Vaccination against SARS-CoV-2 in patients with rheumatic diseases: doubts and perspectives

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Competing interests: none declared.

ABSTRACT

Since January 2020, the whole world has been facing the worst epidemic for a century. SARS-CoV-2 infection has so far caused more than one million deaths, with the only measures capable of containing the spread of the virus being social distancing, frequent hand washing, and the wearing of masks. Vaccine development was urgently needed and there are now more than 90 candidate vaccines being developed using different technologies. The European Medicines Agency has recently approved a second mRNA-based vaccine, but the introduction of vaccines has raised some doubts about patients with rheumatic disease, who are at high risk of infection because of disease activity and the therapies used to treat it.

The aim of this study was to investigate how vaccines may interact with the immune system and treatment of such patients, and how to monitor the post-vaccine antibody titres and T cell responses in order to assess their efficacy and safety.

Introduction

SARS-CoV-2 is a highly transmissible virus that has rapidly spread from China to the rest of the world since January 2020, causing the worst pandemic for a century. Data from Johns Hopkins University of Medicine indicates that it has so far infected more than 84 million people and killed 1,838,982.

The risk of developing severe complications or death is greater among older patients and those with co-morbidities such as pre-existing respiratory or cardiovascular conditions, diabetes, and rheumatic disease, but there are conflicting data concerning the real incidence of SARS-CoV-2 infection in patients with rheumatic diseases (RMD) (1). In one study of 458 patients, thirteen reported symptoms suggesting SARS-CoV-2 infection, of whom only one of the seven patients who underwent a nasopharyngeal swab test developed severe complications. The prevalence of SARS-CoV-2 infection in this study was therefore 0.22% (0.01–1.21%), which is comparable with that observed in the general population of Tuscany (0.20% [0.20–0.21%]; p=0.597) (2). However, data from a study using a chemiluminescence serological test (3) in the same geographical area found an estimated odds ratio (OR) of 3.01 (95% CI 1.13–8.09; p=0.047) (4). Furthermore, registry data and meta-analyses have shown that the incidence of infection is greater among patients with RMD, that there is a possible association with a prednisone dose of >10 mg/day, and that there is no difference between patients treated with biological or targeted disease-modifying anti-rheumatic drugs (b-DMARDs and ts-DMARDs) (5-6). A retrospective study conducted by the Italian Society of Rheumatology found that 34.1% of 232 patients hospitalised because of COVID-19 had rheumatoid arthritis (RA) and 26.3% ankylosing spondylitis (AS) (7), thus confirming that disease activity status and immunosuppressive treatment places RMD patients at high risk of SARS-CoV-2 infection.

More than 90 candidate vaccines are being developed using various technologies, including recombinant protein-based vaccines, replicating or non-replicating viral vector-based vaccines, DNA vaccines, mRNA vaccines, live attenuated vaccines, and inactivated virus vaccines (Fig. 1). However, their introduction raises some questions about their use in patients with RDM:
1. How do the vaccines work on the immune system?
2. What may be a safe vaccine for patients with RMD?

3. How might DMARDs, b-DMARDs and ts-DMARDs interfere with the vaccines?

4. How can the vaccination of RMD patients be monitored?

1. How do the vaccines work on the immune system?

The Italian Ministry of Health has planned to purchase the following vaccines for the first quarter of 2021: BNT162b2 from Pfizer and BioNTech, mRNA-1273 from Moderna, and ChAdOx1 nCoV-19 from NIHR Oxford Biomedical Research and AstraZeneca. The immune response after immunisation with a conventional protein antigen absorbed by dendritic cells, which are activated by distress signals via pattern recognition receptors (PRRs) in the adjuvant, is transferred to the draining lymph node, where the presentation of vaccine protein antigen peptides by MHC (Major Histocompatibility Complex) molecules activates T cells via T cell receptors (TCRs). In combination with signalling (via soluble antigen) through B cell receptors (BCRs), T cells drive the development of B cells in the lymph node, and T cell-dependent B cells assure the maturation of the antibody response, increase antibody affinity, and induce antibodies against different isotypes. The production of short-lived plasma cells that actively secrete antibodies specific to the vaccine protein leads to a rapid rise in serum antibody levels over the following two weeks. Immune memory is mediated by memory B cells that are also produced, and long-lived plasma cells, which can continue to produce antibodies for decades, are transported to bone marrow niches. CD8$^+$ memory T cells can proliferate rapidly when they encounter a pathogen, and CD8$^+$ effector T cells are important for the elimination of infected cells (8).

BNT162b2 is a lipid nanoparticle-formulated, nucleoside-modified RNA vaccine that encodes a prefusion stabilised, membrane-anchored, full-length SARS-CoV-2 spike protein and elicits RBD-binding IgG and neutralising antibodies. Twenty-one days after the first vaccine dose, geometric mean titres (GMTs) of RBD-specific IgG range from 534 U/
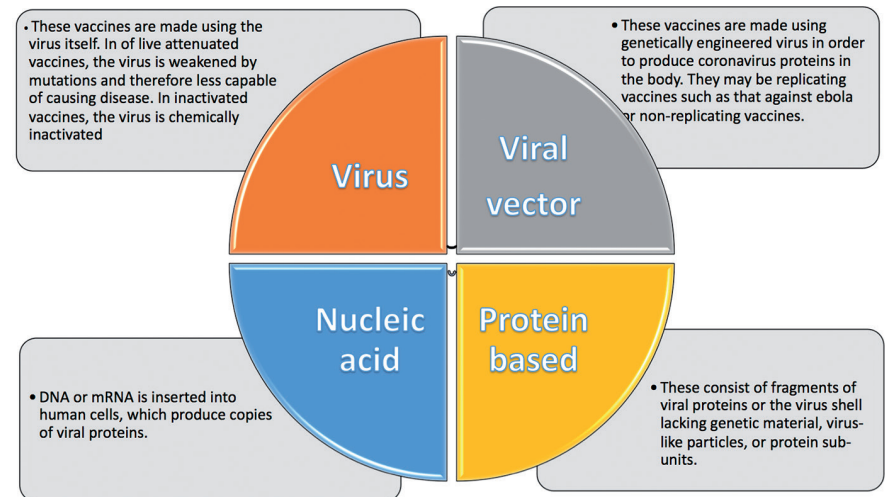

Fig. 1. Different technologies used to develop vaccines against SARS-CoV-2.

mL to 1778 U/mL, and are similar to or higher than those observed in a human convalescent serum panel. Two weeks after the second dose, GMTs of neutralising antibody are 1·9 times higher than those of the panel after a 10 µg dose and 4·6 times higher after a 30 µg dose, thus suggesting the presence of antibody affinity maturation (9-10). BNT162b1 also elicits CD4+ type 1 helper T (Th1) cell responses and strong interferon-γ and interleukin-2-producing CD8$^+$ cytotoxic T-cell responses (11).

Moderna and the American National Institutes of Health have jointly developed the mRNA-1273 vaccine, which consists of sequence-optimised mRNA encoding the spike glycoprotein encapsulated in lipid nanoparticles (12). At a dose of 100 µg, mRNA-1273 produces high levels of binding and neutralising antibodies that decline slightly over time, but remained high in all of the trial participants three months after a booster vaccination (13). By day 119, the GMT was 235,228 (95% CI 177,236–312,195) in the participants aged 18–55 years, 151,761 (95% CI 88,571–260,033) in those aged 56–70 years, and 157,946 (95% CI 94,345–264,420) in those aged >71 years (14). In response to S-specific peptide pools, the vaccine elicits a strong CD4 cytokine response involving Th1 cells: tumour necrosis factor (TNF) α responses are greater than interleukin-2 responses, which are greater than interferon-γ responses (15).

Oxford University in the UK and AstraZeneca have developed a chimpanzee adenovirus-vectored investigational vaccine (ChAdOx1/AZD1222) encoding the spike glycoprotein of SARS-CoV-2 (16). Humoural responses at baseline and up to one year after the booster have been assessed using a standardised in-house enzyme-linked immunosorbent assay (ELISA), a multiplex immunoassay, and a live SARS-CoV-2 microneutralisation assay (MNA80), and cell responses have been assessed using an *ex-vivo* IFN-γ enzyme-linked immunospot assay. Neutralising antibody titres after the booster dose have been found to be similar in all age groups (median MNA80 levels on day 42 in the standard-dose groups were 193 [IQR 113–238] in the subjects aged 18–55 years; 144 [119–347] in those aged 56–69 years; and 161 [73–323] in those aged ≥70 years (p=0·40). Fourteen days after the booster dose, 208 (>99%) of the 209 boosted trial participants had neutralising antibody responses. T-cell responses peaked 14 days after a single standard dose: a median of 1187 spot-forming cells [SFCs] per million peripheral blood mononuclear cells [IQR 841–2428] in the participants aged 18-55 years; 797 SFCs [383–1817] in those aged 56–69 years; and 977 SFCs [458–1914] in those aged ≥70 years (Fig. 2) (17).

2. What may be a safe vaccine for patients with RMD?

Despite the risk of infection in patients with RMD, pneumococcal pneumonia, influenza, and shingles vaccination rates are not optimal. In the United States,
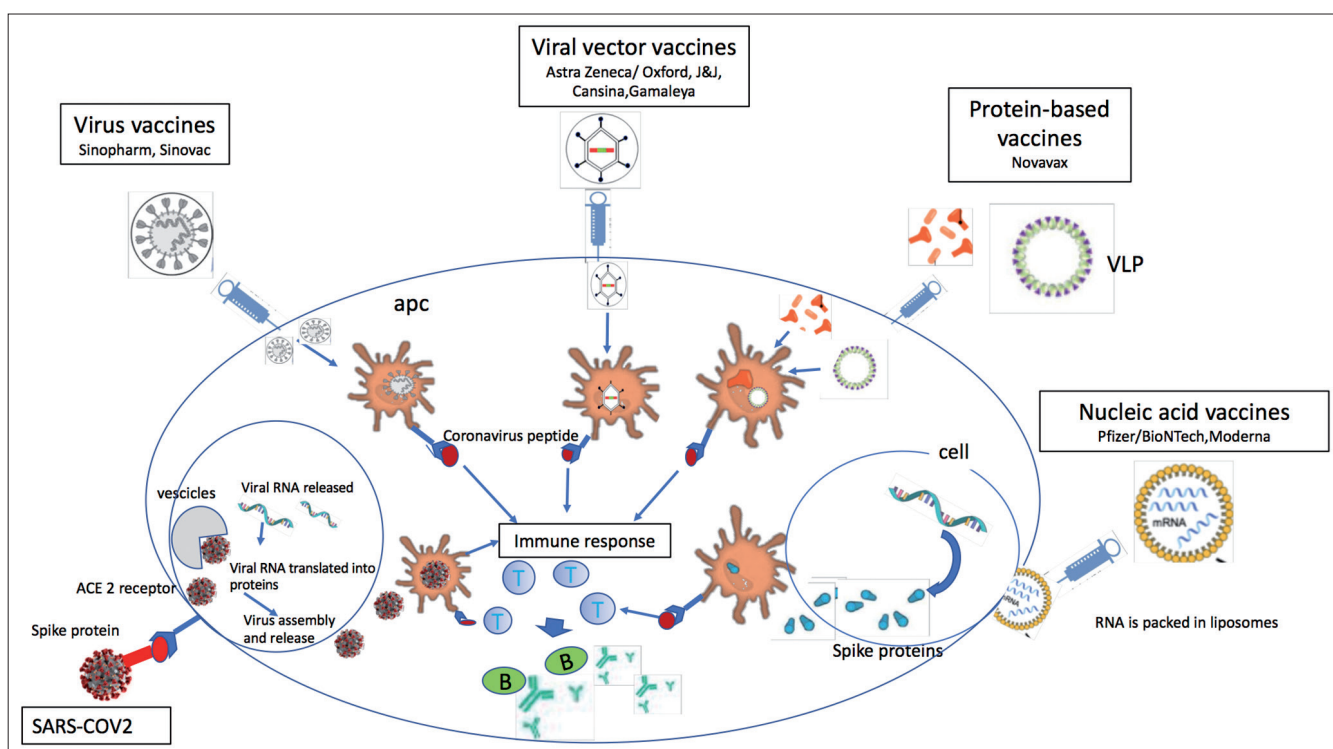
Fig. 2. How different types of vaccines and SARS-CoV-2 stimulate an immune response.
After the binding of the viral surface spike protein with a human cell receptor, the viral membrane fuses with that of the human cell, thus allowing viral genome to enter the cell. Once inside, the viral RNA is translated and more viruses are replicated. Antigen-presenting cells (APCs) ingest the virus and display the viral peptide, consequently activating T helper cells, which stimulate B cells to make antibodies against the virus. A similar immune response occurs with the administration of the different types of vaccine.

only 28.5% of RA patients are optimally vaccinated against pneumococcal pneumonia and 45.8% are optimally vaccinated against influenza (18-19); vaccination against shingles is even less frequent, with 2012 estimates suggesting that only 4.0% of RMD patients aged >60 years had been vaccinated (20).

Anaphylactic reactions to BNT162b2 and mRNA-1273 have been observed, especially in subjects with a history of allergies, and a recent review suggests that polyethylene glycol (PEG) 2000 in the lipid film of the two vaccines plays a pathogenetic role. It is also assumed that IgE-mediated mechanisms and those linked to the activation of tryptase and complement may be involved. The polysorbate 80 contained in the excipients of ChAdOx1 nCoV-19 may also lead to the same mechanism (21). PEG is an attractive means of developing nanoparticle-based cancer treatments because it endows the nanoparticles with extended-circulation properties. Recent studies have shown that the intravenous injection of PEGylated liposomes (SLs) or PEGylated

lipoplex (PLpx) can elicit an anti-PEG immunoglobulin (IgM) response in a T cell-independent manner (22), and anti-drug antibodies (ADAs) such as anti-certolizumab and anti-pegol antibodies have been demonstrated in RA patients using a bridging ELISA (23). Patients with immunodeficiency and autoimmune diseases were included in the trial of BNT162b2, but the data have not yet been published (9-10).

Antibody response is an important component of protective immunity during SARS-CoV-2 infection (24). Heterotypic (non-neutralising) antibodies may facilitate viral entry into cells by interacting with Fc receptors or complement, and this process could lead to the activation of macrophages, monocytes and B cells, and the production of IL-6, TNF-α and IL-10 even in the absence of active viral replication in immune cells (25).

Cases of vaccine-induced, antibody-dependent enhancement have been reported after the use of formalin-inactivated vaccines against respiratory syncytial virus and measles, and after the use of

a vaccine against dengue virus. (26-28), and concerns have therefore been raised about potential antibody-dependent enhancement after vaccination with a COVID-19 vaccine (29). Furthermore, the risk of Fc-mediated antibody-dependent enhancement receptors may be increased by mutations in SARS-CoV-2 spike glycoprotein that may weaken the antibody response of the primary host. Monocytes, macrophages, and B cell infections may affect numerous tissues as a result of subsequently unstable virus-antibody complexes leading to extensive apoptosis of immune cells and the production of inflammatory cytokines (30). An antibody-dependent infection study of the human macrophages of SARS-CoV-1 demonstrated the role of anti-spike glycoprotein IgG in immune cell infection, and antibody-dependent enhancement is activated downstream signalling pathways of FcγRII receptors (31-33).

Moreover, the fact that the new vaccines were released much more quickly than the usual 12–15 years (34) has raised considerable concern, especially

among non-experts. The clinical trial stages for classical and COVID-19 vaccines are well illustrated in the review by Calina *et al*. (35). The shorter approval time can be explained by the fact that research into RNA vaccines started some years before the advent of COVID-19, a large number of people were working on the project, and large amounts of money were given to research in a very short time. Further time was saved because, in comparison with traditional trials, regulatory agency assessments of the results obtained were made as the data were produced and not upon the completion of all of the studies, as is usually the case. Consequently, all of the stages laid down in research protocols to investigate the safety and efficacy of the vaccines were respected.

3. How might DMARDs, b-DMARDs and ts-DMARDs interfere with the vaccines?

Patients with rheumatic or inflammatory bowel diseases (IBDs) may be at higher risk of infection not only because disease activity, co-morbidities, immunosuppressive drugs including glucocorticoids (GCs), DMARDs, conventional synthetic DMARDs (cs-DMARDs), b-DMARDs, ts-DMARDs, and the biological agents currently available for treating patients with IBD are all considered risk factors for infective complications, but also because there are risks inherent to the individual diseases and their treatments (36).

There are currently no published data concerning SARS-CoV-2 vaccinations in patients with RMD, but there data concerning influenza, pneumococcus and shingles vaccines. The immunogenicity of influenza vaccine is evaluated on the basis of haemagglutinin inhibition antibody titres, and a titre of at least 1:40 is considered protective (37). The majority of studies that have evaluated the effect of methotrexate (MTX) on vaccine immunogenicity suggest that haemagglutinin inhibition antibody titres are similar or slightly lower in MTX-treated patients, and that the proportion of patients reaching protective titres is generally similar in patients taking DMARDs and control

RA patients (36), and these data have been confirmed by a meta-analysis of five studies (38).

Two studies of 254 subjects (122 RA patients and 132 healthy controls) have examined MTX exposure and 6B and 23F pneumococcal serotype responses, and found that MTX exposure was associated with a reduced vaccine response (39, 40). Three studies have examined the effect of TNF inhibition on pH1N1 influenza responses and combined the results with seasonal influenza H1N1 responses: TNF inhibition was not associated with reduced SP seroprotection responses to H1N1, H3N2, or B strain (41-43). Two studies of 273 subjects (141 RA patients and 132 healthy controls) have assessed 6B and 23F pneumococcal serotype responses after exposure to TNF inhibition, and found no significant difference the two groups (39, 40). Some data concerning abatacept (ABA) indicate a significantly worse humoral response to H1N1 vaccination in ABA-treated patients than in age-matched MTX-treated patients (44), whereas another study found conserved responses to influenza vaccine in 49.5% of 296 patients exposed to ABA (45). A significant reduction in antibody response rates for seroconversion (SC) against pneumococcal 6B and 6B / 23F was observed in ABA-exposed subjects compared to MTX control groups (46). In contrast, a conserved SP response has been described to PPV vaccination 23 with 55.4% of patients exposed to ABA having an adequate response to treatment (45). Appropriate humoral responses to pH1N1 vaccination have been observed in patients treated with tocilizumab (TCZ) (47), but a comparative study of TCZ monotherapy and combined MTX and TCZ treatment found that the latter led to an attenuated response to the pH1N122 vaccine (48). TCZ monotherapy is not associated with a reduced response to the PPV23 vaccine (49), but its combination with MTX has can blunt combined 6B and 6B/23F serotype responses (50). About two-thirds of patients receiving long-term baricitinib treatment showed humoral and functional responses to the PCV-13 vaccine, but

less robust responses to tetanus toxoid vaccine (TTV); the PCV-13 response was not reduced in those taking concomitant corticosteroids (51). In one study, humoural responses (varicella zoster virus [VZV] with a specific IgG level determined by the immunosorbent assay linked to the glycoprotein enzyme) and cell-mediated responses (enumeration of specific T cells for VZV, as determined) were evaluated from the test linked to the immunospot enzyme). Patients who initiated tofacitinib (TOF) treatment 2–3 weeks after receiving Live-Zoster-Vaccine (LZV) exhibited LZV-specific, cell-mediated, and humoural VZV immune responses similar to those seen in placebo-treated patients; vaccination appeared to be safe in all patients (52). Two studies have evaluated humoural responses to trivalent influenza vaccine, both of which defined a humoural response as a 4-fold increase in at least two of three influenza antigens five weeks after vaccination: in randomised TOF-naive patients, combined TOF + MTX therapy was associated with a worse humoural response than placebo, TOF or MTX alone; the temporary withdrawal of TOF from one week before to one week after vaccination had no significant effect on responses. The TOF + MTX combination was associated with a reduced humoural response to the PPV23 vaccine in comparison with placebo, TOF or MTX alone, with the temporary withdrawal of TOF from one week before to one week after vaccination having little effect on the response (53).

Although it is thought that most autoimmune diseases are mediated by CD4^{+} T cells or antibodies, many respond to CD20-reducing antibodies that have a limited effect on CD4 and plasma cells. These antibodies include rituximab, oblinutuzumab and ofatumumab, which are approved for the treatment of cancer and RA and used for the off-label treatment of a large number of other autoimmune diseases, and ocrelizumab, which is used to treat multiple sclerosis. On the basis of the already known and emerging biology of autoimmunity and COVID-19, it has been hypothesised that B cell depletion

does not necessarily expose people to serious SARS-CoV-2-related problems, but could inhibit protective immunity following the infection or vaccination (54), although drug-induced inhibition of B cells (which control at least some autoimmunity) would not affect the innate and CD8 T cell responses that are central to the elimination of SARS-CoV-2, or the hypercoagulation and innate inflammation that cause severe morbidity. This is clinically supported by the fact that most people infected with SARS-CoV-2 or CD20 autoimmunity have recovered. However, on the basis of B cell repopulation kinetics and vaccine response data from published studies of rituximab and ocrelizumab (NCT00676715, NCT02545868), it is likely that protective neutralising antibodies and vaccination responses will be attenuated until naive B cell repopulation (55), thus suggesting that interrupting the administration of these drugs may control the inflammatory disease while allowing for effective vaccination against SARS-CoV-2. There are currently no recommendations on how to vaccinate for SARS-CoV-2 in patients with rheumatic diseases but the ACR has proposed some safety for those with RNA and for vectors (56). There is also a lack of data on vaccination in subjects who have already had COVID-19. A potential barrier to antibody-based vaccines and therapies is the risk of exacerbating the severity of COVID-19 by antibody dependent enhancement (ADE). ADE can increase the severity of multiple viral infections, including other respiratory viruses such as respiratory syncytial virus (RSV) and measles. ADE in respiratory infections is included in a broader category named enhanced respiratory disease (ERD), which also includes non-antibody-based mechanisms such as cytokine cascades and cell-mediated immunopathology (57). The role of the rheumatologist in the management of SARS-CoV-2 infection was central in the first months of the infection, for the pathophysiological knowledge of the cytokine activation syndrome (58) and its treatment with rheumatological drugs (steroids, hydroxychloroquine, tocilizumab, anakinra) (59), in the future we will have to know how to manage biological and immunosuppressive therapies as a function of vaccination and monitoring the patient's immunity (60).

4. How can the vaccination of RMD patients be monitored?

Vaccine-induced protective immunity should be assessed by evaluating humoural and cell immune responses to COVID-19 antigens. As the T cell response lasts longer than the humoural response, it may be considered the best sign of successful post-vaccination immunity, and a number of authors have recently stated that any vaccine against SARS-CoV-2 should be designed to induce virus-specific T cells rather than antibodies alone (61-62). Laboratory searches for broadly specific cell responses to more than just the spike protein should concentrate on $CD8^+$ and $CD4^+$ T cell responses.

The human IFN-γ release assay has been used to investigate specific T-cell responses to vaccination. Pools of peptides from a range of viral proteins, including spike, nuclear and membrane proteins can be used to stimulate fresh peripheral blood mononuclear cells (PBMCs) in order to determine the magnitude of the global SARS-CoV-2-specific T cell response. However, as the results from some current studies have shown the presence of both CD4 Th1 and CD8 T cell responses (63), the correlation between vaccine-induced immunity and protection requires further investigation. Furthermore, the main limitation of the human IFN-γ release assays that they are still mainly used for research only (not CE-IVD or FDA approved), and their value in the real life scenario will continue to be investigable until they will be used for diagnostic purposes.

Preliminary reports of humoural and T cell responses to three SARS-CoV-2 vaccines for humans (17, 29, 64) and candidate vaccines for non-human primates (65-66) have been published so far. All of these have shown the induction of anti-spike antibodies and spike-reactive T cells over a period of 1–2 months (2–4 weeks in non-human primates), but the T cell responses have not yet been clearly characterised. Moreover, studies of non-human primates have also shown that a T-cell response is a better marker of immunity than an antibody response, and is more marked than after natural COVID-19 infection.

It is worth noting that humoural responses in COVID-19 patients vary widely, and that post-vaccination antibody titres may have different patterns: a rapid spike after disease onset, followed by a decline that stabilises at a higher level than that necessary for protection; lower peak titres during acute infection that subsequently slightly decrease but remain above the protective threshold over time; or peak titres in the acute phase that do not lead to long-term antibody responses (67). The major target of antibodies is the spike protein, particularly the receptor-binding domain (RBD) as binding to this domain prevents the conformational change required to allow the virus to bind ACE2 efficiently and enter human cells. Anti-spike glycoprotein and anti-RBD antibodies should be considered neutralising antibodies specific to SARS-CoV-2 that are induced by a vaccination and essential for viral clearance. Most of the current vaccine studies have reported anti-spike/RBD binding and neutralising IgG responses, and some have also reported antigen-specific T cell responses. Neutralising antibodies can be quantified by neutralisation and immunometric assays, and the quantification of neutralising antibody levels should enable us to determine whether a vaccinated subject is sufficiently protected or needs a revaccination, thus making antibody titres good biomarkers of protective efficacy.

The study by Anderson et al. (13) found that the mRNA-1273 vaccine induced time- and dose-dependent high levels of binding and neutralising antibodies in older adults, and the same trend has also been observed in younger adults (64); responses after the second vaccination were similar to those observed in patients who had recovered from COVID-19 and had donated convalescent serum. Seroconversion of binding antibodies was rapid (within

two weeks of the first vaccination), but pseudovirus neutralising activity was low before the second vaccination, thus indicating that two doses are necessary. However, the IFN-γ production response was similar in the one- and two-dose groups.

The durability of antibody and T cell responses has not yet been assessed, and so how and when a laboratory should monitor post-vaccination immune responses is still unclear. However, COVID-19 serological assays (68) may help to ascertain such responses to vaccines. There is a wide range of different, commercially available antigen assays, but the added value of targeting the spike or RBD protein is that the titres are more likely to reflect post-vaccination protection. The availability of international standards for SARS-CoV-2 antibodies will facilitate the comparability of the results of different assays, and eventually harmonise vaccine evaluations, but the immunological thresholds required to establish vaccine efficacy are still undefined (69).

Take home messages

- There are conflicting data concerning the real incidence of SARS-CoV-2 infection in patients with rheumatic diseases
- The only measures capable of containing the spread of the virus being social distancing, frequent hand washing, wearing of masks and actually the vaccination.
- 90 candidate vaccines are being developed using various technologies.
- There are currently no recommendations on how to vaccinate for SARS-CoV-2 rheumatic patients or subjects who have already had COVID-19.
- Interrupting the administration of rituximab may control the inflammatory disease while allowing for effective vaccination against SARS-CoV-2.
- Based on previous vaccinations, it is recommended that MTX be discontinued one week before vaccination and restarted the third week after vaccination.
- A potential barrier to antibody-based vaccines and therapies is the risk of exacerbating the severity of

COVID-19 by antibody dependent enhancement (ADE).
- Vaccine-induced protective immunity should be assessed by evaluating humoural and cell immune responses to COVID-19 antigens.
- Neutralising antibody titres are good biomarkers of protective efficacy.

References

1. SARZI-PUTTINI P, MAROTTO D, CAPORALI R *et al.*: Prevalence of COVID infections in a population of rheumatic patients from Lombardy and Marche treated with biological drugs or small molecules: A multicentre retrospective study. *J Autoimmun* 2021; 116: 102545.
2. EMMI G, BETTIOL A, MATTIOLI I *et al.*: SARS-CoV-2 infection among patients with systemic autoimmune diseases. *Autoimmun Rev* 2020; 19: 102575.
3. INFANTINO M, GROSSI V, LARI B *et al.*: Diagnostic accuracy of an automated chemiluminescent immunoassay for anti-SARS-CoV-2 IgM and IgG antibodies: an Italian experience. *J Med Virol* 2020; 92: 1671-5.
4. BENUCCI M, DAMIANI A, GIANNASI G *et al.*: Serological tests confirm the low incidence of COVID-19 in chronic rheumatic inflammatory diseases treated with biological DMARD. *Ann Rheum Dis* 2020 Jul 6 [Online ahead of print].
5. GIANFRANCESCO M, HYRICH KL, AL-ADELY S *et al.*: Characteristics associated with hospitalisation for COVID-19 in people with rheumatic disease: data from the COVID-19 global rheumatology alliance physician-reported registry. *Ann Rheum Dis* 2020; 79: 859-66.
6. AKIYAMA S, HAMDEH S, MICIC D, SAKURABA A: Prevalence and clinical outcomes of COVID-19 in patients with autoimmune diseases: a systematic review and meta-analysis. *Ann Rheum Dis* 2020 Oct 13 [Online ahead of print].
7. SCIRÈ CA, CARRARA G, ZANETTI A *et al.*; Italian Registry of the Italian Society for Rheumatology (CONTROL-19). COVID-19 in rheumatic diseases in Italy: first results from the Italian registry of the Italian Society for Rheumatology (CONTROL-19). *Clin Exp Rheumatol* 2020; 38: 748-53.
8. POLLARD AJ, BIJKER EM: A guide to vaccinology: from basic principles to new developments *Nat Rev Immunol* 2020 Dec 22 [Online ahead of print].
9. POLACK FP, THOMAS SJ, KITCHIN N *et al.*: C4591001 Clinical Trial Group. Safety and efficacy of the BNT162b2 mRNA Covid-19 vaccine. *N Engl J Med* 2020; 383: 2603-15.
10. WALSH EE, FRENCK RW JR, FALSEY AR *et al.*: Safety and immunogenicity of two RNA-based Covid-19 vaccine candidates. *N Engl J Med* 2020; 383: 2439-50.
11. SAHIN U, MUIK A, DERHOVANESSIAN E *et al.*: COVID-19 vaccine BNT162b1 elicits human antibody and TH1 T-cell responses. *Nature* 2020; 586: 594-9. Sep 30
12. CORBETT KS, FLYNN B, FOULDS KE *et al.*: Evaluation of the mRNA-1273 vaccine

against SARS-CoV-2 in nonhuman primates. *N Engl J Med* 2020; 383: 1544-55.
13. ANDERSON EJ, ROUPHAEL NG, WIDGE AT *et al.*: Safety and immunogenicity of SARS-CoV-2 mRNA-1273 vaccine in older adults. *N Engl J Med* 2020; 383: 2427-38.
14. WIDGE AT, ROUPHAEL NG, JACKSON LA *et al.*: Durability of responses after SARS-CoV-2 mRNA-1273 vaccination. *N Engl J Med* 2021; 384: 80-2.
15. BADEN LR, EL SAHLY HM, ESSINK B *et al.*: Efficacy and safety of the mRNA-1273 SARS-CoV-2 vaccine. *N Engl J Med* 2020 Dec 30 [Online ahead of print].
16. VAN DOREMALEN N, LAMBE T, SPENCER A *et al.*: ChAdOx1 nCoV-19 vaccination prevents SARS-CoV-2 pneumonia in rhesus macaques. *bioRxiv* 2020 May 13 [Online ahead of print].
17. RAMASAMY MN, MINASSIAN AM, EWER K *et al.*: Oxford COVID Vaccine Trial Group. Safety and immunogenicity of ChAdOx1 nCoV-19 vaccine administered in a prime-boost regimen in young and old adults (COV002): a single-blind, randomised, controlled, phase 2/3 trial. *Lancet* 2021; 396: 1979-93.
18. SHEA KM, EDELSBERG J, WEYCKER D *et al.*: Rates of pneumococcal disease in adults with chronic medical conditions. *Open Forum Infect Dis* 2014; 1: ofu 024.
19. HMAMOUCHI I, WINTHROP K, LAUNAY O, DOUGADOS M: Low rate of influenza and pneumococcal vaccine coverage in rheumatoid arthritis: data from the international COMORA cohort. *Vaccine* 2015; 33: 1446-52.
20. ZHANG J, XIE F, DELZELL E *et al.*: Association between vaccination for herpes zoster and risk of herpes zoster infection among older patients with selected immune-mediated diseases. *JAMA* 2012; 308: 43-9.
21. CASTELLS MC, PHILLIPS EJ: Maintaining safety with SARS-CoV-2 vaccines. *N Engl J Med* 2020 Dec 30 [Online ahead of print].
22. ANDO H, ABU LILA AS, KAWANISHI M *et al.*: Reactivity of IgM antibodies elicited by PEGylated liposomes or PEGylated lipoplexes against auto and foreign antigens. *J Control Release* 2018; 270: 114-9.
23. BERKHOUT LC, VOGELZANG EH, HART MM *et al.*: The effect of certolizumab drug concentration and anti-drug antibodies on TNF neutralisation. *Clin Exp Rheumatol* 2020; 38: 306-13.
24. ARVIN AM, FINK K, SCHMID MA *et al.*: A perspective on potential antibody-dependent enhancement of SARS-CoV-2. *Nature* 2020; 584: 353-63.
25. TAYLOR A, FOO SS, BRUZZONE R, DINH LV, KING NJ, MAHALINGAM S: Fc receptors in antibody-dependent enhancement of viral infections. *Immunol Rev* 2015; 268: 340-64.
26. RUCKWARDT TJ, MORABITO KM, GRAHAM BS: Immunological lessons from respiratory syncytial virus vaccine development. *Immunity* 2019; 51: 429-42.
27. IANKOV ID, PANDEY M, HARVEY M, GRIESMANN GE, FEDERSPIEL MJ, RUSSELL SJ: Immunoglobulin g antibody-mediated enhancement of measles virus infection can bypass the protective antiviral immune response. *J Virol* 2006; 80: 8530-40.
28. KATZELNICK LC, GRESH L, HALLORAN ME:

Antibody-dependent enhancement of severe dengue disease in humans. *Science* 2017; 358: 929-32.

29. ZHU F-C, LI Y-H, GUAN X-H *et al.*: Safety, tolerability, and immunogenicity of a recombinant adenovirus type-5 vectored COVID-19 vaccine: a dose-escalation, open-label, non-randomised, first-in-human trial. *Lancet* 2020; 395: 1845-54.

30. GRAHAM BS: Rapid COVID-19 vaccine development. *Science* 2020; 368: 945-6.

31. YIP MS, LEUNG NH, CHEUNG CY *et al.*: Antibody-dependent infection of human macrophages by severe acute respiratory syndrome coronavirus. *Virol J* 2014; 11: 82.

32. JAUME M, YIP MS, CHEUNG CY *et al.*: Anti-severe acute respiratory syndrome coronavirus spike antibodies trigger infection of human immune cells via a pH- and cysteine protease-independent FcγR pathway. *J Virol* 2011; 85: 10582-97.

33. LIU L, WEI Q, LIN Q *et al.*: Anti-spike IgG causes severe acute lung injury by skewing macrophage responses during acute SARS-CoV infection. *JCI Insight* 2019; 4: 123158

34. HAN S: Clinical vaccine development. *Clin Exp Vaccine Res* 2015; 4: 46-53.

35. CALINA D, DOCEA AO, PETRAKIS D *et al.*: Towards effective COVID-19 vaccines: updates, perspectives and challenges (Review). *Int J Mol Med* 2020; 46: 3-16.

36. SARZI-PUTTINI P, MAROTTO D, ANTIVALLE M *et al.*: How to handle patients with autoimmune rheumatic and inflammatory bowel diseases in the COVID-19 era: An expert opinion. *Autoimmun Rev* 2020; 19: 102574.

37. COUCH RB, ATMAR RL, FRANCO LM *et al.*: Antibody correlates and predictors of immunity to naturally occurring influenza in humans and the importance of antibody to the neuraminidase. *J Infect Dis* 2013; 207: 974-81.

38. FRIEDMAN MA, WINTHROP K: Vaccinations for rheumatoid arthritis. *Curr Opin Rheumatol* 2016; 28: 330-6.

39. SUBESINGHE S, BECHMAN K, RUTHERFORD AI, GOLDBLATT D, GALLOWAY JB: A systematic review and metaanalysis of antirheumatic drugs and vaccine immunogenicity in rheumatoid arthritis. *J Rheumatol* 2018; 45: 733-44.

40. KAPETANOVIC MC, SAXNE T, SJOHOLM A, TRUEDSSON L, JONSSON G, GEBOREK P: Influence of methotrexate, TNF blockers and prednisolone on antibody responses to pneumococcal polysaccharide vaccine in patients with rheumatoid arthritis. *Rheumatology* 2006; 45: 106-11.

41. KAPETANOVIC MC, ROSEMAN C, JONSSON G, TRUEDSSON L, SAXNE T, GEBOREK P: Antibody response is reduced following vaccination with 7-valent conjugate pneumococcal vaccine in adult methotrexate treated patients with established arthritis, but not those treated with tumor necrosis factor inhibitors. *Arthritis Rheum* 2011; 63: 3723-32.

42. IWAMOTO M, HOMMA S, ONISHI S *et al.*: Low level of seroconversion after a novel influenza A/H1N1/2009 vaccination in Japanese patients with rheumatoid arthritis in the 2009 season. *Rheumatol Int* 2012; 32: 3691-4.

43. FRANCA IL, RIBEIRO AC, AIKAWA NE *et al.*: TNF blockers show distinct patterns of immune response to the pandemic influenza A H1N1 vaccine in inflammatory arthritis patients. *Rheumatology* 2012; 51: 2091-8.

44. RIBEIRO AC, GUEDES LK, MORAES JC *et al.*: Reduced seroprotection after pandemic H1N1 influenza adjuvant-free vaccination in patients with rheumatoid arthritis: implications for clinical practice. *Ann Rheum Dis* 2011; 70: 2144-7.

45. RIBEIRO AC, LAURINDO IM, GUEDES LK *et al.*: Abatacept and reduced immune response to pandemic 2009 influenza A/H1N1 vaccination in patients with rheumatoid arthritis. *Arthritis Care Res* 2013; 65: 476-80.

46. ALTEN R, BINGHAM CO 3RD, COHEN SB *et al.*: Antibody response to pneumococcal and influenza vaccination in patients with rheumatoid arthritis receiving abatacept. *BMC Musculoskelet Disord* 2016; 17: 231.

47. MIGITA K, AKEDA Y, AKAZAWA M *et al.*: Effect of abatacept on the immunogenicity of 23-valent pneumococcal polysaccharide vaccination (PPSV23) in rheumatoid arthritis patients. *Arthritis Res Ther* 2015; 17: 357.

48. MORI S, UEKI Y, HIRAKATA N, ORIBE M, HIDAKA T, OISHI K: Impact of tocilizumab therapy on antibody response to influenza vaccine in patients with rheumatoid arthritis. *Ann Rheum Dis* 2012; 71: 2006-10.

49. TSURU T, TERAO K, MURAKAMI M *et al.*: Immune response to influenza vaccine and pneumococcal polysaccharide vaccine under IL-6 signal inhibition therapy with *tocilizumab*. *Mod Rheumatol* 2014; 24: 511-6.

50. BINGHAM CO 3RD, RIZZO W, KIVITZ A, HASSANALI A, UPMANYU R, KLEARMAN M: Humoral immune response to vaccines in patients with rheumatoid arthritis treated with tocilizumab: Results of a randomised controlled trial (VISARA). *Ann Rheum Dis* 2015; 74: 818-22.

51. WINTHROP KL, BINGHAM CO 3RD, KOMOCSAR WJ *et al.*: Evaluation of pneumococcal and tetanus vaccine responses in patients with rheumatoid arthritis receiving baricitinib: results from a long-term extension trial substudy. *Arthritis Res Ther* 2019; 21: 102.

52. WINTHROP KL, WOUTERS AG, CHOY EH *et al.*: The safety and immunogenicity of live zoster vaccination in patients with rheumatoid arthritis before starting tofacitinib: a randomized phase II trial. *Arthritis Rheumatol* 2017; 69: 1969-77.

53. WINTHROP KL, SILVERFIELD J, RACEWICZ A *et al.*: The effect of tofacitinib on pneumococcal and influenza vaccine responses in rheumatoid arthritis. *Ann Rheum Dis* 2016; 75: 687-95.

54. BENUCCI M, QUARTUCCIO L, LI GOBBI F *et*

al.: Persistence of rT-PCR-SARS-CoC-2 infection and delayed serological response, as a possible effect of rituximab according to the hypothesis of Schulze-Koops et al. *Ann Rheum Dis* 2020 Aug 4 [Online ahead of print].

55. BAKER D, ROBERTS CAK, PRYCE G *et al.*: COVID-19 vaccine-readiness for anti-CD20-depleting therapy in autoimmune diseases. *Clin Exp Immunol* 2020; 202: 149-61.

56. December 2020 update: Information from the American College of Rheumatology Regarding Vaccination Against SARS-CoV-2 December 21-2020.

57. LEE WS, WHEATLEY AK, KENT SJ, DEKOSKY BJ: Antibody-dependent enhancement and SARS-CoV-2 vaccines and therapies. *Nat Microbiol* 2020; 5: 1185-91.

58. SARZI-PUTTINI P, GIORGI V, SIROTTI S *et al.*: COVID-19, cytokines and immunosuppression: what can we learn from severe acute respiratory syndrome? *Clin Exp Rheumatol* 2020; 38: 337-42.

59. FERRO F, ELEFANTE E, BALDINI C *et al.*: COVID-19: the new challenge for rheumatologists. *Clin Exp Rheumatol* 2020; 38: 175-80.

60. FERRO F, ELEFANTE E, PUXEDDU I *et al.*: COVID-19: the new challenge for rheumatologists. First update. *Clin Exp Rheumatol* 2020; 38: 373-82.

61. ZHAO J, ALSHUKAIRI AN, BAHAROON SA: Recovery from the Middle East respiratory syndrome is associated with antibody and T-cell responses. *Sci Immunol* 2017; 2: eaan5393.

62. LIU L, WEI Q, LIN Q, FANG J, WANG H, KWOK H: Antispike IgG causes severe acute lung injury by skewing macrophage responses during acute SARS-CoV infection. *JCI Insight* 2019; 4: 1172.

63. ZUO J, DOWELL A, PEARCE H *et al.*: Robust SARS-CoV-2-specific T-cell immunity is maintained at 6 months following primary infection. *bioRxiv* 2020 [Online ahead of print].

64. JACKSON LA, ANDERSON EJ, ROUPHAEL NG *et al.*: An mRNA Vaccine against SARSCoV-2 - Preliminary report. *N Engl J Med* 2020; 383: 1920-31.

65. MERCADO NB, ZAHN R, WEGMANN F *et al.*: Single-shot Ad26 vaccine protects against SARS-CoV-2 in rhesus macaques. *Nature* 2020; 586: 583-8.

66. YU J, TOSTANOSKI LH, PETER L *et al.*: DNA vaccine protection against SARS-CoV-2 in rhesus macaques. *Science* 2020 14; 369: 806-11.

67. GRIGORYAN L, PULENDRAN B: The immunology of SARS-CoV-2 infections and vaccines. *Semin Immunol* 2020; 50: 101422.

68. INFANTINO M, DAMIANI A, LI GOBBI F *et al.*: Serological assays for SARS-CoV-2 infectious disease: benefits, limitations and perspectives. *Isr Med Assoc J* 2020; 22: 203-10.

69. VABRET N, BRITTON GJ, GRUBER C *et al.*: Sinai Immunology Review Project. Immunology of COVID-19: current state of the science. *Immunity* 2020; 52: 910-41.