Letter to the Editor

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

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 $\geq$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 $\geq$60 years, steroids, and methotrexate; and for mortality were age $\geq$60 years, male sex, steroids, methotrexate, and tacrolimus. Vaccination was a protective factor against infection, admission, and death (Fig. 1).

Steroid doses $\geq$7.5 mg/day were associated with a higher risk of hospital admission and $\geq$5 mg/day with higher mortality. This is in line with the literature in which doses $\geq$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
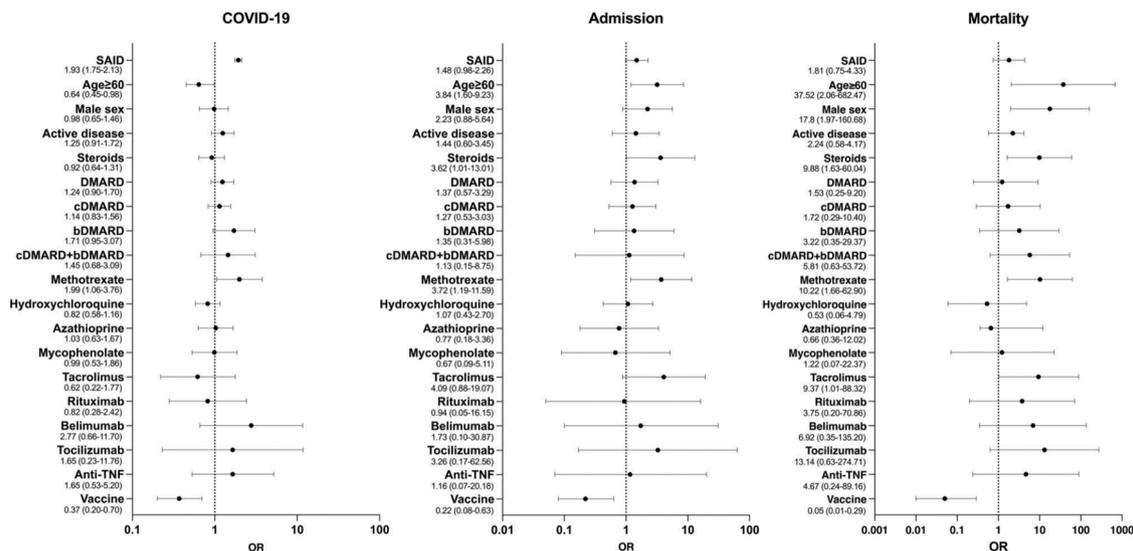
Fig. 1. Forest plot of risk factors of infection, hospital admission, and mortality due to COVID-19.

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 research 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.

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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.

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Declaration of Competing Interest

The authors have no conflict of interest to declare.

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