Since January 2020 Elsevier has created a COVID-19 resource centre with free information in English and Mandarin on the novel coronavirus COVID-19. The COVID-19 resource centre is hosted on Elsevier Connect, the company's public news and information website.

Journal of Autoimmunity 121 (2021) 102649

Contents lists available at ScienceDirect

Journal of Autoimmunity

journal homepage: www.elsevier.com/locate/jautimm

A recommended paradigm for vaccination of rheumatic disease patients with the SARS-CoV-2 vaccine

Haralampos M. Moutsopoulos

Department of Pathophysiology, School of Medicine, National and Kapodistrian University of Athens and Academy of Athens, Athens, Greece

ARTICLE INFO

Keywords:
SARS-CoV-2
Vaccination
Autoimmune rheumatic diseases
Immunosuppression

ABSTRACT

Autoimmune and autoinflammatory rheumatic disorders (ARD) are treated with antimetabolites, calcineurin inhibitors and biologic agents either neutralizing cytokines [Tumor Necrosis Factor (TNF), Interleukin (IL)-1, IL-6, IL-17, B-cell activating factor] or being directed against B-cells (anti-CD-20), costimulatory molecules or JAK kinases. Similarly for the influenza or pneumococcal vaccines, there is limited data on the effectiveness of vaccination against SARS-CoV-2 infection and COVID-19 prevention for this susceptible patient population. Moreover, preliminary data from vaccinated organ transplanted, inflammatory bowel and connective tissue disease patients suggests only limited immunogenicity after the first vaccine dose, particularly in patients on immunosuppressive regimens. Herein a set of recommendations for the vaccination of immune suppressed patients with the SARS-CoV-2 vaccines is proposed aimed at achieving optimal vaccine benefit without interfering with disease activity status. Moreover, rare autoimmune adverse events related to vaccinations are discussed.

Thanks to biotechnology and the coordinated efforts of the international medical community, in a short period of time, safe and effective vaccines have been implemented to combat the pandemic induced by SARS-CoV-2. However, there is limited data available on the effectiveness and safety of these vaccines in autoimmune rheumatic disease (ARD) patients receiving immunosuppression/immunomodulation since such individuals were not included in phase I–III vaccine trials.

Most ARD patients are treated with antimetabolites (methotrexate, leflunomide, azathioprine and mycophenolate mofetil), calcineurin inhibitors (cyclosporine and tacrolimus), alone or in combination with biologic agents either neutralizing cytokines [Tumor Necrosis Factor (TNF), Interleukin (IL)-1, IL-6, IL-17, B-cell activating factor] or being directed against B-cells (anti-CD-20), costimulatory molecules or JAK kinases [1]. It is therefore reasonable to take appropriate measures ensuring maximum benefit from the vaccination, avoiding at the same time, disease exacerbations.

Considering the precautions taken for the influenza vaccination [2], effective vaccination of ARD patients on immunosuppressive/immunoregulatory therapy should follow certain rules (Table 1). First, it would be ideal to have the patient in clinical remission, to minimize a disease exacerbation risk. Second, initiation of immunosuppressive therapy should be delayed until the vaccination is completed, if possible. Third, antimetabolite medications, JAK and calcineurin inhibitors along with other immunosuppressive agents should be withheld 10 days before and 10 days after each vaccination dose. Fourth, prednisone dosage (>0.5 mg/kg body weight) or an equivalent synthetic steroid dose, should be decreased to <10mg/daily, for 10 days before and after of each vaccination dose, whenever and if possible. Fifth, patients on intravenous rituximab or sixth with intravenous monthly pulse therapy with cyclophosphamide should be vaccinated one month prior to initiation of the therapeutic scheme or 6–8 months after the last rituximab dose. In case of cyclophosphamide, we anticipate immunoglobulin levels returning to normal values one month following the administration of the last intravenous dose. Seventh, immunization of patients on anti-cytokine therapy should be performed, if possible, 7 days after the drug levels have returned to baseline. Eighth, if patients are reluctant to follow the above precautions, they should be vaccinated without withholding their immunoregulatory/immunosuppressive therapy. Finally, given the lack of robust data regarding the immunogenicity of SARS-CoV-2 vaccination in immunosuppressed individuals, in all patients and regardless of adherence to these recommendations, antibody titers against SARS-CoV-2 (previously shown to correlate well with neutralizing antibodies at least in some commercial assays tested) [3] should be checked 2–4 weeks after the final vaccination dose and at 3 and 6 months thereafter. This data will provide information to the medical community on how ARD patients with or without temporary discontinuation of immunosuppression/immunomodulation respond to vaccination against SARS-CoV-2.

E-mail address: hmoutsop@med.uoa.gr.

https://doi.org/10.1016/j.jaut.2021.102649
Received 9 April 2021; Received in revised form 27 April 2021; Accepted 28 April 2021
Available online 1 May 2021

Table 1
Suggested recommendations on SARS-CoV-2 vaccination in ARD patients under immunosuppressive/immunomodulatory agents.

1. Clinical remission prior to vaccination is desirable.
2. Initiation of immunosuppressive therapy should be delayed until the vaccination is completed, if possible.
3. Anti-metabolites, calcineurin and JAK inhibitors should be held 10 days before and 10 days after each vaccination dose.
4. Prednisone dosage (>0.5 mg/kg body weight) or an equivalent synthetic steroid dose, should be decreased to <10 mg/daily for 10 days before and after each vaccination dose (if possible).
5. Patients on rituximab therapy should be vaccinated either one month prior to initiation of the therapeutic scheme or 6–8 months after the rituximab infusion.
6. Patients on intravenous monthly pulse cyclophosphamide/methyl prednisone therapy should be vaccinated either prior to therapeutic scheme or one month after the completion of 6 months pulse therapy.
7. Immunization should be performed after the anti-cytokine drug therapy has reached baseline sera levels (if possible).
8. If some patients are reluctant to follow the above precautions, they should be vaccinated without withholding their immunoregulatory/immunosuppressive therapy.
9. In all cases, regardless of adherence to these recommendations, antibody titers against SARS-CoV-2 should be checked 2–4 weeks after the final vaccination dose and at 3 and 6 months thereafter.

Table 2
Antibody response (%) after the first dose of the SARS-CoV-2 vaccination[a].

Patient group	Number	Medications			Reference
		Immunomodulatory/Immunosuppressives	Biologic	Immunomodulatory + Biologic	
		Antibody response (%)			
Organ Transplantation	436	8.8	N/A	N/A	Boyarsky et al. [5]
IBD	865	N/A	31.4	23.3	Kennedy et al. [6]
ARDs	123	69.6	64.7	71.1	Boyarsky et al. [7]

N/A: Not applicable.
IBD: Inflammatory bowel syndrome.
ARD: Autoimmune rheumatic diseases.[a]
[a] Rates of antibody responses were calculated using data from the original publications

It should be emphasized that these recommendations are somewhat different than those proposed by the ACR COVID-19 Vaccine Clinical Guidance Task Force [4], supporting the continuation of therapy in patients receiving all anti-cytokine therapies, azathioprine and calcineurin inhibitors. Moreover, while temporary cessation of methotrexate and JAK inhibitors is suggested, this should be limited only after and not prior to administration of each vaccination dose. Finally, testing for antibody titers against SARS-CoV-2 is discouraged, despite the lack of sufficient evidence regarding immunogenicity of SARS-CoV-2 among immunosuppressed individuals. On the other hand, according to three recent studies, antibody responses following various immunosuppressive/immunomodulatory treatments seem to compromise optimal antibody responses following SARS-CoV-vaccination (Table 2). Thus, less than one fifth of organ transplanted individuals after the first vaccine dose developed antibodies against SARS-CoV-2 virus, with those on antimetabolites displaying the poorest immune response against viral antigens [5]. Additionally, patients with inflammatory bowel disease treated with infliximab demonstrated an attenuated serological response against SARS-CoV-2, which was further blunted when anti-TNF agents were combined with other immunomodulators [6]. Furthermore, sera derived from patients with connective tissue diseases were tested after the first dose of the SARS-CoV-2 mRNA vaccine and the majority of participants developed detectable anti-SARS-CoV-2 antibodies; however, patients on regimens including mycophenolate mofetil or rituximab were less likely to develop an antibody response [7]. Though data is not available, in case that adequate antibody responses against SARS-CoV-2 cannot be mounted, repeat of vaccination or change to the type of vaccine administered could be considered.

A recently emerging issue concerns the recognition of a rarely observed syndrome mainly occurring in young females, after administration of the first dose of the ChAdOx1 nCoV-19 vaccine. This entity-named vaccine-induced immune thrombotic thrombocytopenia (VITT)- is mediated by antibodies against platelet factor-4 (PF-4) and manifests by thrombosis in atypical sites and concomitant thrombocytopenia [8]. PF-4 has been designated as a dominant ligand for beta2 glycoprotein I, the main antigenic target for antiphospholipid syndrome [9]. Given that a small percentage of patients with lupus and antiphospholipid syndrome have been previously shown to display serum antibodies against PF-4 in association with thrombotic events [10], constant vigilance is warranted following vaccination of this patient population.

Taken together, we suggest that immunomodulatory/immunosuppressive therapy should be modified accordingly in ARD patients to ensure a maximum benefit from the vaccination avoiding at the same time the risk for disease exacerbation. Close monitoring of adverse events in this population and identification of potential risk contributors is eagerly needed.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

References

[1] H.M. Moutsopoulos, E. Zampeli, Treatment and management of rheumatic diseases, in: H.M. Moutsopoulos, E. Zampeli (Eds.), Immunology-Rheumatology in Questions, Springer-Nature publishers, 2021.
[2] J.K. Park, Y.J. Lee, K. Shin, et al., Impact of temporary methotrexate discontinuation for 2 weeks on immunogenicity of seasonal influenza vaccination in patients with rheumatoid arthritis: a randomized clinical trial, Ann. Rheum. Dis. 77 (2018) 898–904.
[3] N. Kohmer, S. Westhaus, C. Rühl, S. Ciesek, H.F. Rabenau, Brief clinical evaluation of six high-throughput SARS-CoV-2 IgG antibody assays, J. Clin. Virol. 129 (2020) 104480.
[4] COVID-19 Vaccine Clinical Guidance Summary for Patients with Rheumatic and Musculoskeletal Diseases Developed by the ACR COVID-19 Vaccine Clinical Guidance Task Force, Updated, April 28, 2021.
[5] B.J. Boyarsky, W.A. Werbel, R.K. Avery, et al., Immunogenicity of a single dose of SARS-CoV-2 messenger RNA vaccine in solid organ transplant recipients, J. Am. Med. Assoc. (March 15, 2021), https://doi.org/10.1001/jama.2021.4385. Published online.

[6] N.A. Kennedy, S. Lin, J.R. Goodhand, N. Chanchlani, B. Hamilton, C. Bewshea, et al., Infliximab is associated with attenuated immunogenicity to BNT162b2 and ChAdOx1 nCoV-19 SARS-CoV-2 vaccines in patients with IBD, Gut (2021 Apr 26), https://doi.org/10.1136/gutjnl-2021-324789 gutjnl-2021-324789. Epub ahead of print. PMID: 33903149; PMCID: PMC8076631.

[7] B.J. Boyarsky, J.A. Ruddy, C.M. Connolly, et al., Antibody response to a single dose of SARS-CoV-2 mRNA vaccine in patients with rheumatic and musculoskeletal diseases, Annals of the Rheumatic Diseases Published Online First (23 March 2021), https://doi.org/10.1136/annrheumdis-2021-220289.

[8] D.B. Cines, J.B. Bussel, SARS-CoV-2 vaccine-induced immune thrombotic thrombocytopenia, N. Engl. J. Med. (2021 Apr 16), https://doi.org/10.1056/NEJMe2106315. Epub ahead of print. PMID: 33861524.

[9] M.P. Sikara, J.G. Routsias, M. Samiotaki, G. Panayotou, H.M. Moutsopoulos, P. G. Vlachoyiannopoulos, β2 Glycoprotein I (β2GPI) binds platelet factor 4 (PF4): implications for the pathogenesis of antiphospholipid syndrome, Blood 115 (2010) 713–723.

[10] D. Alpert, L.A. Mandl, D. Erkan, W. Yin, E.I. Peerschke, J. Salmon, Anti-heparin platelet factor 4 antibodies in systemic lupus erythematosus are associated with IgM antiphospholipid antibodies and the antiphospholipid syndrome, Ann. Rheum. Dis. 67 (2008) 395–401.