vaccine as per general population recommendations.

Hepatitis B Vaccination

Background:

There are three different single-antigen recombinant HBV vaccines available worldwide and several combination vaccines; however, the most common HBV vaccine is a yeast-derived single-antigen vaccine. HBV vaccine immunogenicity is measured by anti-HBV surface antibody, where a titer of ≥ 10 IU/L is considered to be seroprotective. [102]

Effect of DMARD therapy on vaccine efficacy:

TNF and IL-12/23 inhibitors have been found to reduce HBV vaccine immunogenicity[103–105], while most other medications have not been extensively evaluated.

TNF-inhibitors reduce HBV vaccine immunogenicity,[103–105] although there may be differences among TNF-inhibitors, with the lower antibody response rates for infliximab and higher response rates for etanercept.[105] Ustekinumab was evaluated in one study of 25 patients where vaccine responses were moderately reduced.[105] A recent trial of a high dose HBV vaccine in DMARD-treated patients resulted in higher antibody response rates (anti-HBs titer over 10 iU/mL) when compared with a standard-dose vaccine, however this result did not reach significance (61.1% vs. 49.3%, p>0.05).[105]

Recommendations:

In the United States, HBV vaccination is recommended for adults at high risk (Table 1).[1261106–108] Ideally patients who require HBV vaccination should be vaccinated prior to starting DMARD therapy, particularly for high-risk patients starting rituximab. [109]

Human Papilloma Virus Vaccination

Background:

Three HPV vaccines are approved; however, the 9-valent vaccine is the only HPV vaccine currently available in the United States. Women with rheumatic diseases on immunosuppressive therapies are at increased risk of HPV and cervical cancer; this has been particularly well described in SLE but is seen in other inflammatory diseases.[110–115] HPV vaccine immunogenicity is measured by seroconversion to subtypes contained in the vaccine, although a minimum threshold for seroprotection is not defined.

Effect of DMARD therapy on vaccine efficacy:

MTX and TNF-inhibitors have been evaluated in patients with juvenile idiopathic arthritis (JIA), juvenile dermatomyositis, inflammatory bowel disease and systemic

lupus erythematosus (SLE); in these patients, MTX and TNF-inhibitors do not appear to impact post-vaccination seroconversion rates.[116–119] Patients with SLE on combination mycophenolate mofetil and low dose glucocorticoids show moderately reduced seroconversion rates for HPV6 and 18, but not for other subtypes.[118] Other DMARD therapies have not been evaluated in patients with rheumatic diseases.

Recommendations:

The CDC recommends HPV vaccination for all patients (regardless of sex) at age 11 or 12 up through age 26.[12] No specific changes in medications are recommended for the HPV vaccines. It is important to remember that HPV vaccines are given as a series and the treating rheumatologist should ensure that the entire series have been completed.

Tetanus Vaccination

Background:

The tetanus toxoid, reduced diphtheria toxoid and acellular pertussis (Tdap) vaccine is a single dose vaccine. Tetanus toxoid is a T cell-dependent antigen. Tetanus vaccine immunogenicity is typically measured by anti-tetanus toxoid IgG concentrations 4 weeks post-vaccination, where an antibody concentration of ≥0.10 IU/mL is typically considered seroprotective, however, an endpoint of ≥4-fold increase in antibody concentration is also sometimes used.[120]

Effect of DMARD therapy on vaccine efficacy:

Rituximab reduces response to the tetanus vaccine, however, the degree of this reduction is inconsistent between studies.[18121] Studies of abatacept[122123], JAK-inhibitors[53120], and TNF-inhibitors[121124] suggest a modest impairment in immunogenicity. IL-6[55], IL-17[55], and IL-12/23[54] inhibitors have not been shown to impair tetanus vaccine immunogenicity.

Rituximab may have less of a profound impact on tetanus immunogenicity than other vaccines, possibly because most patients have previously had tetanus vaccine and may have residual tetanus-specific memory B cells. RA patients on rituximab + MTX and MTX monotherapy were able to mount similar rates of humoral response, defined as a ≥4-fold rise in anti-tetanus IgG (39.1% vs. 42.3%, 95% CI −25.7 to 19.2).[18] However, another study found that rituximab was associated with lower rates of protective antibodies titers (≥0.1 IU/mL) compared to other inflammatory disease patients or controls (73% vs. 96–100%) and only 9% of rituximab-treated patients had a ≥4 fold rise in antibody titers.[121]

A study of patients with inflammatory bowel disease on TNF-inhibitors found lower antibody titers relative to those on thiopurines or healthy controls ($p<0.001$), though average titers were still in the protective range.[124] Other data have shown similar antibody response rates in TNF-treated patients relative to health controls.[121] An uncontrolled study of subcutaneous abatacept found satisfactory tetanus vaccine response in 219 juvenile idiopathic arthritis patients (regardless of MTX or concomitant glucocorticoids),[122] while a smaller study of 20 adults vaccinated 2 weeks after a single dose of intravenous abatacept found approximately 10% lower rates of protective antibody development relative

to controls.[123] Delaying the tetanus vaccine to 8 weeks after abatacept improved response rates to close to that of healthy controls.[123] Studies of JAK inhibitors are uncontrolled, making it difficult to estimate the drug effect. However, relative to expected responses in the general population, baricitinib plus MTX-treated patients with RA show reduced anti-tetanus antibody concentrations[53], while tofacitinib-treated patients with psoriasis mount a seemingly satisfactory response.[120] In a study of baricitinib and tetanus vaccination, concomitant glucocorticoids did not appear to have an adverse effect on rates of adequate humoral response; 52% (95% CI 34.8–68) of those taking glucocorticoids vs 39% (95% CI 28.9–51.1) of those not taking glucocorticoids.[53]

Studies of psoriasis patients on ustekinumab[54] and ixekizumab[55] did not find any change in post-vaccination tetanus antibody response relative to untreated controls. Tocilizumab similarly does not appear to hamper antibody response to the tetanus vaccine.[125]

Recommendations:

Adults and adolescents should receive a Tdap followed by boosters of tetanus and diphtheria toxoids (Td) every 10 years or when indicated due to a wound, although a booster may be either Td or Tdap. [12] Tetanus vaccination should ideally be done prior to starting rituximab therapy.

Yellow Fever vaccination

Background:

The YF vaccine is recommended to immunocompetent persons who live or travel to endemic areas.[61126] However, this vaccine is live and is contraindicated in immunosuppressed patients including those receiving biologics and JAKi.[41] YF vaccine immunogenicity is measured by post-vaccination neutralizing antibody titers.

Effect of DMARD therapy on vaccine efficacy:

Because the YF vaccine is live, few studies have addressed the immunogenicity of this vaccine in patients with rheumatic diseases. A study from Brazil evaluated 31 patients who were inadvertently re-vaccinated (patients had primary immunity from a previous vaccine) while on biologics; these patients had lower, yet adequate antibody titers.[127] Another 17 patients on infliximab + MTX achieved satisfactory antibody levels in all but 1 patient.[128] Among 15 patients on MTX, all achieved seroprotection.[129] Patients on corticosteroids (mean 7 mg/day, range 5–20 mg/day), 18/34 of whom were vaccine naive, also appeared to have satisfactory titers.[130]

Safety in patients with rheumatic diseases:

Small studies suggest that the vaccine may be safer than previously thought for patients on MTX[127129131], infliximab[127128] and corticosteroids <20 mg/day[130]. A retrospective Swiss study of 92 patients on immunosuppressive medications (16 on MTX, 40 on corticosteroids, small numbers on other medications) who received the yellow fever vaccine developed similar rates of side effects as healthy controls (controls had a similar proportion of patients with a primary YF vaccine history) and no serious adverse events.[131] A prospective study

of 15 patients on MTX (≤ 20 mg/week) receiving a primary YF vaccine found slightly increased rates of yellow fever RNA viremia in MTX-treated patients relative to controls ($p>0.39$), however these levels were never of clinical significance.[129] In the study from Brazil above, 31 patients re-vaccinated on biologics had no adverse events.[127]

Recommendations:

The yellow fever vaccine should be avoided in patients who are immunosuppressed. In travels or patients in endemic areas at very high risk, patients and their providers may consider holding immunosuppressive therapy for vaccination. The typical requirement for doing this would be to hold for a sufficient time to allow for the medication to wash out and its biologic effect to dissipate depending on half-life, then vaccinate, and then wait 2–4 weeks before resuming medication.

Conclusion:

Vaccinations are critical in the care of patients with inflammatory diseases, especially for those on DMARD therapy, yet DMARD therapy can impair vaccine response. This issue is only becoming more important with the emergence of novel pathogens and resultant innovative vaccines. In this review we have summarized the available data regarding DMARDs and vaccine responses. While the impact of DMARD therapy on vaccines is variable, there are consistent themes. Rituximab substantially reduces antibody response to vaccines, although T cell responses may be preserved. MTX and abatacept reduce the immunogenicity of many vaccines. TNF and JAK-inhibitors typically reduce absolute post-vaccination antibody titers, though most patients (particularly those on TNF-inhibitors) still achieve seroprotective levels. Other anti-cytokine therapies, including IL-6, IL-12/23, and IL-17 inhibitors do not appear to have a measurable impact on vaccine immunogenicity.

Vaccine immunogenicity studies are limited by inconsistency in immunogenicity measures and heterogeneity of control groups. More data are needed for the SARS-CoV-2, HBV, HPV and zoster vaccines, and for less common medications such as belimumab and newer anti-cytokine therapies. Lastly, few clinical trials have directly evaluated strategies to overcome this issue, such as timing vaccines around DMARD dosing, or utilizing drug-holidays. As our arsenal of DMARD therapy and vaccines grow, more clinical trials will be needed to assess the impact of DMARD therapy on vaccines, and to test strategies to optimize vaccine response.

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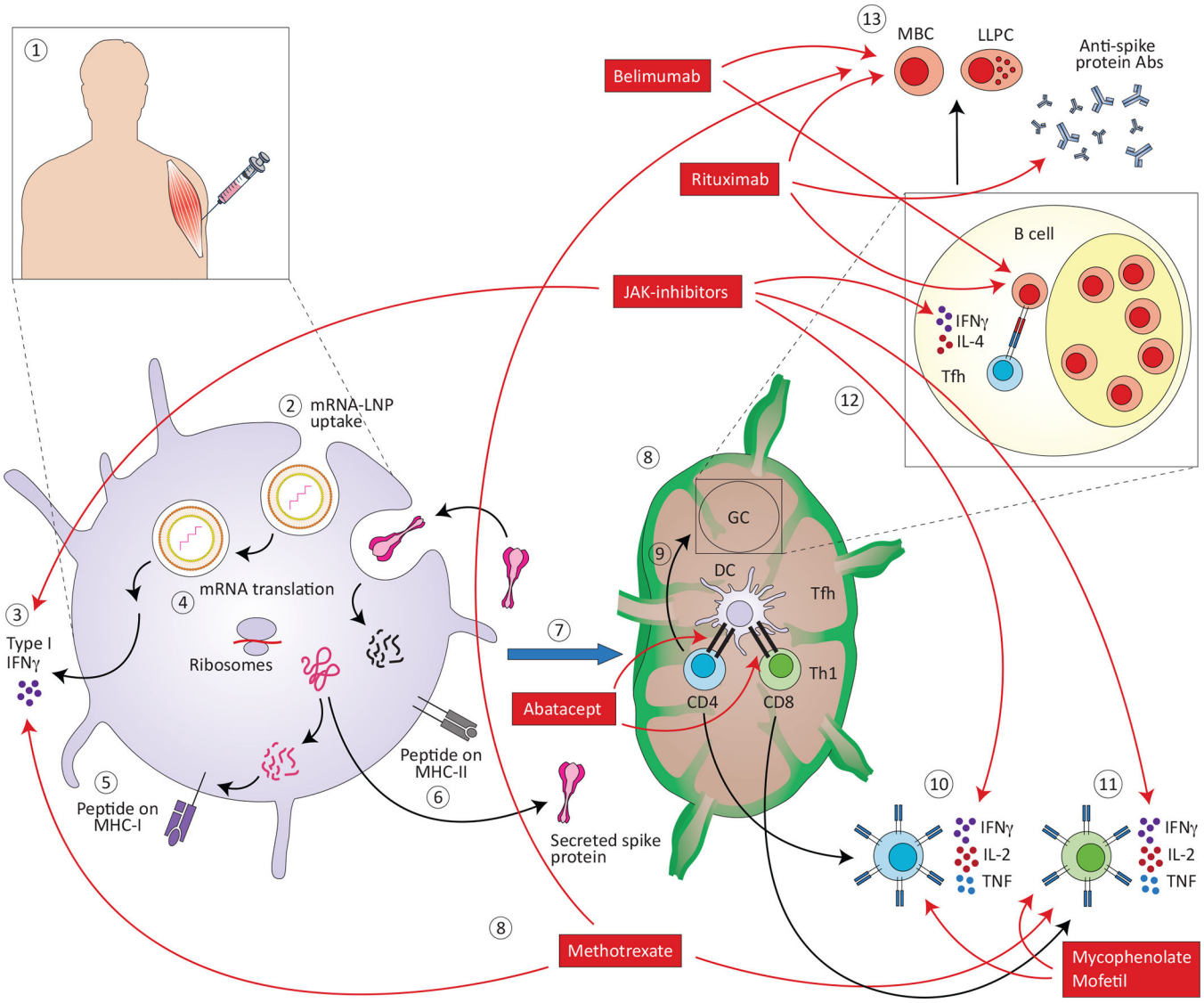

Figure 1: Mechanism of the mRNA SARS-CoV-2 vaccine and potential impact of DMARD therapy:

1) The mRNA vaccine is given as an intramuscular injection. 2) Lipid nanoparticles (LPN) coating the mRNA allow uptake into antigen presenting cells (APCs).[136] 3) mRNA is recognized by toll-like receptors (TLR)/retinoic acid-inducible gene (RIG)-I, triggering a type I interferon (IFN) response. 4) mRNA is translated by ribosomes into peptides. 5) Peptides are processed by the proteasome and presented on MHC-I or 6) post-translationally modified into secreted proteins, which can then be taken up by APCs and presented by MHC-II. 7) Dendritic cells (DCs) are trafficked to lymph nodes where they 8) prime CD4+ and CD8+ T cells. 9) CD4+ T cells differentiate into T follicular helper (Tfh) cells, which form germinal centers (GC) or 10) Th1 cells. 11) CD8+ T cells become circulating cytotoxic T cells. 12) In the GC, Tfh cells interact with B cells, resulting in 13) memory B cells (MBC) and long-lived plasma cells (LLPCs) secreting anti-spike protein antibodies (Abs).[136137] Low dose methotrexate (MTX) impacts expression of cytokines[138], B cell and CD8+ T cell responses, with apparent preservation of CD4+ response.[85] Mycophenolate

mofetil reduces B and T lymphocyte proliferation.[139] Abatacept is a soluble fusion CTLA-4 IgG, which prevents T cell costimulation.[140] Janus kinase (JAK)-inhibitors reduce signaling by numerous cytokines, of particular importance in mRNA vaccines response are IFNγ, interleukin (IL)-4 and IL-2 signaling.[141] Rituximab depletes B cells by targeting CD20, which is expressed by early B cells but not mature plasma cells.[142] Belimumab binds soluble B lymphocyte stimulator (BLyS), reducing B cell survival.[143] SARS-CoV-2 mRNA vaccine mechanisms depictions are modified from figures attributed to Cagigi/Loré [136] and Bettini/Locci[137], licensed under CC BY 4.0.

Table 1:

Impact of disease modifying antirheumatic drugs on vaccine immunogenicity:

	Influenza	**Pneumococcal**	**Herpes Zoster**	**Hepatitis B**	**Human papilloma virus**	**Tetanus**	**SARS-CoV-2 (mRNA)**
Methotrexate	↓[142224]	↓[5051]	OK (ZVL)[52]		OK[117132133]	↓[121]	↓[828485]
TNF-inhibitors	OK[1416202728]	OK[1456]	OK (ZVL) [64]	↓[103–105]	OK [117132]	OK[121124]*	OK [848588]
Rituximab	↓↓[14–1719–2124134]	↓↓[141845–47]				↓[18121]	↓↓[8182–84]
Abatacept	↓[2426]	↓[4546]				OK (SQ) [122] ↓(IV)[123]	↓[84]
JAK-inhibitor	OK[30]	↓[30]				OK (tofacitinib)[120] ↓(baricitinib)[53]	↓[8284]
IL-6R inhibitor	OK[31]	OK[31]				OK[125]	OK[54]
IL-12/23 inhibitor	OK[32]	OK[54]		↓[105]		OK[84]	OK [82]
IL-17 inhibitor	OK[33–35]	OK[55]				OK[55]	OK[84]

OK: No significant/meaningful effect on vaccine immunogenicity (may include reduction in absolute post-vaccination titers if rates of protective titers are unchanged.) ↓: Reduces vaccine immunogenicity. ↓↓: Significantly reduces vaccine immunogenicity. For OK, ↓, and ↓↓: if no control group is available, data are compared to expected vaccine responses in the general population. Empty cells indicate a lack of data. TNF = tumor necrosis factor, JAK = Janus kinase, IL = interleukin, ZVL = zoster vaccine live, RZV = recombinant zoster vaccine, SQ = subcutaneous

Table 2:

Vaccination Schedule Recommendations for Patients with Rheumatic Diseases:

	Vaccination recommendation	Recommended modification of DMARD therapy relative to vaccine timing based on guidelines and best available evidence [*], as compatible with disease activity.
Influenza	Yearly quadrivalent vaccination for all patients. [†‡§] Patients older than 65 should receive the high-dose quadrivalent vaccine. [†] [*]May consider high-dose vaccine for all immunocompromised patients. [4244]	Rituximab: vaccinate before starting rituximab, or as long as possible after the last dose (ideally ≥ 6 months) and 4 weeks before the next dose. [§] Methotrexate: consider holding for two weeks after vaccination. [*2223]
Pneumococcal	Recommended for all immunosuppressed patients. [†‡§] Give 1 dose of PCV13 followed by PPSV23 at least 8 weeks later. Give a second PPSV23 dose 5 years after the first PPSV23 dose. [†]	Rituximab: vaccinate before starting rituximab, or as long as possible after the last dose (ideally ≥ 6 months) and 4 weeks before the next dose. [§] Methotrexate: consider holding MTX for two weeks after vaccination. [*]
Herpes zoster	Recombinant zoster vaccine for adults over age 50. [†¶] Use live Zoster vaccine where recombinant is not available. Consider in all high-risk rheumatic disease patients. [†§]	Rituximab: vaccinate before starting rituximab, or as long as possible after the last dose (ideally ≥ 6 months) and 4 weeks before the next dose. [*]
Hepatitis B	All nonimmune adults at risk for HBV infection. [£†‡§]	Rituximab: vaccinate before starting rituximab, or as long as possible after the last dose (ideally ≥ 6 months) and 4 weeks before the next dose. [§]
Human papilloma virus	As per general population guidelines, especially for SLE patients. [§‡]	Rituximab: vaccinate before starting rituximab, or as long as possible after the last dose (ideally ≥ 6 months) and 4 weeks before the next dose. [§]
Tetanus	As per general population and consider for all rituximab treated patients. [§]	Rituximab: vaccinate before starting rituximab. [§]
Yellow fever	Avoid for immunocompromised patients. [‡§]	N/A, contraindicated
SARS-CoV-2	All patients as per the general population. [135]	ACR guidance summary: [135] Rituximab: as long as possible after the last dose, 2–4 weeks before the next dose. MTX: hold for 1 week after each mRNA dose; hold for 2 weeks after single-dose vaccine. MMF and JAK inhibitors: hold for 1 week after each vaccine dose. Abatacept subcutaneous: hold one week before and one week after the first vaccine dose, no interruption for the second vaccine dose. Abatacept intravenous: time the first vaccine dose 4 weeks after abatacept and postpone next infusion by 1 week; no adjustment for the second vaccine dose Cyclophosphamide: time cyclophosphamide 1 week after each vaccine dose. TNF, IL-6R, IL-1, IL-17, IL-12/23, IL-23, oral calcineurin inhibitors, belimumab [**], azathioprine, sulfasalazine, leflunomide, hydroxychloroquine, apremilast, IVIG and glucocorticoids <20 mg/day [**]: no modification

[*]Authors' recommendations based on best available evidence

[†]2021 Advisory Committee on Immunization Practices recommendations[12]

[‡]2015 American College of Rheumatology guideline for the treatment of rheumatoid arthritis [40]

[§]2019 European League Against Rheumatism recommendations for vaccination in adult patients with autoimmune inflammatory rheumatic diseases [41]

[¶]Per CDC guidelines, adults with immunocompromising conditions were not included in initial clinical trials and therefore no recommendations regarding vaccination age for this population was made. However, this may change in the future.

[£] Risk factors include: persons at risk through sexual exposure (sex partners of hepatitis B surface antigen positive persons, sexually active persons not in a long term monogamous relationship, persons seeking evaluation or treatment for a sexually transmitted disease, men who have sex with men), persons with a history of current or recent injection drug use, persons at risk for infection by percutaneous or mucosal exposure to blood (household contact or sexual partner who is hepatitis B surface antigen positive, resident or staff of a facility for the developmentally disabled, health care or public safety workers with anticipated risk for exposure to body fluids, patients with end-stage renal disease, persons with diabetes mellitus aged <60 or those over age 60 at the discretion of the treating physicians), travelers to endemic areas, patients with chronic liver disease or hepatitis C infection, incarcerated persons, and patients with human immunodeficiency virus.

[**] Data published since guideline development suggest that lower doses of prednisone and belimumab may adversely impact the SARS-CoV-2 mRNA vaccine immunogenicity. [84]