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Short communication

COVID-19 vaccination in rituximab-treated patients with rheumatic disorders

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Introduction

Different viral agents including severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) are associated with an increased risk of more severe disease course in patients with autoimmune and inflammatory rheumatic diseases (Conway et al., 2022). Prioritized vaccination for COVID-19 is recommended in these patients before the general population of similar age and sex. (ACR COVID-19 Vaccine Clinical Guidance, 2022).

Although vaccines against SARS-CoV-2 remain the most important way to stop the pandemic, patients with rheumatic and musculoskeletal diseases who are currently on treatment with rituximab show impaired immunogenicity toward vaccines. Rituximab is a chimeric monoclonal antibody that targets the CD-20 antigen on B-lymphocytes. Its use is associated with prolonged B-cell depletion, severe disease and prolonged hospitalization in patients with rheumatic diseases infected with COVID-19 (Levavi et al., 2021).

Regarding COVID-19 vaccination for immunocompromised patients, The American College of Rheumatology (ACR) has published guidance on supplemental and booster doses and recommendations for the timing of vaccination concerning immunomodulatory medication including rituximab. Vaccination for rituximab-treated patient is recommended 2-4 weeks before the next anticipated rituximab dose (e.g., at month 5.0 or 5.5 for patients on an every 6 month rituximab dosing schedule), when the effect of the previous dose of rituximab is weakest (ACR COVID-19 Vaccine Clinical Guidance, 2022).

There are concerns about risks of COVID-19 breakthrough infections in vaccinated patients with immune-mediated inflammatory diseases, but the data on COVID-19 breakthrough infections in patients with rheumatic disorders treated with immunosuppressant is still limited.

Our objective was to analyze COVID-19 vaccination in rituximab-treated patients with rheumatic disorders and compare characteristics and outcomes of COVID-19 in vaccinated and unvaccinated patients.

Materials and methods

In this retrospective cohort study, we analyzed data from the e-health national system "MojTermin", which included patients from University Clinic of Rheumatology in Skopje, who were 18 years or older with inflammatory rheumatic disorders treated with rituximab. Using this data we analyzed the type, date and doses of SARS-CoV-2 vaccines, demographic characteristics, type of rheumatic disorders, concurrent treatment and comorbidities among the patients. The main focus was put on COVID-19 outcomes related to SARS-CoV-2 pneumonia, hospitalization rate and death between vaccinated and unvaccinated patients. Patients who had received two doses of vaccination and presented with COVID-19 ≥14 days after the second vaccine dose were considered as 'fully vaccinated'. Fisher's exact test and Kaplan-Meier survival analysis were used to compare COVID-19 outcomes between vaccinated and unvaccinated patients. Statistical package MedCalc version 20.1111 was used.

Results and discussion

Between January 2020 and April 2022, 135 patients with rheumatic diseases treated with rituximab (85.92 % women with a mean age of 58 years) were recorded. The most frequent diagnoses were rheumatoid arthritis

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(91.1 %), systemic lupus erythematosus (3.7 %), systemic sclerosis (2.9 %), granulomatosis with polyangiitis and vasculitis (2.9 %), and one patient (0.7 %) with dermatomyositis. Comorbidities were present in about 30% of the patients, with arterial hypertension being the most common. Glucocorticoids were administered to approximately one-third of the patients, with figures similar for treatment with biological and targeted synthetic disease-modifying antirheumatic drugs.

Of these patients, 50 were unvaccinated, while 85 had received two doses of SARS-CoV-2 vaccine, namely, Pfizer/BioNTech in 32 (37.6 %), Sinopharm in 26 (30.5 %), CoronaVac/Sinovac in 17 (20 %), Sputnik V in 5 (5.8 %) and AstraZeneca in 5 (5.8 %). 25 patients had received the third dose of Pfizer/BioNTech. Among the 85 vaccinated patients, 75 had received two doses of COVID-19 vaccine after the last dose of rituximab. The median time from the last rituximab dose to COVID-19 vaccination was 9 months.

51 rituximab-treated patients were with an RT-PCR-confirmed SARS-CoV-2 infection. Of these, 13 (25.4%) were breakthrough infections. Among the breakthrough infections, 12 (92.3%) were female, the median age was 58 years and 10 (76%) patients had ≥1 comorbidity. The median time from the second vaccine dose to COVID-19 diagnosis (positive PCR) was 150 (range 60-240) days.

Between vaccinated and unvaccinated rituximab-treated patients, there were differences in terms of COVID-19 outcomes. The majority of unvaccinated patients (including those who received COVID-19 vaccine after SARS-CoV-2 infection) (26/38, 68.4 %) were with presence of SARS-CoV-2 pneumonia, compared with fully vaccinated patients (7/13, 53.8 %). Hospitalization rates were higher in unvaccinated (24/38, 63.1 %) compared with fully vaccinated (7/13, 53.8%) patients. There were seven deaths among unvaccinated (18.4 %) compared with none among vaccinated patients with COVID-19. Median time till death after rituximab last dose was 120 days.

Taking into consideration that most of the patients were fully vaccinated, this study shows that patients and physicians adhered to the recommendations of ACR COVID-19 Vaccine Clinical Guidance. The majority of the patients got infected 120 days after the second dose. This can be explained by the fact that vaccine efficacy declines over time which why third dose is highly recommended. Only two patients (8 %) got infected, two months after receiving the third dose. Antibody response to vaccination was not routinely measured in this study, even the response might have been weakened by anti-CD20 treatment. Additionally, temporal fluctuations of the viral load during 2021 in our country have an impact in our results. There were no statistically significant differences in SARS-CoV-2 pneumonia and hospitalization rate between vaccinated and unvaccinated groups ($p > 0.05$), possibly due to the low number of patients. It should be noted that unvaccinated patients were associated with lower survival probability (log rank $P = 0.0209$), and no deaths were reported in fully vaccinated patients which is comparable to the results described by a previous similar observational study (Papagoras et al., 2022).

Conclusion

According to our findings fully vaccinated patients with rheumatic disorders have better COVID-19 outcome compared to unvaccinated patients, despite the immunosuppressive treatment with rituximab.

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