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.

Elsevier hereby grants permission to make all its COVID-19-related research that is available on the COVID-19 resource centre - including this research content - immediately available in PubMed Central and other publicly funded repositories, such as the WHO COVID database with rights for unrestricted research re-use and analyses in any form or by any means with acknowledgement of the original source. These permissions are granted for free by Elsevier for as long as the COVID-19 resource centre remains active.
Letter to the Editor

Influence of vaccination and immunosuppressive treatments on the coronavirus disease 2019 outcomes in patients with systemic autoimmune diseases

**ARTICLE INFO**

**Keywords**
Autoimmune diseases
COVID-19
Immunosuppressive agents
Vaccination

Dear editor,

Systemic autoimmune diseases (SAID) are a heterogeneous group of diseases with a common etiopathogenic basis, often requiring immunosuppressive therapies (DMARD) [1]. Although case-control studies reported no significant differences in coronavirus disease 2019 (COVID-19) outcomes, large population-based studies analyzing baseline risk factors reported a 2–3 times higher rate of poor outcomes in patients with SAID [1].

Certain factors could increase the risk of severe COVID-19, such as SAID itself, the use of steroids at intermediate-high doses [2,3], and the type of DMARD [4–6]).

The safety of vaccines against SARS-CoV-2 in people with autoimmune diseases was reassuring and comparable to patients with non-inflammatory diseases [7]. However, there is little evidence regarding the effect of vaccines against COVID-19 on SAID, since these patients were not included in clinical trials [8].

Our main objective was to evaluate the cumulative incidence of SARS-CoV-2 infection and its severity by assessing hospitalization, intensive care unit (ICU) admission, and mortality from March 2020 to March 2022 in SAID. The secondary objectives were to evaluate the effect of DMARD and vaccines and their impact on COVID-19.

We conducted a retrospective single-center study (Systemic Autoimmune Diseases Unit, Internal Medicine Department, Hospital Universitario La Paz (PI-5055). We performed a multivariate analysis to assess the risk of DMARD and vaccines on SARS-CoV2 infection (defined as a positive diagnostic test for SARS-CoV2), hospital admission, and COVID-19-related death. The cumulative incidences (of infection, admission, and mortality) were compared with those available for the Comunidad Autónoma de Madrid (CAM) because it was a similar environment with the same health and vaccination policies.

A total of 662 patients, with compliance to classificatory criteria for SAID and under active follow-up, met the inclusion criteria. Most patients were women (80.9%), and the mean age was 47.5. The three most prevalent SAID in our cohort were Systemic Lupus Erythematosus (30.1%), Antiphospholipid Syndrome (16.3%), and primary Sjögren’s Syndrome (13.4%). However, if taken all vasculitides together, they were the second SAID (20.7%).

One-fourth of the patients (27.1%) were taking steroids, but only 13.5% with doses ≥5 mg/day. Almost half of the patients (49.7%) were under DMARD other than steroids. A total of 46.7% were under cDMARD (classical), 7.4% with bDMARD (biological), and 4.4% with both cDMARD and bDMARD. The DMARD used were hydroxychloroquine (31.9%), azathioprine (12.1%), mycophenolate (6.9%), methotrexate (6.3%), tacrolimus (2.7%), rituximab (2.3%), anti-TNF (1.8%), belimumab (1.2%), tocilizumab (0.6%), anti-IL5 (0.45%), and JAK inhibitors (0.3%).

A third (37.9%) of SAID patients had COVID-19, and 3.8% (n = 25) were infected more than once. Most COVID cases (66.5%) occurred in unvaccinated or pre-vaccinated patients.

The cumulative incidence of infection was 37.9%, admission 3.2%, ICU admission 0.3%, and COVID-19 mortality 0.6%. There was a significant association between COVID-19 and SAID (p < 0.001, OR 1.93) compared with the CAM after adjustment for confounding factors. However, it was not significant for severe disease: hospital admission (p = 0.065), mortality (p = 0.063), or ICU admission (p = 0.691). There were no differences between SAID.

Risk factors for infection (COVID-19) were SAID and methotrexate; for hospital admission were age ≥60 years, steroids, and methotrexate; and for mortality were age ≥60 years, male sex, steroids, methotrexate, and tacrolimus. Vaccination was a protective factor against infection, admission, and death (Fig. 1).

Steroid doses ≥7.5 mg/day were associated with a higher risk of hospital admission and ≥5 mg/day with higher mortality. This is in line with the literature in which doses ≥10 mg/day were related to higher odds of hospitalization [2,3,9]. Doses <5 mg/day were not associated with an increased risk of infection, admission, or mortality. Besides, the steroid influence on admission and mortality disappeared post-vaccination, highlighting its importance, especially within intermediate to high doses.

The role of DMARD on infectious risk is complex to analyze because individual risk (sex, age, comorbidities,...), SAID itself, disease control, and treatments are always intertwined. However, some DMARDs (methotrexate and tacrolimus) did condition poorer results. Hydroxychloroquine did not have any protective effect, which is consistent with
the results of other observational studies [5,9]. Contrary to previous studies [5,6,9], we found no statistically significant association between rituximab and infection, admission, ICU, or mortality. All cases of COVID-19 in patients under rituximab treatment occurred before vaccination, and there were no post-vaccination cases. The risk associated with rituximab should be evaluated prospectively and in larger cohorts.

Most patients (93.6%) were vaccinated: 3.5% received one dose, 25.7% had two, and 63.4% had three. Vaccine types were Pfizer-BioNTech (75.4%), Oxford-AstraZeneca (11.6%), Moderna (10.8%), and Janssen (2.2%). Unvaccinated patients had a higher percentage of SARS-CoV-2 infection, admission, and mortality compared to vaccinated (p < 0.001), regardless of the number of doses or the type of vaccine. There were no safety incidents or significant adverse effects nor flares after vaccination. The number needed to vaccinate (NNV) to avoid one infection was 4.3, for admission was 13.2, and for mortality 17.3. The greater the vaccine doses, the lower the risk of infection, admission, and death (OR 0.29).

Other studies indicated that the antibody response induced by vaccination might be lower in immunosuppressed patients. However, it may help prevent severe disease [10]. Neutralizing antibody titers were not measured, so we cannot correlate these titers with severe outcomes. We have shown that vaccination decreased the risk of infection, admission, and mortality in patients with SAID, and NNV was low. This only reinforces the relevance of vaccination and the need to include SAID patients in vaccination programs against COVID-19, thus protecting groups at higher risk of severe disease.

The limitations of this study are those inherent to a single-center retrospective study. Although we analyzed and adjusted for age and sex, we did not study the role of different comorbidities on the risk of COVID-19.

The strengths of this study include the large sample size, even though SAID are rare diseases and that it is a single-center study. In addition, it is a study from the beginning of the pandemic (March 2020) to March 2022. It is also novel in analyzing the impact of immunosuppressive therapy and the effect of vaccination on COVID-19, hospital admission, and mortality.

In conclusion, this research shows a nearly 2-fold increased risk of SARS-CoV-2 infection in SAID, but no statistically significant relationship between SAID and hospital admission, ICU admission, and COVID-19 mortality. Regarding immunosuppressive treatment, steroids and methotrexate seem to have a higher incidence of infection, admission and mortality due to COVID-19. However, most cDMARD and bDMARD were not associated with worse outcomes. Irrespective of SAID and DMARD, unvaccinated patients were associated with an increased risk of infection, admission, and death from SARS-CoV-2. In view of these data, it is emphasized the enormous protective role of vaccination in SAID.

Source(s) of support

The authors declare that this research was not funded.

Statement of ethics and consent

This study complied with the Declaration of Helsinki and was approved by the Local Ethics Commission. All the authors have read the instructions to authors, and all accept the conditions posed.

Funding statement

The authors declare that this study was not funded.

Declaration of Competing Interest

The authors have no conflict of interest to declare.

References

[1] Brito-Zerón P, Sisó-Almirall A, Flores-Chavez A, Retamozo S, Ramos-Casals M. SARS-CoV-2 infection in patients with systemic autoimmune diseases. Clin Exp Rheumatol 2021;39(3):576–87. doi.org/10.1016/j.climexp.2020.07.001.
[2] 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(7):859–66. doi.org/10.1136/annrheumdis-2020-217871.
[3] Hyrich KL, Machado PM. Rheumatic disease and COVID-19: epidemiology and outcomes. Nat Rev Rheumatol 2020;16(12):710–21. doi.org/10.1038/s41584-020-00562-2.
[4] Kastritis E, Kinas GD, Vassilopoulos D, Giannopoulos G, Dimopoulos MA, Sfikakis PP. Systemic autoimmune diseases, anti-rheumatic therapies, COVID-19 infection risk and patient outcomes. Rheumatol Int 2020;40(9):1353–60. doi.org/10.1007/s00296-020-04629-x.
[5] Sharmane S, Elghawy A, Zarloul F, Yao Q. COVID-19 in rheumatic disease patients on immunosuppressive agents. Semin Arthritis Rheum 2020;50(4):680–6. doi.org/10.1016/j.semarthrit.2020.05.016.
[6] Ouedraogo DD, Tiendrébéogo WJS, Kaboré SO, Ntsiba H, COVID-19, chronic inflammatory rheumatic disease and anti-rheumatic treatments. Clin Rheumatol 2020;39(7):2069–75. doi.org/10.1007/s10067-020-05189-y.
[7] Machado PM, Lawson-Tovey S, Strangfeld A, et al. Safety of vaccination against SARS-CoV-2 in people with rheumatic and musculoskeletal diseases: results from
the EULAR Coronavirus Vaccine (COVAX) physician-reported registry. Ann Rheum Dis 2021;81(5):695–709. https://doi.org/10.1136/annrheumdis-2021-221490.

[8] Felten R, Dubois M, Ugarte-Gil MF, et al. Vaccination against COVID-19: expectations and concerns of patients with autoimmune and rheumatic diseases. Lancet Rheumatol 2021;3(4):e243–5. https://doi.org/10.1016/s2665-9913(21)00039-4.

[9] Strangfeld A, Schäfer M, Gianfrancesco MA, et al. Factors associated with COVID-19-related death in people with rheumatic diseases: results from the COVID-19 Global Rheumatology Alliance physician-reported registry. Ann Rheum Dis 2021;80(7):930–42. https://doi.org/10.1136/annrheumdis-2020-219498.

[10] Mason A, Anver H, Lwin M, Holroyd C, Faust SN, Edwards CJ. Lupus, vaccinations and COVID-19: what we know now. Lupus 2021;30(10):1541–52. https://doi.org/10.1177/09612033211024355.

Jorge Álvarez-Troncoso*,a,b, Lucía López-Caballerob, Ángel Robles-Marhuendia, Clara Soto-Abainades, Juan José Ríos-Blancoc,b

a Unidad de Enfermedades Autoinmunes Sistémicas, Servicio de Medicina Interna, Hospital Universitario La Paz, Hospital General, Secretaría Planta 13, Paseo de la Castellana, 261, Madrid 28046, Spain

b Universidad Autónoma de Madrid, Hospital Universitario La Paz, Spain

* Corresponding author at: Unidad de Enfermedades Autoinmunes Sistémicas, Servicio de Medicina Interna, Hospital Universitario La Paz, Hospital General, Secretaría Planta 13, Paseo de la Castellana, 261, Madrid 28046, Spain.

E-mail address: jorge.alvarez.troncoso@gmail.com (J. Álvarez-Troncoso).