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VIEWPOINT

Point of view on the vaccination against COVID-19 in patients with autoimmune inflammatory rheumatic diseases

Victoria Furer ,[1,2] Christien Rondaan ,[3] Nancy Agmon-Levin,[2,4] Sander van Assen,[5] Marc Bijl,[6] Meliha Crnkic Kapetanovic,[7] Annette de Thurah ,[8,9] Ulf Mueller-Ladner,[10] Daphna Paran,[1,2] Karen Schreiber,[11,12] Klaus Warnatz,[13] Nico M Wulffraat,[14] Ori Elkayam[1,2]

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For numbered affiliations see end of article.

Correspondence to
Dr Victoria Furer;
furer.rheum@gmail.com

ABSTRACT

In view of the COVID-19 pandemic, there is an unmet clinical need for the guidelines on vaccination of patients with autoimmune inflammatory rheumatic diseases (AIIRD). This position paper summarises the current data on COVID-19 infection in patients with AIIRD and development of vaccines against COVID-19, discusses the aspects of efficacy and safety of vaccination, and proposes preliminary considerations on vaccination against COVID-19 in patients with AIIRD, mainly based on the expert opinion and knowledge on the use of other vaccines in this population of patients.

The tremendous global impact of the COVID-19 pandemic has led to the accelerated development of vaccines against COVID-19. The results of phase 1/2/3 studies on the efficacy and safety of two mRNA vaccines, developed by Pfizer (BNTb262) and Moderna (messenger RNA (mRNA-1273), have been recently reported, showing an efficacy rate of about 95% in preventing COVID-19, without major unexpected safety signals.[1–4] A massive vaccination campaign of vaccinations against COVID-19 is underway and raises the issue of vaccination of patients suffering from autoimmune inflammatory rheumatic diseases (AIIRD).

When formulating points to consider concerning vaccination against COVID-19 in patients with AIIRD, the following questions should be addressed:

1. Is the risk to contract COVID-19 increased among AIIRD patients?
2. Is COVID-19 disease more severe in AIIRD patients?
3. Is COVID-19 infection associated with rheumatic and autoimmune manifestations?
4. Which vaccines against COVID-19 are or may be available in the near future?
5. What are the possible safety issues of the COVID-19 vaccine in AIIRD patients?
6. Are the available vaccines effective in AIIRD patients?

The definition of AIIRD used in the present review mainly includes but is not limited to rheumatoid arthritis (RA), spondyloarthrithis (SpA), systemic lupus erythematosus (SLE), connective tissue diseases (CTD), and systemic vasculitides. The main reason for including a diverse population of AIIRD is dictated by the rapidly evolving pandemic of COVID-19 and the need to estimate the clinical impact of the disease on patients with rheumatic diseases in general.

1. IS THE RISK TO CONTRACT COVID-19 INCREASED AMONG AIIRDS PATIENTS?

The first reports on the prevalence of COVID-19 among patients with AIIRD came from Italy, USA, and Spain. These preliminary studies were mostly based on telephonic or face-to- face surveys and suggested a prevalence similar to the background population.[5 6] However, systematic studies published at a later phase of the pandemic reported a mild increase in the prevalence of COVID-19 among patients with AIIRD. A study from seven medical centres in Spain reported an increased OR of 1.31, with the highest prevalence being among patients with SpA and those treated with biological and targeted synthetic disease modifying antirheumatic drugs (bDMARDs and tsDMARDs).[7] This study did not show any increase in the prevalence of COVID-19 among patients with SLE,[7] while others reported an increased risk among patients with SLE[8] and CTD.[9] A survey

study of 42 families from the Hubei province, China, reported a higher rate of COVID-19 in patients with AIIRD compared with their family members living in the same household (63% vs 34%), suggesting that patients with AIIRD might be more susceptible to COVID-19 infection than the general population.[10] Overall, since patients with AIIRD are instructed from the onset of the pandemic to a strict adherence to COVID-19 precautions and isolation measures compared with the general population, the estimation of the risk for disease contraction in the AIIRD population remains challenging.

In conclusion, the risk of COVID-19 in patients with AIIRD seems to be similar to the general population, or at most, mildly increased.

2. IS COVID-19 DISEASE MORE SEVERE IN PATIENTS WITH AIIRD?

The main study published on this topic is based on the database of the Global Rheumatology Alliance (GRA) including 3000 patients with AIIRD.[11] This study analysed the risk factors for hospitalisations among AIIRD patients with COVID-19. It reported an increased risk for hospitalisation (46%) and death (9%) among patients with SLE and vasculitis. For the whole population of patients with AIIRD, the main risk factors for hospitalisation were similar to those known in the general population, such as age and cardiovascular diseases.[11] Patients of Afro-American, Latin and Asian origins were at increased risk for hospitalisation.[12] In the subsequent analysis by the GRA group, factors associated with COVID-19-related death among 3729 patients with rheumatic diseases were reported.[13] In addition to the known general factors (older age, male sex and specific comorbidities), disease-specific factors, including high disease activity at COVID-19 diagnosis and treatment with glucocorticoids (≥10 mg/day prednisolone-equivalent dose), rituximab and some immunosuppressants (not including bDMARDs) were related to a higher rate of COVID-19-related death.[13] Data from the OpenSAFELY electronic platform based on the UK primary care health records identified that within the first 3 months of the pandemic, patients with RA, SLE or psoriasis, analysed as a combined group, had a slightly increased risk of death from COVID-19 compared with subjects without these diseases.[14] Another study from the USA compared the course of COVID-19 in 52 patients with AIIRD and 104 patients without rheumatic diseases.[15] Although the rate of hospitalisation and mortality was similar in both groups, more patients with AIIRD required intensive care and mechanical ventilation. In a US cohort study of 143 patients with AIIRD and 688 controls, no significant association between rheumatic diseases and risk of mechanical ventilation was found after adjusting for comorbidities.[16] A nationwide cohort study from Denmark reported a moderately increased incidence of hospitalisation with COVID-19 infection for patients with RA compared with the general population.[17] A large cohort study conducted in the USA reported a higher rate of venous thromboembolism in patients with AIIRD within 30 days follow-up of COVID-19 infection compared with the matched population without AIIRD.[18] A large US electronic health records based study investigated temporal trends in COVID-19 outcomes in patients with rheumatic diseases over the course of the pandemic.[19] The risks of severe COVID-19 outcomes, including risks of hospitalisation, respiratory failure, mechanical ventilation, renal failure and death after COVID-19 diagnosis, have improved over time in patients with rheumatic but remain substantial.[19] Overall, the interpretation of the presented studies should be cautious in view of a potentially significant selection bias, as compared with the general population, immunosuppressed patients with AIIRD may be evaluated more closely, sent earlier to hospital, and admitted earlier into intensive care units, or been more frequently reported.

In the French Rheumatic Diseases COVID-19 cohort, corticosteroids, mycophenolate mofetil, and rituximab were associated with a more severe disease.[20] The use of methotrexate, tumour necrosis factor alpha or interleukin-6 inhibitors was not associated with severe disease in this study. The use of prednisone at a dosage ≥10 mg/day was an additional risk factor for hospitalisation and worse outcomes.[11 13] This study indicated a possible protective effect of the use of ts/bDMARDs,[11] further supported by other series from USA,[18 21] Spain[22] and Denmark,[17] which did not find a correlation between the use of ts/bDMARDs and the severity of COVID-19.

With regard to SLE patients, a case series of 17 patients from France[23] and a smaller one of 5 patients from the USA[24] suggested a severe disease course in SLE patients, with an increased risk of respiratory failure and mechanical ventilation. Many of these patients suffered from comorbidities and were highly immunosuppressed.[23 24] The common denominator between SLE and a severe course of COVID-19 infection on the pathogenetic level is a dysregulation of type I interferon (IFN) response in both conditions.[25–27] Neutralising autoantibodies against type I IFNs, mostly IFN-a2 and IFN-v were specifically detected in patients with life-threatening COVID-19 disease but not in asymptomatic COVID-19 carriers or patients with only mild disease.[28] Since anti-IFN autoantibodies are also present in some patients with SLE,[29] they may contribute to the susceptibility of SLE patients to a more severe COVID-19 disease, along with visceral involvement and the use of immunosuppressant drugs. In addition, COVID-19 infection was reported to provoke a severe flare of antiphospholipid syndrome (APS) despite treatment with anticoagulants.[30] Likewise, a severe course of COVID-19 has been described in patients with progressive systemic sclerosis (pSS) and granulomatosis with polyangiitis, probably related to the presence of interstitial lung disease at baseline[20] and the treatment with corticosteroids and rituximab.[31–33] This has been further supported by additional studies from Spain,[34 35] which

have identified corticosteroids and rituximab as risk factors for hospitalisation.

Furthermore, based on reports in cancer patients,[36] patient with liver transplant[37] and authors' experience, immunosuppressed patients, including patients with primary immunodeficiencies, might have a prolonged period of positive viral replication and viable virus shedding, requiring an adjustment of isolation precautions, quarantine policies and follow-up in these cases. In conclusion, for most patients with AIIRD, the course of COVID-19 is similar to the background population and is mainly affected by the presence of the classical risk factors for severe COVID-19. However, the course of COVID-19 may be more severe in patients with SLE, pSS and vasculitis. High disease activity at the diagnosis with COVID-19 correlates with increased COVID-19 related mortality. The use of prednisone at a dosage ≥10 mg/day, mycophenolate mofetil, and rituximab has been associated with worse outcomes.

3. IS COVID-19 INFECTION ASSOCIATED WITH RHEUMATIC AND AUTOIMMUNE MANIFESTATIONS?

Infection with COVID-19 has been associated with a variety of rheumatic symptoms and autoimmune diseases. A recently published meta-analysis on rheumatic manifestations of COVID-19 included 51 articles.[38] Myalgia and fatigue have been reported in 16% and 36% of patients with COVID-19, respectively. Case reports on autoimmune cytopenias,[39 40] Guillain-Barré syndrome[41] and encephalitis[42] have been published. In children, COVID-19 has been associated with an inflammatory multisystem syndrome displaying similarities to Kawasaki syndrome.[43] COVID-19 infection may induce autoantibodies, such as antinuclear antibodies, anti-SSA and antiphospholipid antibodies in a substantial proportion of COVID-19 patients.[44–46] These findings suggest that COVID-19, like other viruses, may induce autoimmune antibodies and potentially autoimmune diseases. In conclusion, COVID-19 infection may provoke a variety of rheumatic symptoms, mainly myalgia and almost no arthritis, autoimmune diseases, and autoantibodies.

4. WHICH VACCINES AGAINST COVID-19 ARE OR MAY BE AVAILABLE IN THE NEAR FUTURE?

SARS-CoV-2 is a single-stranded RNA-enveloped virus.[47] The spike (S) protein on the surface of the SARS-CoV-2 virus is a key factor involved in infection, mediating receptor recognition, viral attachment, entry and fusion into host cells. Due to its indispensable functions, S protein represents one of the most important targets for COVID-19 vaccine.[48] The S protein has high antigenicity and proven ability to elicit robust humoral immune responses and neutralising antibodies in convalescent individuals following SARS-CoV-2 infection and COVID-19 disease, making the S protein an ideal candidate for vaccination against SARS-CoV-2 infection.[49] Indeed, most SARS-CoV-2 vaccines in development include at least a portion of the S protein. Concurrently with a robust humoral response, a positive T-cell response also plays a significant role for the efficacy of vaccination, especially in patients with immunodeficiencies. T helper type 1 (TH1)-skewed T cell immune responses were induced by mRNA-based COVID-19 vaccines,[3 50]

Major COVID-19 vaccine candidates

As of 29 January 2021, there are 63 candidate vaccines in clinical evaluation and 174 vaccines in different stages of preclinical evaluation worldwide.

WHO publishes a regularly updated list of vaccines in development (https://www.who.int/publications/m/item/draft-landscape-of-covid-19-candidate-vaccines). The safety, immunogenicity and protective efficacy of experimental vaccines are rigorously evaluated and established in animal models before clinical trials are begun. In the case of pandemic vaccine development, the preclinical and clinical stages of vaccine development are compressed and move forward in parallel. One of the challenges in the vaccine development process is the rapid development of mutations in RNA viruses in genes encoding surface glycoproteins, which trigger the antigenic immune response, leading to uncertainty regarding the duration of vaccine efficacy.

An overview of the technological platforms of candidate vaccines against SARS-CoV-2 is presented in table 1 with the lead candidates including mRNA-based and viral-vectored vaccines.[51]

Nucleic acid-based COVID-19 vaccines

mRNA-based vaccine platforms have recently emerged as a promising tool in vaccine development. The antigen-encoding mRNA complexed with a carrier, such as lipid nanoparticles, can be efficiently delivered in vivo into the cytoplasm of host cells for protein translation and post-translational modifications.[52] mRNA vaccines are non-infectious and are synthesised by in vitro transcription, free of microbial molecules. These beneficial features differentiate mRNA vaccines from live attenuated viral vaccines, inactivated viral vaccines, subunit vaccines and recombinant viral-vectored vaccines in terms of safety, efficacy and issues of antivector immunity, enabling rapid and inexpensive production and repeated vaccination.[53] Both mRNA vaccines available today, BNT162b2 and mRNA-1273, are based on liposome-formulated uracil-modified mRNA, which decrease the toll-like receptor–7 stimulation,[54] and therefore, potentially attenuate the risk of autoimmune disease flare.

DNA-based vaccines are based on plasmids that can be amplified on a large scale in bacteria and expressed in eukaryotic cells. The DNA vaccine plasmids for SARS-CoV-2 encode for the spike protein[55] and are currently under investigation.

BNT162b2 vaccine (Pfizer and BioNTech)

- Structure:
  - mRNA vaccine.

Table 1 Overview of technological platforms in candidate vaccines against SARS-CoV-2

Platform	Advantage	Vaccine type	Vaccine name	Developers	Stage
Inactivated	Well established manufacturing process	**Purified whole SARS-CoV-2 components**	CoronaVac	Sinovac Life Sciences, Beijing, China	Phase III
			New Crown COVID-19	Wuhan Institute of Biological Products/Sinopharm	Phase III
			BIBIBP-CorV	Beijing Institute of Biological Products/Sinopharm	Phase III
Nucleic acid	Rapid and low cost manufacturing	**Lipid-encapsulated mRNA**	mRNA1273	Moderna/NIAID	Phase III
			bNT162b2	BioNTech/Fosun Pharma/Pfizer	Phase III
		Self-amplifying mRNA	LNP-nCoVsaRNA	Imperial College London	Phase I
		Plasmid DNA with medical device	INO-4800	Inovio Pharmaceuticals/ International Vaccine Institute	Phase I/II
Viral vector	Robust cellular and humoral vaccine immunity	**Chimpanzee adenovirus (ChAd)**	ChAdOx1 nCoV-19	AstraZeneca/University of Oxford	Phase III
		Human adenovirus type 5	Ad5-nCoV	CanSino Biological Inc./Beijing Institute of Biotechnology	Phase III
		Human adenovirus type 26	Ad26.COV2-S	Janssen Pharmaceutical companies	Phase III
		Vesicular stomatitis virus	IIBR-100	Israel Institute for Biological Research	Phase I/II

Adopted from Ura *et al*.[51]
mRNA, messenger RNA.

- Phase 1 clinical trial (USA, Germany):
  - Two 30 µg doses of BNT162b2 elicited high titre SARS-CoV-2 neutralising antibodies and robust antigen-specific CD8 +and Th1-type CD4 +T cell responses among healthy men and women.[50 56] The 50% neutralising geometric mean titers elicited by 2 doses of 30 µg of BNT162b2 in older and younger adults exceeded the geometric mean titre measured in a human convalescent serum panel, despite a lower neutralising response in older adults compared with younger adults.
  - Good safety profile; mild side effects in only 17% of volunteers aged 15–55 years and none in older volunteers.
- Phase 3 clinical trial
  - n=43 661 adults aged 16–85 years.
  - The study included 118 patients with rheumatic diseases (62 patients in the vaccine group and 56 patients in placebo group).
  - A two-dose regimen of BNT162b2 (30 µg per dose, given 21 days apart) was found to be safe and 95% effective against COVID-19 across age, gender and ethnicities.[1] The vaccine met both primary efficacy end points, with more than a 99.99% probability of a true vaccine efficacy greater than 30%.
  - Key exclusion criteria: a medical history of COVID-19, treatment with immunosuppressive therapy, or diagnosis with an immunocompromising condition.
  - These results met the prespecified success criteria, which were to establish a probability above 98.6% of true vaccine efficacy being greater than 30%, and greatly exceeded the minimum Food and Drug Administration (FDA) criteria for authorisation. (https://www.fda.gov/media/144245/download).
  - Safety profile: no serious adverse effects. Fatigue and headache were reported in up to 59% and 52% of the participants, respectively.
  - This is the first SARS-CoV-2 vaccine granted an emergency use authorisation by the FDA on 11 December 2020 and by the EMA on 21 December 2020.
  - The vaccine needs to be stored at a low temperature (−60°C to −80°C), which may limit its diffusion in remote areas.

mRNA-1273 vaccine (Moderna)

- Structure:
  An mRNA vaccine, mRNA-1273, which encodes SARS-CoV-2 prefusion-stabilised spike protein encapsulated in lipid nanoparticles.
- Phase 1 open-label clinical trial[2]
  Two injections of the vaccine, spaced 28 days apart, resulted in a strong cellular (primarily CD4 + T cell) response, while humoral responses were above the median of the antibody level in the convalescent serum of a panel of persons who recovered from COVID-19.
  A well-tolerated safety profile and dose-dependent, mild-to-moderate adverse events (AEs) after the second immunisation.
  Mice and rhesus macaques that were given mRNA-1273 and were subsequently challenged with high-dose intranasal SARS-CoV-2 rapidly cleared the virus from the upper and lower airways.[57]
- Phase 3 clinical trial (USA)[4]
  - n=30 000 adults, with more than 7000 participants of age ≥65 years

- Randomised, 1:1 placebo-controlled study testing mRNA-1273 at the 100 µg dose level.
- Key exclusion criteria: immunosuppressive or immunodeficient state, including HIV infection, asplenia and recurrent severe infections, systemic immunosuppressants or immune-modifying drugs for >14 days in total within 6 months prior to screening (for corticosteroids, ≥20 mg/day of prednisone equivalent.
- Efficacy: symptomatic COVID-19 illness was confirmed in 185 participants in the placebo group (56.5 per 1000 person-years; 95% CI 48.7 to 65.3) and in 11 participants in the mRNA-1273 group (3.3 per 1000 person-years; 95% CI 1.7 to 6.0); vaccine efficacy was 94.1% (95% CI 89.3% to 96.8%; p<0.001). Efficacy was similar across key secondary analyses, including assessment 14 days after the first dose, in participants who had evidence of SARS-CoV-2 infection at baseline, and in participants 65 years of age or older.
- Safety: most AEs were mild to moderate with influenza-like symptoms in 1%–10% and were generally short lived.
- Moderna was authorised for the emergency use by the FDA on 18 December 2020 and by the EMA on 6 January 2021.
- The mRNA-1273 vaccine can be kept refrigerated for 30 days or frozen (−15°C to −25°C) for long-term storage.

SARS-CoV-2 mRNA vaccine CVnCoV (CureVac AG)

- Structure:
  - mRNA vaccine.
- Dose: 12 µg
- Ongoing phase 2a (NCT04515147) and phase 2b/3 (NCT04652102) clinical trials.

Protein-based vaccines

Protein-based vaccines use harmless fragments of proteins or protein shells that mimic the COVID-19 virus and may safely generate an immune response. The protein subunit vaccine is based on synthetic peptides or recombinant proteins. The spike protein is the most suitable antigen to promote neutralising antibodies; others use the spike protein's receptor-binding domain. These recombinant proteins are produced in various systems, including insect cells. Proteins alone are poorly immunogenic and generally require an adjuvant to elicit a sufficient response to vaccine.

NVX-CoV2373 (Novavax)

- Structure:
  - A recombinant full-length spike glycoprotein optimised in the established baculovirus Spodoptera frugiperda (Sf9) insect cell-expression system and matrix-M1 adjuvant. NVX-CoV2373 contains purified protein antigen and cannot replicate, nor can it cause COVID-19.
- Phases 1–2 placebo controlled randomised trial[52] :
  - At 35 days, NVX-CoV2373 appeared to be safe, and it elicited immune responses that exceeded levels in COVID-19 convalescent serum. The Matrix-M1 adjuvant induced CD4 +T cell responses that were biased toward a Th1 phenotype.
- Phase 3 clinical trial has been launched in USA and Mexico (NCT04611802).
- The vaccine will only require refrigeration for storage.

Viral vector vaccines

Viral replicating and non-replicating vaccines induce robust immune responses and can increase both humoral and cellular immunity.[58] The replicating vector vaccines infect cells that produce the antigen and more viral vectors that will infect more cells. These replicating vectors are usually derived from attenuated viruses or strains of viruses developed for vaccination and shuttle a gene expressing a viral protein, commonly the viral spike protein. Vesicular stomatitis virus (VSV) vector-based vaccines are well studied, particularly VSVDG-ZEBOV-GP, a vaccine against Ebola virus that was tested in clinical trials with 20 000 participants[59] and licensed by the FDA in 2019. VSV vectors have low viral pathogenicity and rarely have pre-existing antivector immunity in humans. Most of the replicating viral vectors are in the early phases of development.[60]

The non-replicating viral vectors include four vaccines (recombinant adenovirus type-5-vectored COVID-19 vaccine (Ad5-nCoV) by CanSino Biological; Gam-COVID-Vac by the Gamaleya Research Institute; recombinant adenovirus (Ad26) by Janssen Pharmaceutica; the ChAdOx1 nCoV-19 vaccine (AZD1222) by University of Oxford and AstraZeneca). These vectors are mostly based on recombinant human or simian adenovirus vectors. However, they can also use platforms based on the adeno-associated virus, parainfluenza virus, alphavirus, herpesvirus and poxviruses. The recombinant viral vectors are replication-deficient and produce the antigen in infected cells. All non-replicating viral vectors in phase III clinical trials are carriers of a gene coding for the viral spike protein.

For the production of this kind of vaccines, expensive production facilities are needed.

ChAdOx1 nCoV-19 vaccine (AZD1222) Oxford–AstraZeneca

- Structure:
  - A replication-deficient chimpanzee adenoviral vector ChAdOx1, containing the SARS-CoV-2 structural surface glycoprotein antigen (spike protein; nCoV-19) gene.
- Phase 1[61] and 2[62] clinical trials/UK:
  - Phase 1: 1077 healthy adults aged 18–55 years.
  - Phase 2: included adults≥56 years.
  - Both trials had an acceptable safety profile for the vaccine with induction of binding and neutralising antibodies as well as generation of IFN-γ enzyme-linked immunospot responses, with 91%

neutralising antibodies after the first dose and 100% after two doses. ChAdOx1 nCoV-19 had similar immunogenicity across all age groups after a boost dose.[62]

- Four ongoing blinded, randomised controlled trials (COV001 (phase 1/2; UK), COV002 (phase 2/3; UK), COV003 (phase 3; Brazil) and COV005 (phase 1/2; South Africa). The interim efficacy was assessed by a prespecified global pooled analysis combining data from COV002 and COV003. The safety of the vaccine is being assessed using data from all four studies[63]:
  - Random assignment (1:1) to ChAdOx1 nCoV-19 vaccine or control (meningococcal group A, C, W and Y conjugate vaccine or saline). Participants in the ChAdOx1 nCoV-19 group received two doses containing 5×10^{10} viral particles (vp) (standard dose; SD/SD cohort); a subset in the UK trial received a half dose as their first dose (low dose (LD)) and an SD as their second dose (LD/SD cohort).
  - Pooled interim analysis of 4 trials (n=11 636)[63]:
  - Significant vaccine efficacy of 70.4% was seen after two doses and protection of 64.1% against symptomatic disease after at least one standard dose.
  - UK cohort—the strategy with a low first dose of vaccine had a particularly high efficacy of 90.0%. The observed differences in efficacy by dose were not consistent with results from previous immunogenicity trials of this vaccine, which were similar for participants receiving two low doses and two standard doses; no immunogenicity data exist for the mixed-dose regimen. Thus, the results of these trials are under further investigation required by the regulatory authorities.
  - Safety: 74 341 person-months (median 3.4 months) follow-up with an acceptable safety profile. A case of transverse myelitis was reported 14 days after ChAdOx1 nCoV-19 booster vaccination as being possibly related to vaccination, with the independent neurological committee considering the most likely diagnosis to be of an idiopathic demyelination.[63]
  - The vaccine has been first approved for use in UK and since 29 January 2021 in Europe.

Ad26.COV2.S by Janssen Pharmaceutica

- Structure
  - Non-replicating adenovirus 26-based vector expressing the stabilised prefusion spike (S) protein of SARS-CoV-2
- Phase 1/2a clinical trial (NCT04436276)/ongoing.
- Interim results[64 65]
  - Ad26.COV2.S was administered at a dose level of 5×10^{10} or 1×10^{11} vp per vaccination, either as a single dose or as a two-dose schedule spaced by 56 days in healthy adults, including healthy elderly >65 years old.
  - The safety profile and immunogenicity after only a single dose were supportive for further clinical development of Ad26.COV2.S at a dose level of 5×10^{10} vp.
  - A single dose of Ad26.COV2.S elicited a strong humoral response in a majority of vaccine recipients, with the presence of S-binding and neutralising antibodies in more than 90% of the participants, regardless of either age group or vaccine dose. During 71 days of follow-up after the first dose, antibody titers further increased and stabilised.[65] The vaccine induced S-specific Th1-skewed cellular response and S-specific CD8 +T cell responses, identified by the expression of IFN-γ or interleukin-2 cytokines on S-peptide stimulation, in some participants.[65]
  - The most frequent local AE was injection site pain and the most frequent solicited AEs were fatigue, headache and myalgia. The most frequent systemic AE was fever.
- Phase 3 clinical trial (NCT04505722) with a single-dose vaccine is ongoing.

Recombinant VSV-ΔG-spike vaccine (Brilife/Israel Institute for Biological Research)

- Structure
  - A replication competent recombinant VSV-ΔG-spike vaccine, in which the glycoprotein of VSV is replaced by the spike protein of the SARS-CoV-2. In vitro characterisation of the recombinant VSV-ΔG-spike indicated expression and presentation of the spike protein on the viral membrane with antigenic similarity to SARS-CoV-2.
- In vivo model: a golden Syrian hamster in vivo model for COVID-19[66]:
  - Vaccination of hamsters with recombinant VSV-ΔG-spike results in rapid and potent induction of neutralising antibodies against SARS-CoV-2. A single-dose vaccination was able to protect hamsters against a SARS-CoV-2 challenge, as demonstrated by the abrogation of body weight loss of the immunised hamsters compared with unvaccinated hamsters. Whereas lungs of infected hamsters displayed extensive tissue damage and high viral titers were observed, immunised hamsters' lungs showed only minor lung pathology, and no viral load was observed. Recombinant VSV-ΔG-spike represents a safe, efficacious and protective vaccine against SARS-CoV-2 infection.[66]
- Phase 1/2 clinical trial of the recombinant VSV-ΔG-spike vaccine is undertaken in Israel.[67]

Gam-COVID-Vac (Sputnik V)

- Structure:
  - A recombinant adenovirus vector. The vaccine comprises two vector components, recombinant adenovirus type 26 (rAd26) and recombinant adenovirus type 5 (rAd5), both of which carry the

Box 1 Research agenda

1. Do vaccines prevent any COVID-19 contraction (such as asymptomatic disease) or severe disease phenotype only?
2. Given the observation that many individuals with asymptomatic or mild COVID-19 had highly durable and functionally replete memory T cell responses,[74] will vaccines that induce a strong T cell response be efficient in preventing asymptomatic infections?
3. What is short-term and long-term safety of the vaccines in special populations and immunosuppressed patients? Is there a risk of inducing of autoimmune disease or exacerbation of the baseline disease?
4. What is the duration of humoral and cellular response to vaccination? What is the impact of synthetic, targeted and biological DMARDs on the efficacy of vaccination?
5. What is duration of viral replication and shedding in immunosuppressed patients?
6. What is the policy of vaccination of COVID-19 convalescent individuals with AIIRD?
7. What is the vaccination policy in the paediatric population with AIIRD?

gene for SARS-CoV-2 full-length glycoprotein S (rAd26-S and rAd5-S).
  - A full dose of the vaccine consisted of 1011 vps per dose for both recombinant adenoviruses and all participants received full doses. The dose was set based on findings of preclinical studies (unpublished data).
- Two open, phase 1/2 non-randomised studies at hospitals in Russia.
  - n=120 healthy adult volunteers (aged 18–60 years) in each study.
  - Strong humoral and cellular immune responses were reported in 100% of healthy participants.
  - Good safety profile: all reported AEs were mostly mild.
- Criticism: granted use by the Russian government on 11 August 2020 without conducting phase III clinical trials, thus questioning the safety and efficacy of the vaccine.

While efficacy and safety of vaccines against COVID-19 have been thoroughly studied thoroughly in clinical trials, there is a number of important open clinical questions pertaining to vaccination of patients with AIIRD, as summarised in box 1.

5. WHAT ARE THE POSSIBLE SAFETY ISSUES OF THE COVID-19 VACCINE IN PATIENTS WITH AIIRD?

Up to January 2021, there is no information on the possible AEs of vaccines against COVID-19 in patients with AIIRD. In general, knowledge on the safety of COVID-19 vaccines is limited. Most clinical trials studying the vaccines against COVID-19 excluded immunosuppressed patients, although phase 3 trial with BNT162b2 vaccine included 118 patients with rheumatic diseases, without specific details on the type of rheumatic disease and/or treatment.[1] Whether vaccines against COVID-19 may have the potential to provoke a flare of the underlying rheumatic disease is unknown. Part of the mechanism of action of mRNA vaccines against COVID-19 involves triggering the IFN pathway, raising some concern about its use in conditions associated with activation of the IFN pathway, such as in interferonopathies and SLE. No information is available on the potential effect of COVID-19 vaccines on the underlying rheumatic disease.

6. ARE THE AVAILABLE VACCINES EFFECTIVE IN PATIENTS WITH AIIRD?

As immunosuppressed patients were mainly excluded from the currently ongoing clinical trials, there is no data on the efficacy of COVID-19 vaccination in patients with AIIRD. There are no data or consensus whether b/tsDMARDs should be withheld at the time of vaccination. Based on the observation that high disease activity at the diagnosis of COVID-19 might predispose to worse outcomes[13] and the reassuring data related to other vaccines immunogenicity under sDMARDs and bDMARDs,[68] except for rituximab, there is a rationale to continue antirheumatic treatment during vaccination. On the other hand, in patients in remission/stable disease, a temporary withholding of antirheumatic treatment (such as methotrexate) might be considered to optimise the immune response to vaccination. The rationale for this approach is based on two studies conducted in Sweden reporting an impaired antibody response to pneumococcal vaccine in patients with RA treated with methotrexate[69 70] and two studies conducted in Korea showing that temporal discontinuation of methotrexate after vaccination improved the immunogenicity of seasonal influenza vaccination in patients with RA.[71 72]

Points of considerations regarding COVID-19 vaccine in patients with AIIRD

1. The risk of contracting COVID-19 for patients with AIIRD seems to be similar to the general population, or at most, mildly increased.
2. For most patients with AIIRD, the course of COVID-19 is similar to the background population and is mainly affected by the presence of the classical risk factors for severe COVID-19. Immunosuppressed patients, including patients with primary immunodeficiencies, might have a prolonged period of positive viral replication and viable virus shedding, requiring an adjustment of isolation precautions and follow-up in these cases.
3. The course of COVID-19 may be more severe in patients with SLE, APS, pSS, vasculitis and congenital or acquired interferonopathies.
4. The use of prednisone at a dosage above 10 mg/day, mycophenolate mofetil and rituximab has been associated with worse COVID-19 prognosis.
5. In general, non-live vaccines are recommended in patients with AIIRD.[73] To date, the available (non-live) vaccines mainly did show sufficient humoral and

cellular immune responses in patients with AIIRD, except in patients on high dose corticosteroid or rituximab, with a good safety profile.
6. In the midst of the COVID-19 pandemic, vaccination against influenza and streptococcus pneumonia should be highly encouraged. COVID-19 vaccine series should routinely be administered alone, with a minimum interval of 14 days before or after administration of any other vaccine.
7. RNA vaccines against COVID-19 are non-live vaccines and do not provoke COVID-19 infection.
8. In view of the COVID-19 pandemic, the possible adverse course of COVID-19 in AIIRD patients and the favourable safety profile of the mRNA vaccines in the general population, mRNA vaccines should be administered to patients with AIIRD as recommended in the general population.
9. The same statement is valid for other non-live future vaccines if their efficacy and safety profile is found to be similar to BNTb262 and mRNA-1273 vaccines.
10. As for other vaccines, the efficacy of a COVID-19 vaccine may be reduced in patients treated with high-doses corticosteroids and rituximab. For patients treated with rituximab, it is preferable to administer the vaccine at least 6 months after the last infusion. However, the vaccine is not contraindicated in this population and the treating physician should discuss with the patient the appropriate timing of vaccination taking into consideration the context of pandemic, the risk of poor COVID-19 disease prognosis, and a possibly reduced humoral response to vaccination under rituximab treatment,
11. There is an urgent need for studies on the immunogenicity and safety of COVID-19 vaccines in patients with AIIRD.

In summary, we have presented the current data up to the beginning of 2021 on COVID-19 in patients with AIIRD and formulated preliminary considerations on vaccination against COVID-19 in this population of patients which are mainly based on the general knowledge on vaccines in patients with AIIRD. Although there is a lack of data on efficacy and safety of COVID-19 vaccines in patients with AIIRD, it should be emphasised that the available non-live vaccines against other agents, such as influenza and others, showed a sufficient humoral and cellular response in the majority of patients with AIIRD (except for patients treated with high-dose corticosteroids or rituximab), with an acceptable safety profile. We presume that within months, this point of view will be updated once studies on vaccination against COVID-19 in the general population and AIIRD will be published.

Author affiliations
[1]Rheumatology, Tel Aviv Sourasky Medical Center, Tel Aviv, Israel
[2]Sackler Faculty of Medicine, Tel Aviv University, Tel Aviv, Israel
[3]Medical Microbiology and Infection Prevention, UMCG, Groningen, The Netherlands
[4]Clinical Immunology, Angioedema and Allergy Unit, Zabludowicz Center for Autoimmune Diseases, Sheba Medical Center at Tel Hashomer, Ramat Gan, Israel
[5]Internal Medicine (Infectious Diseases), Treant Care Group, Hoogeveen, The Netherlands
[6]Internal Medicine and Rheumatology, Martini Hospital, Groningen, The Netherlands
[7]Department of Clinical Sciences, Lund, Section for Rheumatology, Lund University, Lund and Skåne University Hospital, Lund, Sweden
[8]Rheumatology, Aarhus University Hospital, Århus N, Denmark
[9]Clinical Medicine, Aarhus University, Aarhus, Denmark
[10]Rheumatology and Clinical Immunology, Campus Kerckhoff, Justus-Liebig-University, Giessen, Germany
[11]Danish Hospital for Rheumatic Diseases, University of Southern Denmark, Sønderborg, Denmark
[12]Thrombosis and Haemophilia, Guy's King's College and Saint Thomas' Hospitals, London, UK
[13]Center for Chronic Immunodeficiency, Department of Rheumatology and Clinical Immunology, Medical Center - University of Freiburg, Freiburg, Germany
[14]Pediatric Rheumatology, Wilhelmina Children's Hospital, University Medical Center Utrecht, Utrecht, The Netherlands

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ORCID iDs
Victoria Furer http://orcid.org/0000-0001-5193-4207
Christien Rondaan http://orcid.org/0000-0002-4558-1270
Annette de Thurah http://orcid.org/0000-0003-0103-4328

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