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Effect of DMARDs on the immunogenicity of vaccines

Yannick van Sleen¹✉, Kornelis S. M. van der Geest¹, Anke L. W. Huckriede², Debbie van Baarle²
& Elisabeth Brouwer¹✉

Abstract

Vaccines are important for protecting individuals at increased risk of severe infections, including patients undergoing DMARD therapy. However, DMARD therapy can also compromise the immune system, leading to impaired responses to vaccination. This Review focuses on the impact of DMARDs on influenza and SARS-CoV-2 vaccinations, as such vaccines have been investigated most thoroughly. Various data suggest that B cell depletion therapy, mycophenolate mofetil, cyclophosphamide, azathioprine and abatacept substantially reduce the immunogenicity of these vaccines. However, the effects of glucocorticoids, methotrexate, TNF inhibitors and JAK inhibitors on vaccine responses remain unclear and could depend on the dosage and type of vaccination. Vaccination is aimed at initiating robust humoral and cellular vaccine responses, which requires efficient interactions between antigen-presenting cells, T cells and B cells. DMARDs impair these cells in different ways and to different degrees, such as the prevention of antigen-presenting cell maturation, alteration of T cell differentiation and selective inhibition of B cell subsets, thus inhibiting processes that are necessary for an effective vaccine response. Innovative modified vaccination strategies are needed to improve vaccination responses in patients undergoing DMARD therapy and to protect these patients from the severe outcomes of infectious diseases.

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Key points

- Vaccines should ideally evoke efficient interactions between antigen-presenting cells and T cells and B cells; certain DMARDs disturb these interactions, leading to reduced vaccine responses and protection from infection.
- The immunogenicity of influenza and SARS-CoV-2 vaccines is often reduced in patients with rheumatic diseases, depending on the type of DMARD used during vaccination.
- A few DMARDs substantially inhibit responses to both vaccines (such as B cell depletion therapy or mycophenolate mofetil), whereas other DMARDs likely have no effect (including IL-6 inhibitors and hydroxychloroquine).
- The effect of some DMARDs (including TNF inhibitors, methotrexate and glucocorticoids) on vaccine responses could depend on the type of vaccine or DMARD dose used.
- The differential effects of DMARDs on vaccine responses are likely explained by the varying ways in which these drugs target disease and the functioning of antigen-presenting cells, T cells and B cells.
- Specific vaccine strategies, such as a drug holiday, should be considered for patients on each type of DMARD, depending on their effects on vaccine effectiveness and on controlling disease activity.

Introduction

Infectious diseases have a high global burden and are one of the leading causes of mortality worldwide¹. In the past decade, outbreaks of infectious diseases have increased, and because of the exponential growth of the human population and enhanced circulation of pathogens, the risk of novel infectious diseases is substantial². Additionally, the increased contact between humans and wild animals augments the risk of zoonosis³. All these factors have probably contributed to the SARS-CoV-2 pandemic. Even though the peak of this pandemic seems to have passed, resurgence of the virus owing to new variants is expected to occur in the coming years. Moreover, the risk of new epidemics and pandemics in the future remains high.

Vaccines provide the most efficient and safest interventions in the prevention and control of infectious diseases. All vaccines are based on the same basic principle: exposing the immune system to either an attenuated version or an immunogenic subunit of the pathogen, thereby generating an immune response that will protect the individual from becoming severely ill after infection⁴. Classical vaccines expose individuals to either whole inactivated or live-attenuated pathogens that have lost their virulence. More novel vaccine approaches include subunit vaccines, viral-vector vaccines, and, most recently, messenger RNA (mRNA) vaccines⁵.

Vaccines are particularly important to protect individuals at increased risk of developing severe disease from infections, including individuals with underlying immune deficits. Immunodeficiency can be a consequence of various factors, including the use of immunosuppressive drugs⁶. DMARDs are prescribed for the treatment of various immunopathological conditions, including most autoimmune disorders⁷. A wide range of different DMARDs are currently being used, each

targeting different parts of the immunological processes underlying these diseases⁸. DMARDs are selected on the basis of the type and severity of disease and other criteria such as age, the presence of comorbid conditions and the use of concomitant medication (Supplementary Boxes 1–3). Generally, DMARDs can be split into three types: conventional synthetic DMARDs that target a wide range of immunological processes, biological DMARDs that specifically target one protein (typically a cytokine, its receptor or a cell surface marker), and lastly targeted synthetic DMARDs, which mainly target the Janus kinase (JAK)–signal transducer and activator of transcription (STAT) pathway. Regardless of their therapeutic benefits, however, DMARDs are accompanied by the risk of a long list of severe adverse effects, including an increased susceptibility to infections such as influenza and SARS-CoV-2 (refs. 9–11). In addition, patients using certain immunosuppressive drugs (for example, high-dose glucocorticoids) are thought to have a delay in viral clearance that leads to prolonged SARS-CoV-2 infections¹².

Given the necessity for proper protection of these patients, the aim of this Review is to assess the effect of DMARDs on vaccine-induced immune responses. Given that influenza and SARS-CoV-2 vaccines have been investigated most rigorously, these vaccines are the main focus of this Review. In this Review, we first introduce the different vaccine platforms and the immunological responses after vaccination. Next, we provide an overview of clinical studies concerning the immunogenicity of influenza and SARS-CoV-2 vaccines in patients receiving DMARD treatment. Finally, we discuss the mechanisms that might underlie the effects of DMARDs on vaccine responses in patients with autoimmune disorders.

Vaccine-evoked immunity

Immune responses to vaccinations are complex and involve the participation of various immune cell subsets and a wide range of cytokines. Even in healthy people these responses can be highly variable; however, a number of common denominators are required for an effective response to vaccination. In this section, we discuss immune responses to vaccination as they occur in non-immunocompromised individuals, and the different types of vaccine platforms that are used to initiate these immune responses.

Immune response induction

The induction of immune responses, whether through infection or through vaccination, relies on an intricate interplay between innate and adaptive immune mechanisms¹³. Dendritic cells, the sentinels of the immune system, take up microbes or vaccine components in the periphery and transport them to nearby lymph nodes. Recognition of danger signals, such as pathogen-associated molecular patterns of the microorganism or adjuvants of the vaccine by pattern recognition receptors (PRRs), leads to the activation of dendritic cells, which in turn produce activation markers and cytokines.

The lymph nodes provide the microenvironment for the physiological interaction of dendritic cells and different subsets of lymphocytes that results in the induction of adaptive immune responses. Dendritic cells process internalized antigens to small peptides. Presentation of antigenic peptides on major histocompatibility complex (MHC) molecules of activated dendritic cells stimulates CD4⁺ and CD8⁺ T cells carrying the cognate T cell receptor (TCR) and induces their proliferation and differentiation to effector and memory T cells.

CD4⁺ T cells are important for the activation of CD8⁺ T cells and for the promotion of B cell maturation that is necessary for an effective

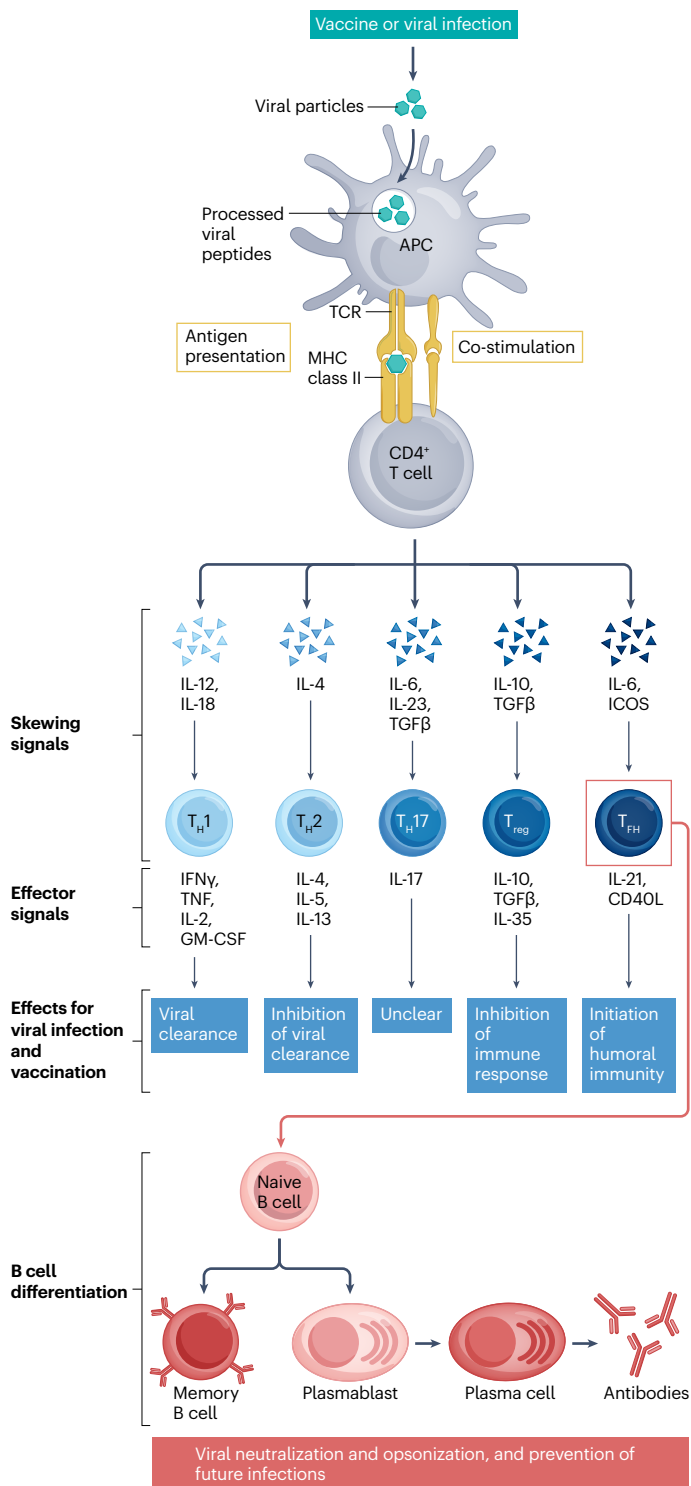


Fig. 1 | Immune responses after vaccination. Following vaccination, viral particles are taken up by antigen-presenting cells (APCs), which, upon activation, mature and migrate to secondary lymphoid organs to present the antigen. Antigen recognition by CD4⁺ T cells occurs through the T cell receptor (TCR) and antigen-containing MHC class II complex. Costimulatory molecules, such as CD28 and CD80–CD86, initiate further differentiation of CD4⁺ T cells into T helper 1 (T_{H1}) cells, T_{H2} cells, T_{H17} cells, regulatory T (T_{reg}) cells and follicular helper T (T_{FH}) cells. The lineage-specific differentiation is particularly dependent on the cytokine environment and the costimulatory molecules present. All subsets of CD4⁺ T cells have their own repertoire of cytokine production, and each subset has specific effects on viral infection and vaccine responses. In the context of vaccinations against influenza and SARS-CoV-2, CD4⁺ T cell skewing towards T_{H1} and T_{FH} cells is likely the preferred response, mediating viral clearance and the initiation of humoral immunity, respectively. Naive B cells, after antigen recognition and stimulation by T_{FH} cells, differentiate into memory B cells and plasmablasts and subsequently into plasma cells. These plasma cells produce antibodies that are particularly important in providing protection against infection.

cells), extracellular parasites (T helper 2 (T_{H2}) cells), and extracellular bacteria and fungi (T helper 17 (T_{H17}) cells)^{14,15}. In addition, regulatory T (T_{reg}) cells are required to maintain self-tolerance^{15,16}. Finally, follicular helper T (T_{FH}) cells are important cells for mediating humoral immunity. Efficient responses to viral pathogens, such as influenza virus or SARS-CoV-2, most likely require a particularly strong T_{H1} and T_{FH} response, whereas T_{H2} and particularly T_{reg} responses probably inhibit viral clearance¹⁷ (Fig. 1). CD8⁺ T cells are activated through dendritic cells, which present antigenic peptides on MHC class I molecules, after which these cells gain a cytotoxic function¹⁸. Even though CD8⁺ T cells are important in killing virus-infected cells, only some vaccine platforms are potent activators of these cells^{18,19}.

B cells produce antibodies that are essential for protection against almost all pathogens¹³. B cell activation requires the interaction of the B cell receptor (BCR) with its cognate antigen, often displayed on the surface of follicular dendritic cells. Cross-linking of BCRs alone can trigger the production of antibodies, but T cell help is needed for the formation of memory B cells¹⁵. Upon interaction of an antigen with the BCR, the antigen is taken up, processed and presented on MHC class II molecules to T_{FH} cells. Further interaction of B cells with T_{FH} cells via CD40–CD40L interactions and cytokines results in the full activation and proliferation of B cells. Some of the activated B cells differentiate into plasmablasts, which further develop into short-lived plasma cells that are characterized by a high proliferation rate but only produce antibodies for a short time span of 3–5 days. Other activated B cells enter the germinal centres, where they differentiate into long-lived plasma cells and memory B cells. In addition, the long-lived plasma cells undergo a process of maturation that results in the production of high-affinity antibodies. These plasma cells have a limited proliferative capacity but also have a very long lifespan, during which they keep secreting antibodies that can provide protection against infection¹³. The exact role of memory B cells in recall responses after vaccination remains unclear.

Vaccines

Vaccination is aimed at inducing protective immune responses against pathogens without causing the damage associated with infection. Upon encounter with the respective pathogen, these immune responses can prevent infection and/or colonization, thereby avoiding or mitigating the symptoms of the disease. Classical vaccine platforms involve either attenuated or inactivated pathogens or consist of pathogen-specific antigens, which can be proteins or – in the case

antibody response. CD4⁺ T cells are activated through the interaction of their TCR with antigenic peptides presented by MHC class II molecules on the surface of activated dendritic cells. Cytokines are essential in determining the differentiation of CD4⁺ T cells to certain subsets specialized in the defence of intracellular pathogens (T helper 1 (T_{H1}))

of bacterial pathogens – polysaccharides. In the past decade, so-called nucleic acid vaccines, in particular, viral vector-based and mRNA-based vaccines, have become available. These vaccines do not contain the antigen of interest but rather the genetic information for its synthesis by cells that take up the vaccine⁵. Upon vaccination, the antigens – either present in the vaccine or produced by recipient cells of the vaccine – are taken up by dendritic cells and transported to the draining secondary lymphoid organ.

Current influenza vaccines for the adult population are typical examples of classical vaccines. These vaccines are produced from influenza virus grown in embryonated chicken eggs or cultured cells and further processed to generate split vaccines, containing all viral proteins, or subunit vaccines, consisting mainly of the viral surface protein haemagglutinin. Split and subunit influenza vaccines do not usually contain an adjuvant, although adjuvanted formulations for the elderly or immunocompromised are also available²⁰. As most (adult) recipients of these vaccines have experienced several influenza infections during life, the vaccines evoke recall responses to conserved T cell and B cell epitopes, as well as primary responses to novel epitopes. Seasonal influenza vaccines are typically trivalent or quadrivalent, meaning that these vaccines contain antigens from three or four influenza virus strains, respectively.

Inactivated virus vaccines have also been used on a large scale for protection against SARS-CoV-2, mainly in China, Latin America and some African countries²¹. Moreover, a subunit vaccine consisting of the SARS-CoV-2 spike protein arranged on a nanoparticle is available²². Yet, few studies have assessed the effect of DMARDs on immune responses to these vaccines. Most SARS-CoV-2 vaccines used in Europe and the USA fall into the category of nucleic acid vaccines and consist either of viral vectors or mRNA encoding the spike protein of the SARS-CoV-2 (ref. 5). Viral vector vaccines make use of harmless viruses to deliver genetic information into human cells²⁰. During the initial phase of the pandemic, adenovirus-based viral vector vaccines, Ad26.COV2.S and ChAdOx1, were developed and showed strong effectiveness against severe SARS-CoV-2 infections²³. Even more recently, mRNA vaccines (that is, BNT162b2 and mRNA-1273) have been developed. The mRNA is packaged in lipid nanoparticles that are mainly taken up by antigen-presenting cells (APCs) such as dendritic cells. To avoid rapid degradation of the mRNA in the cytoplasm and overstimulation of the PRRs, both the BNT162b2 and mRNA-1273 contain modified uridine nucleotides (N1-Methylpseudouridine)²⁴. mRNA vaccines have been widely distributed and administered, showing impressive effects on the prevention of infection and severe disease²³.

Before a vaccine is approved for use in the general population, adequate vaccine performance in terms of reducing rates of infection or severity of disease must be demonstrated in clinical trials. However, assessing the performance of a vaccine in specific populations, such as in patients using DMARDs, is difficult, as the recruitment of a sufficiently high number of patients would be both laborious and time consuming. Accordingly, studies of vaccine performance in these populations often look at correlates of protection, most importantly the capacity of the vaccine to induce presumably protective immune responses. Usually, such studies measure the amount and the neutralizing capacity of serum antibodies, as antibody responses are considered particularly important in the early elimination and neutralization of pathogens²⁵. Generally, antibody concentrations correlate strongly with their neutralizing capacity, although this correlation depends on the extent to which the infecting pathogen deviates from the original. Indeed, the neutralization of novel SARS-CoV-2 variants requires

much higher concentrations of vaccine-evoked antibodies than the neutralization of the original variant^{26,27}. Additional, non-neutralizing antibody functions, such as their involvement in antibody-dependent cell-mediated cytotoxicity or complement activation, can be assessed by commercial assays, and should be considered when evaluating vaccine responsiveness.

Various forms of evidence emphasize the importance of cellular responses after vaccination²⁸. The golden standard for measuring T cell responses is the ELISpot assay, which quantifies the frequency of antigen-specific T cells producing a certain cytokine, typically IFN γ ; however, other robust methods such as an ex vivo IFN γ release assay, are also in use^{29,30}. Monitoring cytokine production or activation markers in specific T cells after vaccination using flow cytometry could reveal other aspects of the quality of response¹².

Vaccine responses depend on efficient interactions between APCs and T cells in the secondary lymphoid organs, resulting in the formation of memory T cells, preferably T_{H1} cells and T_{FH} cells, and memory B cells and plasma cells³¹. These responses could differ among individuals and might be compromised for various reasons, including the use of immunosuppressive therapy. Dysfunctional regulation of T helper cell skewing is thought to be essential in the development of autoimmune diseases, which could also lead to a hampered vaccine response in these patients^{14,32,33}.

DMARD effects on vaccine immunogenicity

DMARD use has been associated with more severe outcomes of influenza and SARS-CoV-2 infection in various large registry studies^{10,34,35}; hence, patients undergoing DMARD therapy are among those individuals who would benefit the most from vaccination. However, the question remains whether vaccines work as effectively in this group as in the general population. A substantial number of studies have therefore investigated the immunogenicity and efficacy of influenza and SARS-CoV-2 vaccines in patients on DMARD therapy (Table. 1).

Influenza vaccines

Several studies have investigated the effect of DMARDs on the induction of humoral immunity upon influenza vaccination. B cell depletion therapy (such as rituximab treatment) stands out as the most detrimental treatment for developing an adequate antibody response^{36–40}. For patients on this therapy, the time since the last infusion seems particularly important in determining whether the influenza vaccine response is effective^{38,40}. Ideally, vaccines should be administered at least 6 months after the last infusion, according to the European Alliance of Associations for Rheumatology (EULAR) recommendations⁴¹. Both the EULAR recommendations and the American College of Rheumatology (ACR) guideline, however, recommend no delay in influenza vaccination, owing to the seasonality of influenza^{41,42}. If possible, the next rituximab infusion should be delayed for at least 2–4 weeks after vaccination. T cell responses are less affected by rituximab treatment, but responses in treated patients still seem to be less robust than responses in healthy individuals receiving no rituximab treatment^{43,44}. Moreover, mycophenolate mofetil, azathioprine and abatacept also seem to affect humoral influenza vaccine responses in patients with autoimmune diseases^{36–39,45–49}. The data on the effect of glucocorticoids, methotrexate, TNF inhibitors and JAK inhibitors on vaccine responses are conflicting.

Concerning glucocorticoids, evidence of a negative effect of these drugs on the immunogenicity of influenza vaccines is still under debate³⁸. Possibly, the negative effect of glucocorticoid therapy on

Table 1 | The effect of DMARDs on the immunogenicity of influenza and SARS-CoV-2 vaccines

DMARD therapy	Impact on influenza vaccine immunogenicity ^{37–39?}	Impact on SARS-CoV-2 vaccines immunogenicity ^{10,38,59?}
Conventional synthetic DMARDs		
Azathioprine	Yes (humoral and cellular) ^{39,46,47}	Yes (humoral) ^{77,78}
Cyclophosphamide	Not enough information	Yes (humoral) ⁹⁰
Glucocorticoids	Unclear	Yes (humoral and cellular) ^{62,92,99a}
Hydroxychloroquine	No ^{39,59a}	No ^{75,104,105a}
Methotrexate	Unclear	Yes (humoral and cellular) ^{62,92,99a}
Mycophenolate mofetil	Yes (humoral) ³⁹	Yes (humoral) ^{74,77,114a}
Sulfasalazine	No ^{39a}	No ^{78,99,103a}
Biological DMARDs		
Abatacept	Yes (humoral and cellular) ^{45,48,49a}	Yes (humoral and cellular) ^{74,76,77a}
B cell depletion	Yes (humoral and cellular) ^{39,40,44a}	Yes (humoral and cellular) ^{61,63,64a}
IL-6 inhibitors	No ^{45,56}	No ^{75,76}
IL-17 inhibitors	No ^{230,231}	No ^{91,97}
IL-12–IL-23 inhibitors	No ^{232a}	No ^{76,91,97a}
TNF inhibitors	Unclear	Yes (humoral) ^{76,98,100}
Targeted synthetic DMARDs		
JAK inhibitors	Not enough information	Yes (humoral and cellular) ^{71,72,74a}

^aThis effect has a high degree of certainty, on the basis of the number of studies showing the effect, agreeability amongst the studies and sample sizes assessed.

humoral vaccine responses is dose dependent, with more detrimental effects occurring with daily doses of 7.5–10 mg or more than with lower doses^{39,42,46,50}. The studies that did not find reduced humoral responses in patients on glucocorticoid therapy tended to include patients receiving lower dosages and/or receiving a wider range of concomitant medication, which complicates the assessment of immunogenicity. In a systematic review of influenza immunogenicity studies in patients with RA and patients with systemic lupus erythematosus (SLE), the effect of glucocorticoids was only observed in patients with SLE, potentially owing to the typically higher glucocorticoid dosing used in patients with SLE than in patients with RA^{51,52}. Only one study has investigated the effects of glucocorticoids on the induction of influenza-specific T cells upon influenza vaccination. The patients with SLE receiving treatment with prednisone and/or azathioprine had less influenza-specific IFN γ -producing T cells, as assessed by ELISpot, than the patients not receiving these drugs⁴⁷. Furthermore, the patients on prednisone and/or azathioprine had fewer influenza-specific IFN γ -producing, TNF-producing and IL-2-producing CD4⁺ T cells, as assessed by flow cytometry. No influenza-specific CD8⁺ T cell responses were detected in any of the patients (irrespective of treatment) or in the healthy individuals. According to the ACR guideline, glucocorticoids should be tapered to <20 mg/day for most vaccinations, but not for influenza vaccination, owing to its seasonal nature⁴².

Numerous studies have investigated the effect of methotrexate on the immunogenicity of influenza vaccines, with varying results^{37,38}. Two large studies on responses to the 2009 pandemic H1N1 vaccine found an effect for methotrexate on antibody levels in a multivariate analysis^{39,53}. However, a meta-analysis of responses in patients with RA showed that methotrexate had no effect on vaccine immunogenicity³⁶. Additionally, another systematic review revealed a negative effect for methotrexate on vaccination responses, but only when assessing response rates to at least two influenza strains and not when assessing individual strains⁵⁴. Potentially, these discrepancies could be explained by the pooling of data from influenza vaccines that invoke mainly primary immune responses (such as the 2009 H1N1 monovalent vaccine) and the seasonal trivalent or quadrivalent influenza vaccines that mainly induce memory responses. Despite the relatively weak evidence for impaired vaccine responses with methotrexate, some data show that delaying methotrexate therapy right after vaccination for 2 weeks can improve humoral vaccine responses^{55,56}. The ACR guideline therefore recommends pausing methotrexate treatment for 2 weeks after vaccination⁴².

The effects of TNF inhibitors on responses to the influenza vaccines also vary in studies, but most studies found no negative effect^{37,38,54}. A 2018 meta-analysis of patients with RA concluded that TNF inhibitors probably do not reduce vaccine immunogenicity. However, a head-to-head comparison showed that patients on TNF inhibitor monotherapy had worse vaccine responses than patients on methotrexate therapy alone⁵⁷.

Influenza vaccination responses are probably not affected by hydroxychloroquine, sulfasalazine, IL-6 inhibitors, IL-12–IL-23 inhibitors or IL-17 inhibitors^{36–39}. Data on the effect of JAK inhibitors remain limited; possibly these drugs only affect vaccine responses when used in combination with methotrexate⁵⁸. Interestingly, one study found that hydroxychloroquine might counterbalance the negative effects of immunosuppressives on vaccine immunogenicity, although this finding requires further investigation and confirmation⁵⁹.

Primary SARS-CoV-2 vaccination

Since the approval of the first SARS-CoV-2 vaccines in late 2020, an important question has been whether the immunogenicity of the vaccines is similar in immunosuppressed patients and the general population. The effect of DMARDs on the immune response to SARS-CoV-2 vaccination could differ from that on influenza vaccination responses, because of the use of different vaccination platforms or the fact that a primary response rather than a memory response is needed for protection against SARS-CoV-2. The number of studies investigating the immunogenicity of the SARS-CoV-2 vaccination in patients undergoing immunosuppressive therapy (such as DMARD therapy) has steadily increased, with the majority of studies focusing on the humoral immune responses of these patients. Whereas some of these studies have investigated the effects in relatively homogeneous populations of patients with one type of disease, many other studies have assessed a mixture of patients with a wide range of diseases. Most studies assessed antibody concentrations and seroconversion, but a few studies also assessed the neutralizing capacity of the patients or SARS-CoV-2-specific cellular responses. The majority of studies investigated effects on mRNA vaccine responses, whereas data on the effects of DMARDs on whole virus or viral vector vaccine responses are scarcer. Nevertheless, studies of different vaccine platforms tended to find uniform patterns in terms of the effects of DMARDs.

As also observed for influenza vaccination, the use of B cell depletion therapy stands out as the most impactful medication that affects not only the absolute SARS-CoV-2 antibody titre post vaccination, but also often prevents seroconversion, indicating a total lack of humoral protection^{10,37,60–67}. In one study, a positive serological response after vaccination was associated with a lower total number of B cell depletion treatments, and an extended interval (more than 6–10 months) between the last treatment course and the vaccination⁶⁸. In contrast to vaccinated patients, a humoral vaccine response can occur in some B cell-depleted patients after a SARS-CoV-2 infection⁶⁹. Despite the substantial decrease in humoral responses, patients on B cell depletion therapy seem to have a relatively intact T cell response^{63,64,70}. Other DMARDs, used in smaller patient populations, that clearly affect humoral and/or cellular vaccine responses include JAK inhibitors, mycophenolate mofetil, abatacept, azathioprine and cyclophosphamide^{10,60,66,71–81}. Humoral responses are generally weakened but not completely lacking in these patients, indicating an increased risk of breakthrough infections.

In addition to the aforementioned therapies, most data suggest that humoral vaccine responses are also impaired in patients on glucocorticoid therapy^{10,37,62,75,77,82–87}. In these studies, the seroconversion rates after two doses of vaccine were typically unaffected by glucocorticoid therapy, unlike that seen with B cell-depleting therapy, but the antibody concentrations were reduced when compared with other patients or healthy individuals. The effects of glucocorticoid seem to be dose dependent, with higher doses (>7.5 mg) having more notable effects than lower dosages^{61,82,88,89}. Furthermore, a few studies showed that glucocorticoids had notable effects on the neutralizing capacity of the patients^{84,87,89}. Also, treatment with (higher dosages of) glucocorticoids was associated with lower frequencies of IFN γ -producing antigen-specific T cells^{77,82,85,86,90}.

Methotrexate use is also associated with reduced SARS-CoV-2 vaccine immunogenicity. Although a systematic review from 2021 indicated that the evidence for a negative effect of methotrexate was not yet strong enough, more recent studies have indicated that methotrexate has a moderate effect. These findings were mostly based on assessments of humoral responses, whereas the effect of methotrexate on cellular responses is less clear. A number of studies have investigated T cell responses by flow cytometry or ELISpot, finding no evidence of impaired immunity with methotrexate therapy^{82,90,91}. However, in two studies, methotrexate use was associated with impaired SARS-CoV-2-specific cytokine responses in T cells and a lack of increase in activation markers on CD8⁺ T cells when compared with responses in healthy individuals^{77,92}. As seen for influenza vaccination, pausing methotrexate therapy during vaccination seems to prevent impairment of immune response induction. This positive effect occurred across the different vaccine platforms, as primary immune responses to mRNA vaccines, viral vector vaccines and whole virus vaccines were all improved in patients who paused methotrexate during or directly after vaccination compared with those patients who remained on treatment^{93–96}. However, pausing methotrexate might increase the risk of disease flares or disease activity in patients with rheumatic diseases, although so far the evidence suggests that this strategy only mildly increases the incidence and severity of flares^{95,96}.

TNF inhibitors might also affect SARS-CoV-2 vaccine responses. In initial studies, including in a meta-analysis, the data suggested that these drugs had no effect^{37,60}. However, the meta-analysis was only based on seroconversion rates rather than on antibody concentrations. Furthermore, more recent studies that included larger groups of

patients found that TNF inhibitors had a moderate effect on humoral immunity, including effects on both antibody concentrations and neutralizing capacity^{66,74,76,97–100}. Interestingly, some data suggest that TNF inhibitor use is associated with a greater decay over time in antibody concentrations^{97,100,101}, as well as an increased occurrence of breakthrough infections¹⁰⁰. By contrast, cellular immunity is likely less affected by TNF inhibitors^{100,102}.

Excluding TNF inhibitors, DMARDs that specifically target cytokines seem to have no effect on SARS-CoV-2 vaccine immunogenicity. Patients on inhibitors of IL-6, IL-17 or IL-12–IL-23 signalling have typical humoral and/or cellular vaccine responses that are similar to those of healthy individuals^{10,60,71,77,91}. For both hydroxychloroquine and sulfasalazine, the available evidence suggests that not only is the vaccine response not impaired, but these responses are possibly even improved^{78,83,89,99,103–105}. Indeed, vaccine responses were impaired in patients undergoing immunosuppressive therapy, but not in patients who used hydroxychloroquine or sulfasalazine in combination with the immunosuppressive drugs^{99,104}. Finally, only one study has assessed the effect of leflunomide on humoral immunity after SARS-CoV-2 vaccination (in this case, vaccination with an inactivated whole virus vaccine) in a large group of patients, finding no evidence of a negative effect⁸⁹.

SARS-CoV-2 booster vaccinations

Data are also emerging on the effect of DMARDs on humoral and/or cellular immunity after SARS-CoV-2 booster vaccinations. However, in some of these studies, whether DMARDs affect the immunogenicity of the booster vaccination is difficult to determine. This difficulty arises from the cross-sectional design of these studies, in which only immunity after the booster vaccination is measured, without information on prior immunity. Even though these studies often report lower humoral and/or cellular immunity after booster vaccination in patients receiving DMARD therapy, whether this effect is because of a weaker primary vaccine response or an impaired reaction to the booster vaccine is difficult to discern^{106,107}.

Other studies did have a longitudinal design, theoretically enabling a comparison between the primary and booster response; however, not all the studies assessed the fold change increase in booster response compared with the primary response or the antibody concentrations post booster adjusted for concentrations prior to the booster⁷¹. The findings from these studies exhibit a range of diverse outcomes. B cell depletion therapy, particularly when given shortly before booster vaccination, still prevented seroconversion in a substantial proportion of patients^{66,69,108–110}. However, some of the patients still benefited from the booster vaccinations, particularly when there was a large gap between the last infusion and vaccination. Methotrexate also dampens the increase in humoral immunity after a booster vaccination, as assessed by studies of patients randomly assigned to pausing or not pausing methotrexate treatment during or after a booster vaccination^{61,94,111}. In two longitudinal studies comparing the effect of a number of DMARDs on booster vaccination^{61,110}, patients receiving treatment with methotrexate, JAK inhibitors and/or cytokine inhibitors (including TNF inhibitors) had stronger humoral booster responses than patients receiving treatment with glucocorticoids, abatacept or B cell-depleting agents. Other studies, however, have shown that after a booster vaccination, TNF or JAK inhibitor therapy was associated with lower humoral responses, and lower cellular responses in the case of JAK inhibitors, compared with the responses in healthy individuals^{71,112,113}. Finally, some data suggest that patients on DMARD

therapy who received the primary vaccination after a SARS-CoV-2 infection have a reduced boost of their humoral immunity compared with healthy individuals, although the power of these studies was too low to determine the effects of specific types of DMARDs^{65,114}.

Effect on primary versus memory vaccine responses

The current literature, as discussed in the previous section, suggests that some types of DMARDs have a larger effect on the response to SARS-CoV-2 vaccination than on the response to influenza vaccination. Glucocorticoids, methotrexate, TNF inhibitors and JAK inhibitors clearly affect primary SARS-CoV-2 vaccine responses but seem to have a lower effect on influenza vaccine responses. There might be several explanations for these differences. The vast majority of individuals have some immunity to influenza virus infection prior to vaccination (owing to previous infections and/or vaccinations), including long-lived plasmablasts and memory T cells and B cells¹¹⁵. Hence, influenza vaccination could be viewed as a booster of an previously induced immune response. The extent of overlap between this prior immunity and the newly initiated immune response might differ each year, owing to the different compositions of the influenza vaccine in use. Nevertheless, these responses probably differ from the primary SARS-CoV-2 vaccination responses in immune-naïve patients. In such circumstances, the complete immune response, including APC activation, antigen presentation, germinal centre formation and the differentiation of humoral and cellular immunity, has to develop from scratch, which introduces a wide range of processes open to influence by DMARDs. Interestingly, evidence showing reduced immunogenicity of the 2009 pandemic monovalent H1N1 influenza vaccine in patients using methotrexate support the idea that DMARDs affect primary vaccine responses more than memory vaccine responses^{39,53}. Of course, other factors, such as the different platforms typically used for influenza vaccination (subunit or split vaccines) versus SARS-CoV-2 vaccination (viral vector or mRNA vaccines) might also contribute to these differences. Additionally, responses to influenza vaccines could be more difficult to quantify than responses to SARS-CoV-2 vaccines, owing to the variation in prior humoral and cellular immunity, and the multiple antigens included in the vaccine.

Influence of DMARDs on immune responses

The typical immunosuppressive effects of DMARDs probably underlie the hampered vaccine response observed in patients on these therapies; however, the mechanisms do differ. Whereas some DMARDs have very specific effects, such as abatacept (CTLA4 co-stimulation blocker) or IL-6 inhibitors, other drugs rely on a wide range of mechanisms, such as glucocorticoids and methotrexate. Differences in these underlying mechanisms might also explain why some DMARDs impair vaccine immunogenicity, whereas others seem to have no effect. In this section, we discuss a number of routes in which DMARDs could affect the interaction between immune cells and thus interrupt an effective vaccine response.

Effects on APC initiation of vaccine responses

The importance of APCs in the initiation of vaccine responses is often overlooked; nevertheless, the number and functionality of these cells might underlie the hampered vaccine responses of patients on DMARD therapy. DMARDs have variable effects on numbers of APCs, depending on the type of cell and type of DMARD. High-dose glucocorticoids, for example, are associated with reduced numbers of myeloid and plasmacytoid dendritic cells, and non-classical monocytes, but not

with reductions in classical monocytes^{116–119}. Enhanced apoptosis of these cells probably underlies these reduced counts, as observed after treatment with glucocorticoids, methotrexate or TNF inhibitors^{118,120–126}. By contrast, higher frequencies of classical monocytes are predictive of reduced SARS-CoV-2 vaccine immunogenicity in patients with haematological malignancies¹²⁷, an association also seen for hepatitis B vaccination¹²⁸. This finding implies that higher frequencies of classical monocytes prevent an effective vaccine response. This higher frequency of classical monocytes might reflect a chronic state of immune system activation, as seen in people with an aged immune system (inflammageing), although this association could potentially also be explained by other associated factors such as comorbidities or treatment.

An essential process for vaccine responses is the detection of pathogens by PRRs, including Toll-like receptors (TLRs), which initiate the activation and maturation of APCs. Whereas subunit vaccines often rely on TLR agonists in the form of adjuvants, the activation of these TLRs typically occurs naturally in the case of mRNA-based vaccines (particularly activation of TLR7 and TLR8)^{129,130}. Activation of the PRRs initiates the maturation of APCs, a process resulting in the upregulation of MHC molecules, cytokines and other costimulatory molecules necessary for antigen presentation¹³¹. With aging, responsiveness to TLR stimulation in myeloid and plasmacytoid dendritic cells (such as reduced TLR-induced cytokine production) is typically decreased, and this decreased responsiveness is strongly associated with hampered humoral influenza vaccine responses in older individuals¹³². Similarly, reduced TLR responses are also observed in APCs following treatment with DMARDs in vitro^{119,133,134}, and various studies have reported increased numbers of dendritic cells with immature phenotypes in these patients^{125,133,135–138}. The impaired maturation of dendritic cells might also impair their capacity to migrate to the secondary lymphoid organs^{135,138,139}.

Repression of dendritic cell maturation is a well-known mechanism in cancer and is associated with the formation of tolerogenic-like dendritic cells. Hence, dendritic cells with this phenotype are also likely to be less capable of initiating strong immune responses after vaccination¹⁴⁰. Dendritic cells with a suppressive immune phenotype have also been associated directly with reduced vaccination response¹⁴¹. This suppressive phenotype of APCs in patients on DMARD treatment is characterized by defects in important vaccine response processes, such as the expression of MHC class II and costimulatory molecules, and the production of pro-inflammatory cytokines, particularly through inhibition of NF- κ B^{120,138,142–148}. The changes likely prevent efficient interaction of APCs with T cells. Indeed, tolerogenic-like dendritic cells can prevent the formation of T_H1 and T_{FH} cells, and steer the T cell response towards a T_{reg} phenotype^{138,149–159}.

Effects on T cell differentiation

DMARDs might also directly affect T cells, thereby disturbing the formation of cellular and humoral vaccine responses. A reduced number of T cells is associated with impaired immunity after SARS-CoV-2 vaccination in patients with autoimmune conditions^{82,90}. T_H1 cell responses after SARS-CoV-2 vaccination typically correlate with antibody concentrations in patients with rheumatic diseases^{82,160,161}. As IFN γ -producing T cells are not required to initiate humoral responses (which instead require a functional T_{FH} response), the observed impaired function in both T_H1 cell and humoral responses could be explained by a defect in their initiation by APCs. Nevertheless, APC-independent defects in T cells have been documented in *in vitro* experiments using

DMARDs. In sorted T cells, TNF inhibitors enhance the production of the anti-inflammatory cytokine IL-10 and delay their activation and proliferation¹⁶². Glucocorticoids and JAK inhibitors also have direct effects on T cells by preventing IL-12-induced and IFN γ -induced STAT phosphorylation as well as the expression of the T_H1 transcription factor T-bet^{149,156,163,164}. Moreover, the presence of glucocorticoids in cultured T cells reduces the production of IL-21, an important T_{FH} cytokine, which implies that the cells have a reduced capacity for stimulating humoral vaccine responses¹⁵⁷.

The induction of T_{reg} cells by DMARDs could prevent efficient vaccine responses. A number of DMARDs, including glucocorticoids and methotrexate but not abatacept, promote T cell skewing towards a T_{reg} cell phenotype^{152,153,158,165,166}. DMARDs might promote T_{reg} cell differentiation indirectly by affecting APCs, but could also have important effects on intrinsic T cell mechanisms. Glucocorticoids upregulate the expression of transforming growth factor- β (TGF β) receptor on T cells and methotrexate induces adenosine signalling in T cells^{120,158}; both processes enhance T_{reg} cell skewing. In congruence with their role in maintaining peripheral tolerance by suppressing immune responses directed against self-tissue, T_{reg} cells also inhibit the development of vaccine responses. Inhibition of these processes is likely mediated via stimulation of inhibitory checkpoint molecules (such as programmed cell death 1 (PD1) and cytotoxic T lymphocyte antigen 4 (CTLA4)) and the release of anti-inflammatory cytokine, particularly IL-10 but also TGF β and IL-35 (refs. 167,168). These inhibitory signals affect a wide range of processes relevant for vaccine responses, such as downregulation of MHC class II and CD28 expression, interference in the formation of germinal centres and prevention of T_{FH} differentiation¹⁶⁹.

Effects on B cell subsets

Circulating numbers of B cells and/or plasmablasts correlate well with antibody concentrations after vaccination^{73,82,90,170}. Indeed, the importance of these cells in mediating antibody responses is clearly evident from the lack of seroconversion after influenza or SARS-CoV-2 vaccination in patients undergoing B cell depletion therapy. In fact, only in those patients on B cell depletion therapies who still had measurable circulating B cells could a humoral vaccine response develop. Similarly, in patients on therapies that affect B cell numbers to a lesser extent, numbers of circulating plasmablasts or total B cells correlate with anti-SARS-CoV-2 antibody titres^{73,82,90}. Similarly, TNF inhibition is associated with a reduced frequency of influenza-specific memory B cells and plasmablasts, and these frequencies correlate with reduced humoral vaccine responses¹⁷⁰.

In these studies, whether these reduced counts are caused by direct effects of DMARDs on B cells, or whether a defect in the immune response prior to the formation of plasmablasts and memory B cells is responsible, remains unclear. For instance, glucocorticoids modulate the interaction between helper T cells and B cells by inhibiting the expression of CD40L on T cells¹⁷¹. CD40L-mediated co-stimulation of CD40 on B cells is an essential step in initiating numerous immunological pathways, including germinal centre formation, immunoglobulin isotype switching and somatic hypermutation, required for an effective humoral response and the formation of long-lived memory B cells¹⁷². By contrast, JAK inhibitors can have T cell-independent effects on plasmablast formation and antibody secretion via the impairment of IL-21 signalling¹⁷³. Furthermore, studies on glucocorticoid and methotrexate treatment showed that these DMARDs can induce the apoptosis of naïve or transitional B cells, but affect the transcriptional profile, rather than the apoptosis, of memory B cells^{174–178}. By contrast, TNF inhibitor

and abatacept therapy tend to reduce the number of memory B cells in particular^{170,179,180}.

Mechanisms of action of DMARDs

Various routes and mechanisms can prevent an optimal immune response to vaccination. DMARDs are a highly heterogeneous group of drugs that can have either strong immunosuppressive or relatively mild effects, can have highly specific targets or a broad range of targets, and can have long-lasting effects or short-term effects (and hence must be administered daily). In this section, we discuss the mechanisms by which each type of DMARD affects the immune responses in such a way that vaccine effectiveness is impaired.

B cell depletion therapy

The main B cell depletion therapies employ antibodies that target CD20 (such as rituximab), although anti-CD19 and anti-BAFF therapies have also been developed¹⁸¹. Importantly, CD20 is expressed by all major circulating B cell populations, but not by long-lived plasmablasts¹⁸¹, which has implications for vaccine responses. Recently administered anti-CD20 therapy typically prevents the formation of new humoral vaccine responses but does not eradicate prior humoral immunity, which is driven by the plasma cells. Studies have shown a strong association between B cell reconstitution and humoral vaccine response, and hence the timing of vaccination in these patients is particularly important⁶⁸. The surprising finding that patients on rituximab treatment infected with SARS-CoV-2 often show humoral responses⁶⁹ indicates that B cell depletion therapy might spare some B cells that reside in protected niches, such as the bone marrow. These spared B cells do not seem to participate in humoral responses to SARS-CoV-2 vaccination but apparently do respond to an infection with SARS-CoV-2. T_H1 cell and CD8⁺ T cell responses are not completely abrogated in these patients, stressing the fact that any vaccination is better than no vaccination in these patients^{43,44,64}. Nevertheless, owing to a reduction in B cell–T cell interactions in B cell-depleted patients, and subsequent processes such as type I IFN production, CD8⁺ T cell responses might also be impaired in these patients. Indeed, the expansion of influenza-specific and SARS-CoV-2-specific CD8⁺ T cells is reduced in B cell-depleted patients compared with healthy individuals^{44,64}. However, some data contrast with these findings, as in another study, some patients on B cell depletion therapy had higher CD8⁺ T cell responses after SARS-CoV-2 vaccination than healthy individuals⁷⁰. T_H1 responses might be less sensitive to B cell depletion than other T cell responses^{64,70}.

Glucocorticoids

Glucocorticoid signalling is mediated by intracellular glucocorticoid receptors¹⁸². The activation of the glucocorticoid receptor results in numerous changes in the transcriptome, in particular via binding of the receptor to glucocorticoid response elements on the DNA. Additionally, non-genomic glucocorticoid signalling also occurs, via accessory proteins that detach from the activated glucocorticoid receptor¹⁸³. Glucocorticoid signalling predominantly affects transcription factors, thereby altering the downstream signal transduction of inflammatory pathways including PRR signalling, suppressing the production and secretion of inflammatory mediators¹⁴² (Fig. 2).

Glucocorticoids affect various aspects of the immune system, including small molecule secretion, immune cell populations and cell-mediated immunity¹⁴². Particularly important in the modulation of immune responses by glucocorticoids is the prevention of NF- κ B and activator protein 1 (API) activation, which are essential for the

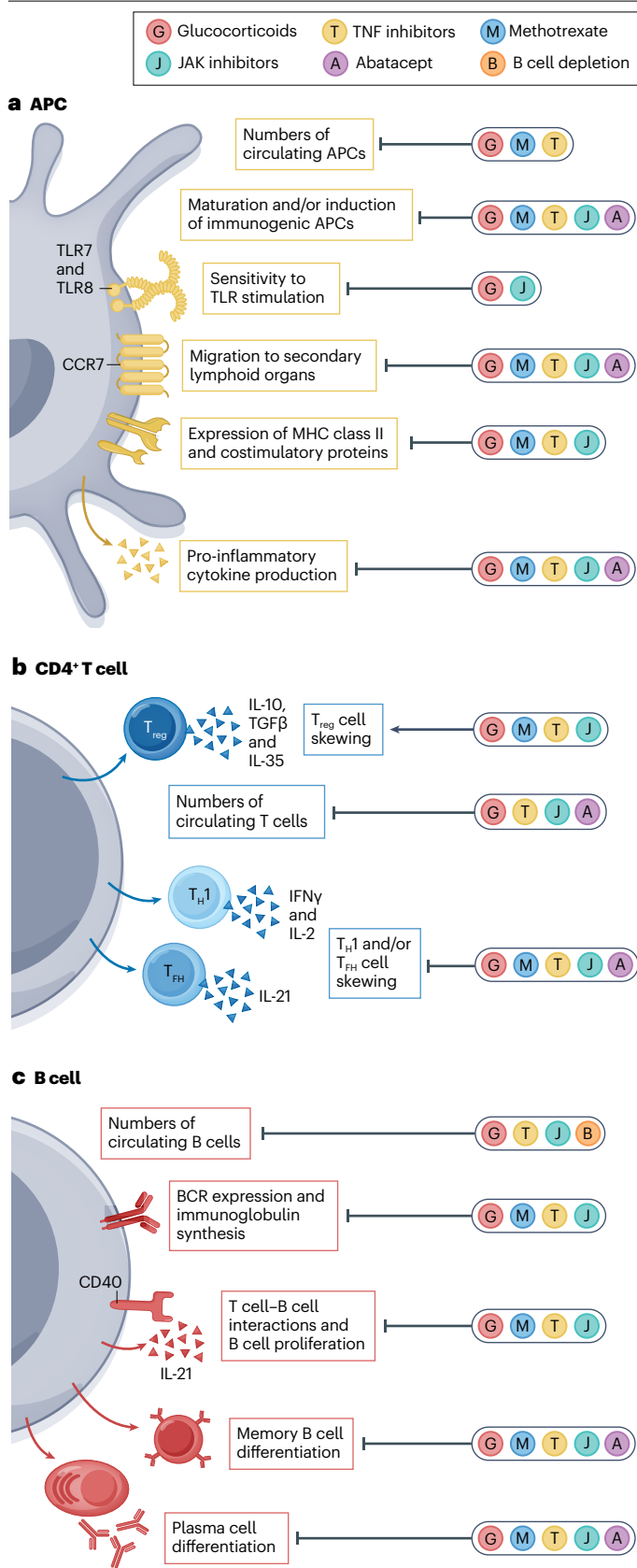


Fig. 2 | The effect of DMARDs on immunological processes important for vaccine responses. Interactions between antigen-presenting cells (APCs), T cells and B cells are essential for the development of robust humoral and cellular vaccine responses. Various data suggest that some DMARDs (including B cell depletion therapies, glucocorticoids, methotrexate, TNF inhibitors, JAK inhibitors, rituximab and abatacept) can disturb immunological processes involved in these responses, as summarized in this figure. For example, in APCs, some DMARDs can reduce the number of circulating cells, lower their sensitivity to stimulation, impair their maturation or migration, reduce the expression of important cell-surface proteins and suppress the production of cytokines. In T cells, various DMARDs can reduce T cell circulating numbers, inhibit skewing towards important T cell subsets (such as T helper 1 cells (T_{H1}) and follicular helper T (T_{FH}) cells) and promote the skewing towards others (such as regulatory T (T_{reg}) cells). Finally, in B cells, numerous DMARDs can reduce circulating B cell numbers, inhibit B cell interactions with T cells and subsequent B cell proliferation, downregulate immunoglobulin synthesis and disturb B cell differentiation into memory B cells and plasma cells. BCR, B cell receptor; TLR, Toll-like receptor.

maturation of APCs and the release of pro-inflammatory cytokines. In addition to reducing the number of dendritic cells, glucocorticoid treatment might also impair the migration of APCs towards secondary lymphoid tissues^{184–187}. Therefore, antigen presentation could occur less frequently and efficiently, hampering crosstalk between the innate and adaptive immune cells. Glucocorticoid-mediated effects on the APC phenotype and on T cells directly impair the differentiation of T cells towards T_{H1} and T_{FH} cells, reducing the expression of CD40L and increasing T_{reg} cell differentiation^{146,154–157,163,171}. B cells, particularly transitional B cells, are sensitive to glucocorticoid-induced apoptosis^{117,174,175,188,189}. In B cell cultures, glucocorticoids can downregulate components of the B cell receptor on B cells and reduce B cell synthesis of immunoglobulins^{176,190}. The effects of glucocorticoids on short-lived and long-lived plasma cells have not been studied extensively, although initiation of glucocorticoid treatment reduces the circulating number of these cells¹⁷⁴.

Methotrexate

The dose of methotrexate used for the treatment of rheumatic diseases is substantially lower than that used for the treatment of cancer, the initial indication for this drug¹²⁰. Therefore, mechanisms of action could differ between these two settings. The main immunomodulatory effect of methotrexate at these lower doses likely occurs through enhancement of adenosine release, which has an effect on a wide range of immunological processes, including activation of NF-κB in APCs, T cells and B cells¹⁹¹. Methotrexate stimulates the release of adenosine in T_{reg} cells in particular, but also in B cells¹²⁰. Other mechanisms of action for methotrexate have been postulated, such as the promotion of apoptosis sensitivity in T cells through the uncoupling of nitric oxide synthase, and the inhibition of pro-inflammatory signalling via the JAK–STAT pathway¹²⁰.

Methotrexate is typically not associated with a reduced number of total T cells and B cells, but is associated with a reduction in APC numbers^{120,192,193}. The latter effect is likely the result of both reduced haematopoiesis and maturation of APCs as well as enhanced apoptosis^{120–122,194}. Methotrexate also affects the transcriptome of APCs, although this drug seems to favour the suppression of the more pro-inflammatory granulocyte-macrophage colony-stimulating factor (GM-CSF)-skewed macrophages rather than macrophage colony-stimulating factor (M-CSF)-skewed macrophages¹⁹⁵.

The underlying mechanisms of methotrexate might overlap with that of TNF inhibitors, as TNF is one of the cytokines most potently suppressed by methotrexate^{195–197}. Methotrexate is postulated to inhibit T_H1 and T_{FH} skewing, but evidence for this effect is mostly lacking^{151,177}. Methotrexate can also directly affect B cells. For example, methotrexate use is associated with a reduction in frequency of transitional and naive B cells, cells of the early stages of B cell development in the blood, but not total memory B cells^{170,177,178}. Vaccine-specific B cell responses are probably also impaired with methotrexate therapy, as the expansion of plasmablasts following influenza and pneumococcal vaccination is dampened in patients with RA undergoing methotrexate therapy when compared with the expansion seen in patients not undergoing DMARD therapy or healthy individuals^{151,170}. Hence, methotrexate might preferably prevent humoral vaccine responses rather than T cell vaccine responses, and indeed studies in patients with GCA found that methotrexate use affected SARS-CoV-2 antibody responses, as assessed by antibody concentrations, but not T cell responses, as measured by ELISpot^{82,90}.

TNF inhibitors

Five TNF inhibitors are currently approved for the treatment of various autoimmune diseases and all target the cytokine TNF, preventing pro-inflammatory signalling via TNF receptors. In addition to attaching to and blocking the action of soluble TNF, the therapeutic antibody attaches to membrane-bound TNF, leading to recognition by the immune system and lysis or apoptosis of cells via the complement system or through the activation of Fc receptors on innate immune cells¹⁹⁸. Two TNF receptors exist – TNFR1 and TNFR2 – of which TNFR2 is particularly important for facilitating antiviral immune responses through the generation of CD8⁺ T cells¹⁹⁹. As TNF is such a pivotal cytokine, inhibition of TNF likely affects all the main players of vaccine immune responses. TNF signalling is particularly important for granuloma formation, suggesting that APCs such as macrophages are predominantly targeted by TNF inhibitors^{198,200}.

The important immunomodulatory effect of TNF inhibitors could be explained by TNF-mediated apoptosis of APCs^{123–125}. However, some data suggest that this therapy prevents IL-12 and IL-23 production rather than instigating apoptosis of APCs¹⁴⁴. Nevertheless, in patients on TNF inhibition therapy, immune interactions at the site of secondary lymphoid organs are disturbed, and the patients have substantially fewer and smaller germinal centres and follicular dendritic cell networks than healthy individuals^{179,201}. A developmental defect in dendritic cells that leads to reduced costimulatory molecule expression and T cell stimulatory capacity might underlie these disturbed germinal centre responses^{125,135,202,203}. Indeed, other studies have shown that T cell activation and subsequent cytokine production is reduced and anti-inflammatory T cell activity (such as IL-10 and TGFβ production) is enhanced in patients with RA on TNF inhibitors compared with patients with active RA or healthy individuals¹⁵³. Surprisingly, and in contrast to other DMARDs, paediatric patients with rheumatic conditions on TNF inhibitors have higher T_{FH} cell numbers than untreated patients²⁰⁴. Total numbers of memory B cells are low in patients being treated with TNF inhibitors, and are lower than in those patients being treated with methotrexate¹⁷⁹. TNF inhibition is also associated with a reduction in the number of influenza-specific memory B cells following vaccination, particularly 6 months later, resulting in reduced humoral influenza vaccine responses¹⁷⁰.

JAK inhibitors

Various JAK inhibitors are approved for the treatment of different autoimmune and rheumatoid diseases, which vary in JAK protein

specificity^{205,206}. These therapies comprehensively block the JAK–STAT signalling downstream of a wide range of pro-inflammatory cytokines, including TNF, IFNγ, IL-21 and IL-6. Consequently, pinpointing the exact mechanism by which JAK inhibitors impair vaccine responses is difficult. JAK inhibition reduces the differentiation of plasmablasts and T_H1 cells, possibly by changing the phenotype of APCs, but also has direct effects on B cells^{138,173,206,207}. JAK inhibitors seem to prevent the development of mature dendritic cells by steering the precursor cells towards a M1-like macrophage phenotype^{133,138}. Germinal centre reactions are consequently also impaired²⁰⁸. Potentially, recall immune responses are less impaired than primary responses with JAK inhibition, as these inhibitors seem to have less of an effect on the immunogenicity of influenza vaccines than of SARS-CoV-2 vaccines. Indeed, JAK inhibition impairs T_H1 cell polarization in vitro and in vivo but does not impair the differentiation of antigen-experienced T_H1 cells¹⁶⁴. Similarly, JAK inhibitors have a stronger inhibitory effect on the development of plasmablasts from naive B cells than on their development from memory cells¹⁷³.

Abatacept

An important costimulatory signal for T cells occurs via interaction of CD28 on T cells with CD80 or CD86 on APCs. CTLA4 is an inhibitory molecule, expressed mainly on T cells, that binds to CD80 and CD86 with greater affinity than CD28, thereby preventing CD28 costimulatory signalling and suppressing immune responses. Abatacept is a CTLA4–immunoglobulin fusion protein that mimics this inhibitory process²⁰⁹. T cells that are stimulated through MHC molecules without proper co-stimulation enter a state of anergy¹⁴. Subsequently, the differentiation of T cells into T_H1 cells and T_{FH} cells, but also T_{reg} cells, is diminished following abatacept treatment^{165,166,210}. This inhibition consequently affects germinal centre reactions, B cell processes and vaccine responses¹⁸⁰. As abatacept directly binds to APCs, these cells might also be affected. Indeed, abatacept treatment of monocytes results in diminished production of pro-inflammatory cytokines; however, this treatment is also associated with increased frequencies of myeloid dendritic cells in patients^{211,212}.

Azathioprine, cyclophosphamide and mycophenolate mofetil

Azathioprine, cyclophosphamide and mycophenolate mofetil are used for the treatment of various rare and severe autoimmune diseases. All three drugs have severe, immunosuppressive and cytotoxic effects that also prevent effective vaccine responses. Azathioprine impedes DNA and RNA synthesis and is therefore a strong inhibitor of leukocyte proliferation²¹³. Prevention of leukocyte proliferation, in addition to induction of T cell apoptosis, likely explains how this drug inhibits the development of cellular and humoral vaccine responses. Cyclophosphamide therapy results in long-lived immunosuppression by inhibiting proliferation and instigating cell death in lymphocytes²¹⁴. Patients on cyclophosphamide treatment have a long-lasting decrease in B cell numbers (including naive and memory B cell numbers)¹⁷⁸. Mycophenolate mofetil also prevents the proliferation of cells, and in particular lymphocytes, by inhibiting the formation of guanine nucleotides²¹³. Furthermore, this drug downregulates the expression of CD40L on T cells. Compared with patients on azathioprine, patients on mycophenolate mofetil had relatively high frequencies of circulating transitional and naive B cells, but much lower frequencies of plasmablasts²¹⁵. As seen for other DMARDs, mycophenolate mofetil is also capable of modulating the polarization of dendritic cells, resulting in tolerogenic dendritic cells that inhibit T_H1 differentiation²¹⁶.

Other DMARDs

Various other DMARDs, including IL-6 inhibitors, IL-17 inhibitors, IL-12–IL-23 inhibitors, hydroxychloroquine and sulfasalazine, are not associated with reduced immunogenicity of influenza and SARS-CoV-2 vaccines, despite the fact that these drugs modulate immune responses in such a way that they are effective in treating rheumatic and autoimmune diseases²¹⁷. IL-6, IL-23 and IL-17 are all associated with T_H17 responses¹⁴, which are important in these autoimmune diseases, but these T cells might not be needed for sufficient vaccine responses. IL-6, however, has additional roles, including the induction of T_{FH} cells, and IL-6 inhibition is associated with reduced plasmablast and memory B cell frequencies²¹⁸. IL-6 could be redundant for these processes, or local IL-6 production in germinal centres could be resistant to systemic IL-6 inhibition. Some studies have even reported that hydroxychloroquine and sulfasalazine have positive effects on vaccine responses^{59,99,104}. Hydroxychloroquine has a wide range of effects on the immune system, one of which is the inhibition of TLR signalling, resulting in impaired APC maturation^{219–221}. Potentially, this reduction of TLR-driven inflammation and clearance of viral material in the cytosol (that is, viral material from the vaccine), provides time for a broad immune response to develop. However, TLR-driven responses are also required for APC maturation, essential for the initiation of vaccine responses; therefore, the mechanisms behind these findings remain unclear.

Implications for patient care

In general, patients with systemic diseases are at an increased risk of a hampered vaccine response owing to the effects of disease activity and ongoing treatment. As systemic diseases and the available treatment options are heterogeneous, the disease, the organ manifestations, the activity of the disease and the intensity of the treatment must be taken into account in the vaccination scheme. Active systemic disease (including new manifestations or relapse of disease), impairment of vital organs owing to illness, use of high-dose and multiple immunosuppressants, comorbidities, neutropenia and lymphopenia all increase the risk of a hampered immune response¹⁰. In particular, ongoing induction therapy, reflecting high disease activity, puts patients at risk of an impaired immune response. In contrast to variations in disease activity, the type of rheumatic disease seems to have less of an effect on vaccine responses, which is also supported by findings that patients with low disease activity and not receiving DMARD therapy have similar vaccine responses to healthy individuals^{39,66,67,82,105}. Although age is a well-known risk factor for impaired vaccine responses^{222,223}, the effect of age on SARS-CoV-2 vaccination immune responses is relatively minor²³. Whether age or sex also interferes with the effect (or lack of an effect) of DMARDs on vaccination is difficult to assess.

Other important aspects of vaccination under DMARD therapy that require further investigation include the optimal timing of a vaccine or booster during DMARD therapy, the dose and adjuvants used, as well as the durability of the primary response to a new vaccine (such as with initial SARS-CoV-2 vaccinations) and the recall response upon a 'booster' vaccination (such as with influenza vaccines and SARS-CoV-2 boosters). Future studies should also explore the benefit of combining different SARS-CoV-2 vaccines and test additional mitigation strategies to overcome waning immunity after primary vaccination in older patients with active disease and on induction treatment. The risk of moderate-to-severe SARS-CoV-2 infection in patients undergoing immunosuppressive therapy, such as B cell depletion, cyclophosphamide and mycophenolate mofetil therapy, should be balanced against the risk of under-treating patients with severe rheumatic and musculoskeletal

diseases. The ACR recommends pausing methotrexate, JAK inhibitors, abatacept, mycophenolate mofetil and B cell depletion therapies during vaccination in certain patients with controlled disease; however, data to support this approach are scarce and more data are needed^{41,42}.

Certain DMARDs clearly affect the immunogenicity of vaccination. However, the effect of some DMARDs varies among different studies, particularly for glucocorticoids, methotrexate, TNF inhibitors and JAK inhibitors. The discrepancy among studies likely has several causes, such as the use of concomitant medication, the age of the patients, the different vaccine platforms used, the differences in timing of the assessment of vaccine responses, variations in outcome measures of humoral immunity (for example, seroconversion, antibody concentrations and neutralizing capacity) and variations in the type, duration and dosages of the DMARD used. Some studies showed only impaired immunogenicity for a combination of certain DMARDs, such as those involving TNF inhibitors, glucocorticoids and methotrexate^{36,60,66,72,78,89}. The discrepancy between studies seems to be particularly high for influenza vaccination. In these studies, the degree of prior immunity probably differs substantially depending on the year and location, which likely impacts which and how much each DMARD reduces the vaccine's immunogenicity.

A few considerations remain concerning certain DMARDs. Evidence from various studies suggest that, unless used at doses ≥ 7.5 mg per day, glucocorticoids do not seem to increase the risk of a worse vaccine response. Doses above this cut-off of (7.5–10 mg/day) seems to have more apparent effects, which is biologically notable as this concentration is approximately similar to the daily amount of endogenous adrenal glucocorticoid produced in healthy adults²²⁴. Long-term glucocorticoid treatment can cause adrenal insufficiency, in which endogenous glucocorticoid production is reduced and replaced by the oral glucocorticoids¹⁴². Therefore, doses above the cut-off should lead to genuinely increased glucocorticoid levels in the circulation. However, lowering or temporarily stopping treatment at the time of vaccination, which is possible for other drugs such as methotrexate⁹³, is unsafe for glucocorticoid therapy owing to the risk of adrenal insufficiency and return of disease activity. The EULAR guideline, therefore, recommends against this strategy⁴¹. As discussed in an earlier section, B cell depletion therapies should be timed carefully with vaccination. Monitoring of the number of circulating B cell subsets might help to guide treatment decisions, as these cells are required for the humoral, and potentially even the cellular (CD8⁺ T cell), vaccine responses. Finally, some evidence points at accelerated waning of (primary) vaccine responses in patients on certain DMARDs such as TNF inhibitors. Potentially, specific defects in developing memory responses, such as memory B cells and long-lived plasma cells, might underlie this defect. If more data confirm these findings, earlier timepoints might be considered for the administration of booster vaccinations in patients on these DMARDs.

Although this Review focuses on the effects of DMARDs on vaccine-induced immune responses, rather than real-life outcomes, various studies have also assessed the risk of (severe) breakthrough infections in patients on DMARDs. Interpreting the data of these studies, which mainly looked at SARS-CoV-2 breakthrough infections, is difficult owing to the possibility that the patients could have been more risk averse than the control population. Nevertheless, some DMARDs, particularly B cell depletion therapy, azathioprine and mycophenolate mofetil, were associated with higher hospitalization rates^{225,226}. However, even though the immunosuppressed patients were at a higher risk of break-through infection and hospitalization, the results varied in terms of the effect by immunosuppressant type:

one study found no differences in SARS-CoV-2 infection among the various types of DMARDs, whereas another found a specific effect for TNF inhibitors^{100,227}. Notably, a lower humoral immunity after primary vaccination is strongly associated with the risk of breakthrough infections in the general population^{228,229}. Therefore, vaccination strategies should be aimed at inducing strong humoral responses, as assessed by high antibody titres, and the effect of specific DMARD therapies on antibody titres is an important aspect to consider when determining the best strategy in particular groups of patients.

New and innovative studies are required to obtain more knowledge on if and how DMARDs affect different aspects of vaccination responses. Currently, most human studies have investigated DMARD effects by *in vitro* stimulation of DMARD-naïve immune cells with certain DMARDs to measure changes in cell function. Although this setting allows for controlled manipulation of immune cells, this approach potentially overlooks the extensive interactions that occur *in vivo* with circulating cytokines and with other cells such as endothelial cells. Also, these setups typically only allow the study of the short-term effects of DMARDs, which might be different from the effects in most patients on systemic DMARD therapy. The latter issue is likely also problematic in studies in which healthy participants are given short-term DMARDs to evaluate their effects. Finally, the interpretation of data from cross-sectional studies in patients requiring immunosuppressive medication could also be challenging. In these studies, associations between DMARD use and immunological changes might be obscured by the timing and route of DMARD administration, concomitant medication, differences in disease activity and other confounders. Potentially, long-term longitudinal studies in patients using DMARD monotherapy at different dosages and in treatment-free remission might provide more reliable data on the effects of each DMARD on different aspects of the immune system. However, even these types of studies have confounding factors such as changes in disease activity and ageing of the immune system.

Conclusion

Some, but not all, DMARDs influence immune responses in such a way that protective features of vaccine responses (such as humoral and cellular immunity) are impaired. Hence, vaccination, although still providing a certain level of protection in patients on DMARDs, is less efficient at preventing serious outcomes of infections in these patients compared with healthy individuals. Strong evidence points to impaired vaccine responses in patients on B cell depletion therapies, cyclophosphamide, azathioprine, mycophenolate mofetil and abatacept. Whether glucocorticoids, methotrexate, TNF inhibitors and JAK inhibitors impair vaccine responses could depend on their dosing, timing, vaccine platforms and whether the vaccine evokes a memory response rather than a primary vaccine response. Effective immune responses after vaccination require efficient interactions between activated, mature APCs and T cells and B cells, which then respectively develop into T_{H1} and T_{FH} cells and memory B cells and plasma cells. DMARDs employ a plethora of mechanisms to interact with and disturb these processes, leading to impaired humoral and cellular protection after vaccination. New vaccination strategies, such as the combination of different types of vaccination, accelerated booster vaccination and vaccination during a so-called ‘drug holiday’, have been and will be developed to improve protection after vaccination in patients with autoimmune diseases on DMARD treatment.

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Author contributions

Y.v.S. researched data for the article and wrote the article. All authors contributed substantially to discussions of content and reviewed and/or edited the manuscript before submission.

Competing interests

The authors declare no competing interests.

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