

# Impact of disease-modifying antirheumatic 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 antirheumatic drugs 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 tumour necrosis factor inhibitors decrease absolute antibody titres for many vaccines, but do not seem to significantly impact the proportions of patients achieving seroprotection. Other biologics (interleukin-6R (IL-6R), IL-12/IL-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 are just now emerging, and early glimpses appear similar to our experience with other vaccines. In this review, we summarise the most recent data regarding vaccine response and efficacy in this setting, particularly in light of current vaccination recommendations for immunocompromised patients.

## INTRODUCTION

Patients with inflammatory rheumatic diseases are at increased risk of vaccine-preventable infectious diseases.<sup>1–6</sup> Vaccinations reduce the risks of infectious complications in patients with rheumatic disease,<sup>7,8</sup> yet are under utilised.<sup>9,10</sup> 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 summarises vaccination recommendations made for this population (table 2).

Vaccine immunogenicity is typically measured as a surrogate for clinical vaccine efficacy. Interpreting and harmonising 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 (eg, differences in Janus

kinase (JAK)-inhibitor targets and JAK selectivity.) Second, 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 measured, definitions of response<sup>11</sup>) 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 summarise here the available data evaluating the effect of DMARDs on vaccine immunogenicity, as well as to summarise current recommendations for how and when to vaccinate patients with rheumatic disease 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.<sup>12,13</sup> Two quadrivalent vaccines are currently recommended for adults age  $\geq 65$ —a high-dose quadrivalent vaccine (Fluzone High-Dose) and an adjuvanted quadrivalent vaccine (Fluad Quadrivalent).<sup>12,13</sup> The live attenuated intranasal influenza vaccine is contraindicated in patients taking biologics or other immunomodulatory therapies (eg, JAK inhibitors). Influenza vaccine efficacy is estimated using a surrogate of haemagglutinin inhibition titres. A titre of 1:40 is considered ‘seroprotected’ (as defined as 50% vaccine efficacy).

### Effect of DMARD therapy of vaccine efficacy

Rituximab<sup>14–21</sup> and MTX<sup>14,22,23</sup> reduce influenza vaccine immunogenicity. Abatacept likely impairs immunogenicity though data are limited.<sup>24–26</sup> Post-vaccination antibody titres are lower in patients on tumour necrosis factor (TNF)<sup>14,20,27–29</sup> and JAK inhibitors,<sup>30</sup> although the proportion of patients achieving seroprotection is similar to patients with



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**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	↓ <sup>14 22 24</sup>	↓ <sup>50 51</sup>	OK (ZVL) <sup>52</sup>		OK <sup>117 132 133</sup>	↓ <sup>121</sup>	↓ <sup>82 84 85</sup>
TNF inhibitors	OK <sup>14 16 20 27 28</sup>	OK <sup>14 56</sup>	OK (ZVL) <sup>64</sup>	↓ <sup>103–105</sup>	OK <sup>117 132</sup>	OK <sup>121 124*</sup>	OK <sup>84 85 88</sup>
Rituximab	↓↓ <sup>14–17 19–21 24 134</sup>	↓↓ <sup>14 18 45–47</sup>				↓ <sup>18 121</sup>	↓ <sup>81–84</sup>
Abatacept	↓ <sup>24 26</sup>	↓ <sup>45 46</sup>				OK (SQ) <sup>122</sup> ↓(IV) <sup>123</sup>	↓ <sup>84</sup>
JAK inhibitor	OK <sup>30</sup>	↓ <sup>30</sup>				OK (tofacitinib) <sup>120</sup> ↓(baricitinib) <sup>53</sup>	↓ <sup>82 84</sup>
IL-6R inhibitor	OK <sup>31</sup>	OK <sup>31</sup>				OK <sup>125</sup>	OK <sup>84</sup>
IL-12/IL-23 inhibitor	OK <sup>32</sup>	OK <sup>54</sup>		↓ <sup>105</sup>		OK <sup>54</sup>	OK <sup>82</sup>
IL-17 inhibitor	OK <sup>33–35</sup>	OK <sup>55</sup>				OK <sup>55</sup>	OK <sup>84</sup>

OK indicates no significant/meaningful effect on vaccine immunogenicity (may include reduction in absolute postvaccination titres if rates of protective titres are unchanged.) ↓ reduces vaccine immunogenicity. ↓↓ significantly reduces vaccine immunogenicity. For OK, ↓ and ↓↓ if no control group is available, data are compared with expected vaccine responses in the general population. Empty cells indicate lack of data.

IL, interleukin; JAK, Janus kinase; RZV, recombinant zoster vaccine; SQ, subcutaneous; TNF, tumour necrosis factor; ZVL, zoster vaccine live.

rheumatic disease not treated with these medications. Interleukin (IL)-6, IL-12/IL-23 and IL-17 inhibitors do not appear to impact the influenza vaccine<sup>31–35</sup> (table 1).

Influenza vaccination responses may be improved for rituximab<sup>16 21</sup> and MTX<sup>22 23</sup> 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 vs 1/11 patients achieved seroprotection,  $p=0.108$ ).<sup>21</sup> In a randomised controlled trial, 316 patients with rheumatoid arthritis (RA) were randomised 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  $\leq 7.5$  mg/week did not show a significant improvement with MTX dose interruption.<sup>23</sup> 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 generalisable to all patients or only a subset with elevated BAFF (which is not routinely evaluated).<sup>36</sup>

Abatacept likely impairs influenza vaccine immunogenicity, though data are limited.<sup>24–26</sup> 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 with 69% of controls ( $p=0.001$ ).<sup>24 26</sup> 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 titres,<sup>25</sup> which is only modestly reduced compared with general population rates (89%–97% for each influenza strain).<sup>37</sup>

Low-dose glucocorticoid use has not been shown to impact influenza vaccine response when added to other DMARD therapy. 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.<sup>38</sup> Similarly, low-dose prednisone (mean 8 mg/day) in RA did not adversely affect influenza vaccine response in a multivariate regression analysis when evaluated alongside other DMARD therapy.<sup>27</sup>

## Recommendations

Routine yearly influenza vaccines are recommended for all people aged 6 months or older.<sup>12 39</sup> The European League Against Rheumatism (EULAR) and American College of Rheumatology (ACR)

both recommend yearly intramuscular influenza vaccinations for all patients with RA.<sup>40 41</sup>

High-dose influenza vaccines may be more effective in patients with rheumatic disease,<sup>42–44</sup> although at this time the high-dose vaccine is recommended only for adults aged  $\geq 65$ .<sup>12</sup> A randomised study of 279 patients with RA found that those receiving the high-dose influenza vaccine were more likely to seroconvert (OR: 2.99, 95% CI: 1.46 to 6.11); this effect was similar in patients on synthetic and biologic DMARDs.<sup>42</sup>

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,<sup>41</sup> 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).<sup>17</sup> Patients on MTX can improve influenza vaccination responses by holding MTX for 2 weeks after vaccination, particularly for those on  $\geq 15$  mg/week; holding MTX 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%,  $p=0.07$ ).<sup>22 23</sup>

## PNEUMOCOCCAL VACCINATION

### Background

Two pneumococcal vaccines are commonly used, pneumococcal conjugate vaccine 13-valent (PCV13) and pneumococcal polysaccharide vaccine 23-valent (PPSV23). PCV13 is conjugated to a diphtheria protein and is more immunogenic than the polysaccharide vaccine. Both PCV13 and PPSV23 vaccine immunogenicity is typically measured by postvaccination antibody titres against serotypes found in each vaccine, although the titre level chosen as ‘protective’ can be variable and is arbitrary, as no level of ‘seroprotection’ against most pneumococcal disease has been established.<sup>11</sup>

### 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<sup>14 18 45–47</sup> and MTX<sup>11 14 48–51</sup> reduce pneumococcal vaccine immunogenicity. JAK inhibitors<sup>30 52 53</sup> and abatacept<sup>25 45 46</sup> appear to modestly

**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. <sup>†‡§</sup> Patients older than 65 should receive the high-dose quadrivalent vaccine. <sup>†</sup> May consider high-dose vaccine for all immunocompromised patients. <sup>*42 44</sup>	Rituximab: vaccinate before starting rituximab, or as long as possible after the last dose (ideally ≥6 months) and 4 weeks before the next dose. <sup>§</sup> MTX: consider holding for 2 weeks after vaccination. <sup>*22 23</sup>
Pneumococcal	Recommended for all immunosuppressed patients. <sup>†‡§</sup> Give one dose of PCV13 followed by PPSV23 at least 8 weeks later. Give a second PPSV23 dose 5 years after the first PPSV23 dose. <sup>†</sup>	Rituximab: vaccinate before starting rituximab, or as long as possible after the last dose (ideally ≥6 months) and 4 weeks before the next dose. <sup>§</sup> MTX: consider holding MTX for 2 weeks after vaccination.*
Herpes zoster	Recombinant zoster vaccine for adults over age 50. <sup>†¶</sup> Use live Zoster vaccine where recombinant is not available. Consider in all high-risk patients with rheumatic disease. <sup>†§</sup>	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 non-immune adults at risk for HBV infection. <sup>†‡§**</sup>	Rituximab: vaccinate before starting rituximab, or as long as possible after the last dose (ideally ≥6 months) and 4 weeks before the next dose. <sup>§</sup>
Human papilloma virus	As per general population guidelines, especially for patients with SLE. <sup>§‡</sup>	Rituximab: vaccinate before starting rituximab, or as long as possible after the last dose (ideally ≥6 months) and 4 weeks before the next dose. <sup>§</sup>
Tetanus	As per general population and consider for all rituximab-treated patients. <sup>§</sup>	Rituximab: vaccinate before starting rituximab. <sup>§</sup>
Yellow fever	Avoid for immunocompromised patients. <sup>‡§</sup>	N/A, contraindicated
SARS-CoV-2	All patients as per the general population. <sup>101</sup>	ACR guidance summary <sup>101</sup> : 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. Mycophenolate mofetil and JAK inhibitors: hold for 1 week after each vaccine dose. Abatacept subcutaneous: hold 1 week before and 1 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 <sup>††</sup> , azathioprine, sulfasalazine, leflunomide, hydroxychloroquine, apremilast, intravenous immune globulin (IVIG) and glucocorticoids <20 mg/day <sup>††</sup> : no modification.

\*Authors' recommendations based on best available evidence.

†2021 Advisory Committee on Immunisation Practices recommendations.<sup>12</sup>

‡2015 American College of Rheumatology guideline for the treatment of rheumatoid arthritis.<sup>40</sup>

§2019 European League Against Rheumatism recommendations for vaccination in adult patients with autoimmune inflammatory rheumatic diseases.<sup>41</sup>

¶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, healthcare 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), travellers to endemic areas, patients with chronic liver disease or hepatitis C infection, incarcerated persons and patients with HIV.

††Data published since guideline development suggests that lower doses of prednisone and belimumab may adversely impact the SARS-CoV-2 mRNA vaccine immunogenicity.<sup>84</sup>

ACR, American College of Rheumatology; CDC, Center for Disease Control; DMARD, disease-modifying antirheumatic drug; IL, interleukin; JAK, Janus kinase; MTX, methotrexate; PCV13, pneumococcal conjugate vaccine 13-valent; PPSV23, pneumococcal polysaccharide vaccine 23-valent; SLE, systemic lupus erythematosus; TNF, tumour necrosis factor.

reduce immunogenicity, while other biologics (TNF, IL-6, IL-12/IL-23 and IL-17 inhibitors) do not impair vaccine immunogenicity.<sup>14 31 54–56</sup>

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

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 (74%)/46 patients developed protective antibody titres, consistent with expected response.<sup>25</sup> However, another study of 17 patients on intravenous abatacept vaccinated with PCV7 (13 of whom were receiving concomitant MTX) found a lower likelihood of a greater than equal to twofold increase in postvaccination antibody titre compared with patients on tocilizumab or controls.<sup>45</sup> 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.<sup>46</sup>

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

Low-dose glucocorticoids taken concomitantly with other DMARD therapy have not been found to impact pneumococcal vaccine responses,<sup>53 57 58</sup> while high-dose glucocorticoids may adversely impact pneumococcal vaccine immunogenicity.<sup>59</sup> Among patients with inflammatory diseases vaccinated with the PPSV23, 57% of non-responders were taking prednisone  $>20$  mg/day compared with 22% of vaccine responders ( $p=0.07$ ).<sup>59</sup> In an uncontrolled baricitinib study where approximately 30% of participants were taking concomitant low-dose corticosteroids (mean dose: 6.2 mg/day), PCV13 response rates were similar in those taking corticosteroids versus those not taking corticosteroids (71% (95% CI: 53.4% to 83.9%) vs 67% (95% CI: 55.2% to 76.5%)).<sup>53</sup> Similarly, in a study of patients on MTX with or without infliximab, concomitant low-dose glucocorticoids (prednisone equivalent  $<10$  mg/day) did not adversely impact vaccine response.<sup>58</sup>

## Recommendations

The EULAR, ACR and CDC all recommend pneumococcal vaccinations for patients with rheumatic disease taking DMARD therapy.<sup>40 60 61</sup> 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.<sup>46</sup>

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 MTX 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 USA, although it is still used in many parts of the world.<sup>62</sup> Response to zoster vaccine is measured by a humoral varicella zoster virus IgG and/or cell-mediated varicella zoster virus-specific T-cell enumeration. Although both measures correlated with vaccine efficacy, cell-mediated responses correlate more strongly with the risk of future shingles.<sup>63</sup>

### Effect of DMARD therapy on vaccine efficacy

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

Hundred and twelve patients with RA on MTX were vaccinated with the ZVL and then randomised to start tofacitinib or placebo 2–3 weeks postvaccination. Patients in both groups had similar postvaccine responses.<sup>52</sup> In this study, approximately 40% of patients treated with placebo and 47% of patients treated with tofacitinib 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.<sup>52</sup> 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.<sup>64</sup> Zoster vaccines have not been studied in patients with rheumatic disease on rituximab, however, among patients with haematologic malignancies on anti-CD20 therapies (alone or in combination with other chemotherapies), 4 doses of the RZV produced significant T-cell responses.<sup>65</sup> 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 one case of cutaneous vaccine dissemination in a patient on MTX randomised to start tofacitinib, however, this patient lacked primary immunity to varicella (ie, they did not have chickenpox as a child) and were not a candidate for the live vaccine.<sup>52</sup> Among 633 United States Medicare patients inadvertently vaccinated while on biologics, no cases of shingles occurred in the 6 weeks postvaccination.<sup>10</sup> Six hundred patients on TNF inhibitors (with or without MTX and prednisone) randomised 1:1 to receive the ZVL versus placebo and found no cases of varicella infection or zoster within the subsequent 42-day risk period of highest interest.<sup>64</sup> 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 III 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 patients with rheumatic disease 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.<sup>66</sup> 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.<sup>67</sup> 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 2000 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.<sup>68</sup> 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.<sup>12</sup> The European Medicines Agency recently approved the RZV for adults over age 18 with immunocompromising conditions,<sup>69</sup> 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,<sup>40</sup> and EULAR recommends zoster vaccination in high-risk patients,<sup>41</sup> however, neither of these guidelines address the newer RZV. Given that immunocompromised patients with rheumatic diseases are at increased risk of zoster,<sup>6,70</sup> future guidelines may be expanded to recommend the RZV for high-risk patients at a younger age (eg, 18 and older).

## SARS-COV-2 VACCINATION

### Background

A growing number of SARS-CoV-2 vaccines are in use worldwide, including mRNA, adenoviral vector, protein subunit and inactivated virus vaccines.<sup>71</sup> We will focus our discussion on two mRNA vaccines and two 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% to 97.6%)<sup>72</sup> and the mRNA01273 (Moderna) vaccine was 94.1% effective (95% CI: 89.3% to 96.8%)<sup>73</sup> in preventing symptomatic COVID-19 infection following the second dose. Phase III trials found the Ad26.COV2.S (Janssen/Johnson & Johnson) single-dose vaccine to be 66.9% effective (95% CI: 59.0% to 73.4%)<sup>74</sup> and the ChAdOx1 nCoV-19/AZD1222 (University of Oxford/AstraZeneca/Serum Institute of India) vaccine to be 70.4% effective (95% CI: 54.8% to 80.6) following the second dose.<sup>75</sup>

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)- $\gamma$  response to SARS-CoV-2 peptide. Antibody responses are reported as 'seroconversion' (newly positive antispikes protein IgG), or by postvaccination antibody titres. The role of T-cell responses to SARS-CoV-2 vaccines are not fully understood, however emerging evidence suggests that T-cell responses may confer protection<sup>76,77</sup> even in the absence of humoral response.<sup>78,79</sup> However, we do not yet know how immunogenicity cut-offs correlate with efficacy, whether reduced absolute titres may still be adequate titres, 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 are largely consistent with that from other vaccine studies. Data suggest that rituximab,<sup>80–84</sup>

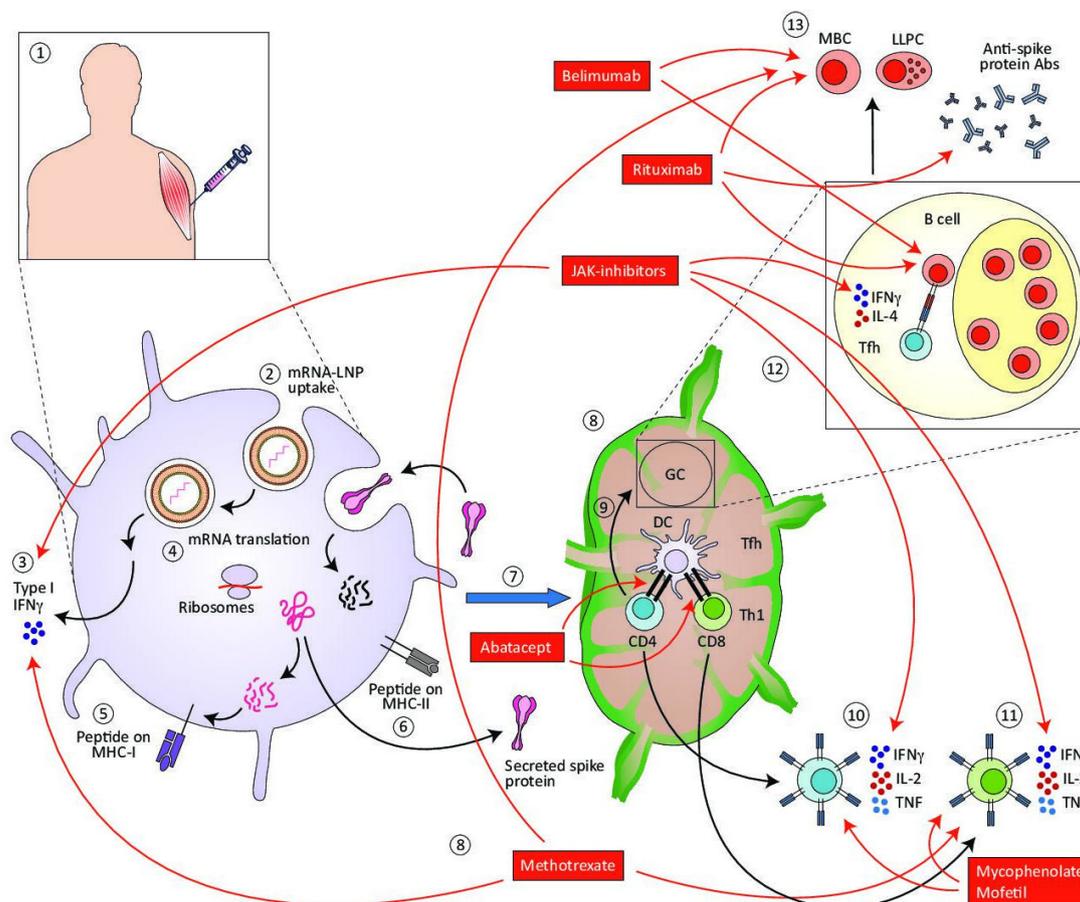
glucocorticoids,<sup>82,84</sup> MTX,<sup>82,84,85</sup> abatacept,<sup>84</sup> mycophenolate mofetil<sup>84</sup> and JAK inhibitors<sup>82</sup> impair SARS-CoV-2 vaccine responses in many patients. The mRNA vaccine mechanism and potential impact of DMARD therapy is described in figure 1.

The largest observational study to date evaluated the BNT162b2 (Pfizer/BioNTech) mRNA vaccine in 686 patients with rheumatic diseases. Compared with controls where 100% seroconverted to vaccination (ie, 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.<sup>84</sup> 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.<sup>84</sup> 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 titres, and other therapies (TNF, IL-12/IL-23 and integrin inhibitors) had a modest impact on antibody formation.<sup>82</sup>

Risk factors for a poor humoral response on rituximab include a shorter duration between rituximab dose and vaccine, and lack of B-cell reconstitution.<sup>81,86</sup> 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%.<sup>84</sup> Despite a reduced humoral response, early data suggest that rituximab-treated patients may still mount a normal cellular vaccine response, such that the net impact on clinical protection is not clear.<sup>86</sup>

MTX appears to reduce some aspects of the SARS-CoV-2 vaccine response.<sup>82,84,85</sup> In a New York cohort of patients with immune-mediated inflammatory disease, 72% of MTX-treated patients had adequate humoral antibody titres (defined as IgG to spike protein  $> 5000$  units) compared with 92.3% of patients with rheumatic disease not on MTX and 96.1% of healthy controls ( $p = 0.023$ ).<sup>85</sup> Patients on MTX also had reduced activated CD8 + T-cell response but a preserved CD4 + T-cell response.<sup>85</sup> 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 with 100% of controls ( $p < 0.05$ ).<sup>84</sup>

TNF inhibitors appear to reduce SARS-CoV-2 postvaccination titres,<sup>82,87,88</sup> but do not seem to substantially impact rates of seroconversion<sup>83,84,87,88</sup>—although antibody cut-offs for seroprotection are not defined. Among 865 infliximab-treated patients with inflammatory bowel disease 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 with those on vedolizumab.<sup>88</sup> 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%,  $p = 0.68$ ).<sup>88</sup> Similarly, in the Furer *et al* cohort, 172



**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) LPN coating the mRNA allow uptake into APCs<sup>135</sup>; (3) mRNA is recognised by Toll-like receptors/retinoic acid-inducible gene-I, triggering a type I 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) DCs are trafficked to lymph nodes where they (8) prime CD4 + and CD8+ T cells; (9) CD4 + T cells differentiate into Tfh cells, which form 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) MBC and LLPCs secreting anti-spike protein Abs.<sup>135,136</sup> Low-dose MTX impacts expression of cytokines,<sup>137</sup> B cell and CD8 + T-cell responses, with apparent preservation of CD4 + response.<sup>85</sup> Mycophenolate mofetil reduces B and T lymphocyte proliferation.<sup>138</sup> Abatacept is a soluble fusion CTLA-4 IgG, which prevents T-cell costimulation.<sup>139</sup> JAK inhibitors reduce signalling by numerous cytokines, of particular importance in mRNA vaccines response are IFN- $\gamma$ , IL-4 and IL-2 signalling.<sup>140</sup> Rituximab depletes B cells by targeting CD20, which is expressed by early B cells but not mature plasma cells.<sup>141</sup> Belimumab binds soluble BlyS, reducing B-cell survival.<sup>142</sup> SARS-CoV-2 mRNA vaccine mechanism depictions are modified from figures attributed to Cagigi/Loré<sup>135</sup> and Bettini/Locci,<sup>136</sup> licensed under CC by 4.0. Abs, antibodies; APCs, antigen-presenting cells; BlyS, B lymphocyte stimulator; CTLA, cytotoxic T-lymphocyte-associated protein 4; DCs, dendritic cells; GC, germinal centres; IL-4, interleukin-4; IFN, interferon; JAK, Janus kinase; LLPCs, long-lived plasma cells; LPN, lipid nanoparticle; MBC, memory B cells; MHC, major histocompatibility complex; MTX, methotrexate; Tfh, T follicular helper.

patients on TNF inhibitors fully vaccinated with BNT162b2 mRNA vaccine showed no significant difference in seroconversion rates compared with healthy controls.<sup>84</sup> Whether reductions in quantitative humoral responses are of clinical significance is unknown.

JAK inhibitors likely reduce antibody titres and have a mild effect on seroconversion, although the clinical importance of these observations is unknown and data are scant. The 10 patients on JAK inhibitors in the Deepak *et al* cohort had a greater than sixfold reduction in titres compared with controls (95% CI: 2.9 to 15.3,  $p < 0.05$ ).<sup>82</sup> 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.<sup>84</sup>

### 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<sup>89-92</sup> and myocarditis/pericarditis<sup>93-95</sup> after vaccination. There have additionally been observational reports of new-onset immune-mediated disease<sup>96</sup> and/or disease flares after SARS-CoV-2 vaccination,<sup>96,97</sup> which must be balanced against the risk of immune-mediated disease resulting from SARS-CoV-2 infection itself.<sup>98-100</sup>

The Furer *et al* cohort of rheumatic disease patients documented two fatalities postvaccination; one ANCA-vasculitis patient developed cutaneous vasculitis with subsequent fatal sepsis 3 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.<sup>84</sup> Small prospective studies thus far have not found an increased in underlying inflammatory disease activity measures after SARS-CoV-2 vaccination,<sup>84–87</sup> 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).<sup>101</sup> 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 titre of  $\geq 10$  IU/L is considered to be seroprotective.<sup>102</sup>

### Effect of DMARD therapy on vaccine efficacy

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

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

### Recommendations

In the USA, HBV vaccination is recommended for adults at high risk (table 1).<sup>12 61 106–108</sup> Ideally patients who require HBV vaccination should be vaccinated prior to starting DMARD therapy, particularly for high-risk patients starting rituximab.<sup>109</sup>

## HPV VACCINATION

### Background

Three HPV vaccines are approved; however, the 9-valent vaccine is the only HPV vaccine currently available in the USA. Women with rheumatic diseases on immunosuppressive therapies are at increased risk of HPV and cervical cancer; this has been particularly well described in systemic lupus erythematosus (SLE) but is seen in other inflammatory diseases.<sup>110–115</sup> 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, juvenile dermatomyositis, inflammatory bowel disease and SLE; in these patients, MTX and TNF inhibitors do not appear to impact postvaccination seroconversion rates.<sup>116–119</sup> Patients with SLE on combination mycophenolate mofetil and low-dose glucocorticoids show moderately reduced seroconversion rates for HPV6 and HPV18, but not for other subtypes.<sup>118</sup> Other DMARD therapies have not been evaluated in patients with rheumatic diseases.

### Recommendations

The Center for Disease Control (CDC) recommends HPV vaccination for all patients (regardless of sex) at age 11 or 12 up through age 26.<sup>12</sup> 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 antitetanus toxoid IgG concentrations 4 weeks postvaccination, where an antibody concentration of  $\geq 0.10$  IU/mL is typically considered seroprotective, however, an endpoint of fourfold increase in antibody concentration is also sometimes used.<sup>120</sup>

### Effect of DMARD therapy on vaccine efficacy

Rituximab reduces response to the tetanus vaccine, however, the degree of this reduction is inconsistent between studies.<sup>18 121</sup> Studies of abatacept,<sup>122 123</sup> JAK inhibitors<sup>53 120</sup> and TNF inhibitors<sup>121 124</sup> suggest a modest impairment in immunogenicity. IL-6,<sup>55</sup> IL-17<sup>55</sup> and IL-12/IL-23<sup>54</sup> 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. Patients with RA on rituximab + MTX and MTX monotherapy were able to mount similar rates of humoral response, defined as a greater than equal to fourfold rise in antitetanus IgG (39.1% vs 42.3%, 95% CI:  $-25.7$  to  $19.2$ ).<sup>18</sup> However, another study found that rituximab was associated with lower rates of protective antibodies titres ( $\geq 0.1$  IU/mL) compared with other patients with inflammatory disease or controls (73% vs 96%–100%) and only 9% of rituximab-treated patients had a greater than equal to fourfold rise in antibody titres.<sup>121</sup>

A study of patients with inflammatory bowel disease on TNF inhibitors found lower antibody titres relative to those on thiopurines or healthy controls ( $p < 0.001$ ), though average titres were still in the protective range.<sup>124</sup> Other data have shown similar antibody response rates in TNF-treated patients relative to healthy controls.<sup>121</sup> An uncontrolled study of subcutaneous abatacept found satisfactory tetanus vaccine response in 219 juvenile patients with idiopathic arthritis (regardless of MTX or concomitant glucocorticoids),<sup>122</sup> 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.<sup>123</sup> Delaying the tetanus vaccine to 8 weeks after abatacept improved response

rates close to that of healthy controls.<sup>123</sup> 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 antitetanus antibody concentrations,<sup>53</sup> while tofacitinib-treated patients with psoriasis mount a seemingly satisfactory response.<sup>120</sup> 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% to 68%) of those taking glucocorticoids versus 39% (95% CI: 28.9% to 51.1%) of those not taking glucocorticoids.<sup>53</sup>

Studies of patients with psoriasis on ustekinumab<sup>54</sup> and ixekizumab<sup>55</sup> did not find any change in postvaccination tetanus antibody response relative to untreated controls. Tocilizumab similarly does not appear to hamper antibody response to the tetanus vaccine.<sup>125</sup>

### 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.<sup>12</sup> Tetanus vaccination should ideally be done prior to starting rituximab therapy.

## YF VACCINATION

### Background

The YF vaccine is recommended to immunocompetent persons who live or travel to endemic areas.<sup>61 126</sup> However, this vaccine is live and is contraindicated in immunosuppressed patients including those receiving biologics and JAK inhibitors.<sup>41</sup> YF vaccine immunogenicity is measured by postvaccination neutralising antibody titres.

### 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 revaccinated (patients had primary immunity from a previous vaccine) while on biologics; these patients had lower, yet adequate antibody titres.<sup>127</sup> Another 17 patients on infliximab + MTX achieved satisfactory antibody levels in all but one patient.<sup>128</sup> Among 15 patients on MTX, all achieved seroprotection.<sup>129</sup> Patients on corticosteroids (mean: 7 mg/day, range: 5–20 mg/day), 18/34 of whom were vaccine naive, also appeared to have satisfactory titres.<sup>130</sup>

### Safety in patients with rheumatic diseases

Small studies suggest that the vaccine may be safer than previously thought for patients on MTX,<sup>127 129 131</sup> infliximab<sup>127 128</sup> and corticosteroids <20 mg/day.<sup>130</sup> A retrospective Swiss study of 92 patients on immunosuppressive medications (16 on MTX, 40 on corticosteroids, small numbers on other medications) who received the YF 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.<sup>131</sup> A prospective study of 15 patients on MTX ( $\leq 20$  mg/week) receiving a primary YF vaccine found slightly increased rates of YF RNA viraemia in MTX-treated patients relative to controls ( $p > 0.39$ ), however these levels were never of clinical significance.<sup>129</sup> In the study from Brazil above, 31 patients revaccinated on biologics had no adverse events.<sup>127</sup>

## Recommendations

The YF 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 summarised 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 postvaccination antibody titres, though most patients (particularly those on TNF inhibitors) still achieve seroprotective levels. Other anticytokine therapies, including IL-6, IL-12/IL-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 anticytokine therapies. Lastly, few clinical trials have directly evaluated strategies to overcome this issue, such as timing vaccines around DMARD dosing, or utilising 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 optimise vaccine response.

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