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ORIGINAL RESEARCH

Outcome of COVID-19 in patients with rheumatic and inflammatory diseases treated with mycophenolic acid: data from the French RMD COVID-19 cohort

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ABSTRACT

Background Patients with inflammatory rheumatic and musculoskeletal diseases (iRMD) receiving mycophenolic acid (MPA) may have a less favourable outcome from COVID-19 infection. Our aim was to investigate whether MPA treatment is associated with severe infection and/or death.

Methods IRMD patients with and without MPA treatment with highly suspected/confirmed COVID-19 were included in this observational multicentre study. The primary outcome was death rate from COVID-19 with secondary objectives to determine the severity of infection and length of hospital stay. Outcome comparisons were made using regression models with and without adjustment on prespecified confounding factors. ORs, sub-HR (sHR) and 95% CIs were calculated using patients not treated with MPA as a reference group.

Results Of the 1977 patients, 1928 were not treated with MPA (393 were MPA eligible), and 49 patients were treated with MPA. MPA-treated patients had more severe disease, longer hospital stays and higher death rate from COVID-19 than non-MPA patients (OR 8.02 (95% CI 3.35 to 19.20), p<0.001; sHR 0.57 (95% CI 0.33 to 0.98), p=0.040; OR 11.58 (95% CI 4.10 to 32.69), p<0.001). In adjusted analyses, however, no outcome was independently associated with MPA treatment. Death rate, severity and length of hospital stay of MPA-treated patients were not significantly different from those of not treated but MPA-eligible patients.

Conclusion MPA therapy is not associated with a more severe COVID-19 infection. However, due to increased vulnerability of developing a severe form of COVID-19, careful consideration should be taken with iRMD patients likely to be treated with MPA.

Trial registration number NCT04353609.

WHAT IS ALREADY KNOWN ON THIS TOPIC

⇒ In the COVID-19 Global Rheumatology Alliance registry analysis, immunosuppressive agents (mycophenolic acid (MPA), but not synthetic/biological targeted disease-modifying antirheumatic drugs), have been pinpointed as providing an increased risk of death from COVID-19 when compared with standard of care methotrexate.

⇒ However, whether patients with inflammatory rheumatic and musculoskeletal diseases (iRMD) receiving MPA treatment have a higher risk of COVID-19 related death remains controversial due to inconsistencies among clinical studies.

WHAT DOES THIS STUDY ADD

⇒ In age and sex adjusted analyses, iRMD patients treated with MPA had similar disease severity, length of hospital stay and death rate following COVID-19 infection to iRMD patients not treated with MPA.

⇒ Our study demonstrates that iRMD patients have increased risk of a poor outcome from COVID-19, but this risk is likely due to confounding factors, not MPA therapy.

HOW THIS STUDY MIGHT AFFECT RESEARCH, PRACTICE OR POLICY

⇒ MPA use should be continued in iRMD patients without fear of an increased risk of severe COVID-19.

⇒ Patients receiving MPA are also the most vulnerable to severe COVID-19, and vaccination against COVID-19 should be a priority, with a close follow-up monitoring of the vaccine response.

INTRODUCTION

Throughout the pandemic, physicians who treat patients with inflammatory rheumatic and musculoskeletal diseases (iRMD) have been concerned their patients would develop more severe forms of the COVID-19 disease due to the disruption of their immune systems as a result of their illness or treatment.[1] The first preliminary published data on this aspect were reassuring in refuting this concern.[2] In a recent systematic review to

inform the European Alliance of Associations for Rheumatology recommendations, patients with rheumatic musculoskeletal diseases (RMDs) do not face worse prognosis of COVID-19 than individuals without RMDs.[3] However, these data are in disagreement with those obtained in the Global Rheumatology Alliance (GRA) database analysis, which showed that RMD patients with moderate to high disease activity had a higher risk of COVID-19 related death.[4] Subsequent recommendations stated that there was no evidence that patients with RMD were at higher risk of SARS-CoV-2 infection than individuals without RMDs or have an inferior prognosis with a COVID-19 diagnosis.[5] In an analysis of the French RMD COVID-19 cohort, which includes iRMD patients with highly suspected or confirmed diagnosis of COVID-19, older age, male gender, obesity, hypertension and interstitial lung disease (ILD) were found to be associated with severe COVID-19, similar to those observed for the general population.[6] In this cohort, the use of methotrexate or TNFα and IL-6 inhibitors was not related to severe infection, but use of corticosteroids at high doses was linked with more severe disease.[6] A potential risk of more severe COVID-19 in patients treated by rituximab (RTX) or by mycophenolic acid (MPA; the pharmacologically active ingredient in mycophenolate sodium or mycophenolate mofetil, both of which are used to treat patients in France) has been suspected. Recent analysis has confirmed the increased risk with RTX,[7] and in the COVID-19 GRA registry, immunosuppressive agents (comprising MPA but not synthetic/biological targeted disease-modifying antirheumatic drugs) have been pinpointed as increasing the risk of a death from COVID-19 when compared with methotrexate.[4]

Currently, treatment with MPA is used under very specific conditions in iRMD, which is characterised by a higher risk of poor prognosis, including connective tissue disorders, with pulmonary or renal involvement.[8 9] Whether iRMD patients treated with MPA have a higher risk of developing severe COVID-19 is still unclear. We hypothesised that iRMD patients are more vulnerable to more severe disease following SARS-Cov-2 infection regardless of their MPA treatment status. Thus, the aim of this study was to investigate whether treatment with MPA by itself is associated with increased disease severity and/or death rate in the French RMD COVID-19 cohort.

PATIENTS AND METHODS

Study design and patients

This is an observational, multicentre study of the French RMD cohort, which has been previously described.[6] Briefly, the cohort enrolled participants ≥18 years old patients with confirmed RMD with highly suspected/confirmed diagnosis of COVID-19.[10]

Data collection

All cases of highly suspected/confirmed iRMD-COVID-19 patients were reported retrospectively. The individual data regarding iRMD diagnosis/specific treatments were captured from physicians via a national data entry portal. Data collection from the patient's medical record was previously described.[6] Data cut-off was 20 August 2021, and the final database was monitored to collect missing data, validate the evolution of COVID-19, remove duplicate or erroneous reports and check data consistency.

Outcomes

The primary endpoint was the death rate from COVID-19. Secondary outcomes were severity of the infection and the length of hospital stay. Severity of COVID-19 was assessed at least 21 days after the first clinical sign of COVID-19 and classified according to the care needed for each patient: mild=ambulatory; moderate=hospitalised out of intensive care unit (ICU); and severe=ICU or deceased. These outcomes were compared between MPA-treated patients and patients not treated with MPA, as well between MPA-treated patients and patients not treated with MPA but who were eligible for MPA treatment (MPA eligible subgroup). A patient was defined as eligible for MPA treatment when affected with a disease that may potentially be treated with MPA according to standard of care recommendations or previous evidence-based medical treatment (ie, systemic lupus erythematosus, systemic sclerosis, inflammatory myopathy, vasculitis associated with cytoplasmic anti-neutrophil antibodies, IgG4-related disease, mixed connective tissue disease, primary Sjögren syndrome, other vasculitis or eye inflammation).

Statistical analysis

Categorical variables were expressed as numbers (percentage) and continuous variables as mean±SD. Length of hospital stay was estimated using a competing risk survival analysis approach (Kalbfleisch and Prentice method)[10] to account for hospital mortality, by estimating the cumulative incidence of discharge alive, treating death as the competing event. We compared outcomes between groups (MPA-treated group vs group with no MPA treatment and MPA-treated group vs MPA eligible subgroup) using multinomial logistic regression model for severity outcome measure (a three-level categorical variable), using binary logistic regression model for binary outcomes (death) and using Fine and Gray regression model for length of hospital stay, with discharge alive as the event of interest and hospital death as the competing event. Analyses were adjusted for age and sex and then for all prespecified confounding factors (ie, age, sex, arterial hypertension, body mass index (BMI), interstitial lung disease (ILD), cardiovascular diseases, corticoid treatment (three-level categorical variable defined as no corticoid treatment, <10 mg treatment and ≥10 mg treatment) and chronic renal failure). To consider all prespecified confounding factors, we made comparisons by using the propensity score overlap weighting (PSOW) method, which allows for consideration of extreme propensity scores.[11] We estimated the propensity score using a multivariable logistic

regression model, with study groups as dependent variables including all prespecified confounding factors. OR and sub-HR (sHR) and the corresponding 95% CIs were calculated as effect size using patients not treated with MPA as reference groups. To avoid case deletion in analyses, missing data for outcomes and prespecified confounding factors were imputed by simple imputation using the regression-switching approach. The imputation procedure was performed under the missing-at-random assumption, with predictive mean-matching method for continuous variables and logistic regression (binary, ordinal or multinomial) models for categorical variables. To test the robustness of our models, we performed bootstrap resampling analysis (200 resamples from the original database) as sensitivity analysis. The method consist to calculate in 200 replicates the propensity score to provide the PSOW adjusted p values for each outcomes comparison in each replicates; the median and 95% CI (ie, the 2.5th and 97.5th percentile) of PSOW adjusted p-values of the 200 replicates were reported. All statistical tests were performed at the two-tailed α level of 0.05 using SAS software, release V.9.4 (SAS Institute).

RESULTS

A total of 1977 records were collected, all with available final evaluation of COVID-19 outcome (table 1). As a cohort, patients were predominately female (66.6%), with a mean age of 55±17 years (52.2% (n=1033) were ≥55 years old) and 68.1% of the patients had at least one comorbidity (n=1343), with hypertension (n=474, 24.0%), obesity (BMI ≥30 kg/m^2, n=438, 24.7%), respiratory disease (n=269, 13.6%) and cardiac disease (n=222, 11.2%) among the most common.

Among the cohort, 49 patients were treated with MPA, mainly for systemic lupus erythematosus (n=22, 44.9%) and systemic sclerosis (SSc) (n=18, 36.7%). Two control groups were considered for comparison with MPA-treated patients: the first included all patients not treated with MPA (n=1928) and the second consisted of a subgroup of patients not treated with MPA but eligible for MPA treatment (n=393). The mean age of the patients was 45±15 years in the MPA treated group, 56±17 years in the patients not treated with MPA and 55±18 years in the MPA-eligible subgroup. ILD was present in 34.7% of the MPA-treated patients (n=17/49), 4.0% of the patients not treated with MPA (n=77/1928) and 8.7% of the MPA eligible subgroup (n=34/393) as shown in table 1. Moreover, chronic renal failure was present in 18.4% of the MPA-treated patients (n=9/49), but only 4.4% of the patients not treated with MPA (n=85/1928) and 10.2% of the MPA-eligible subgroup (n=40/393). Corticosteroids were prescribed to more than 70% of the MPA-treated patients (n=35/49) and to less than 30% of the patients not treated (n=530/1928). In each of the three patient groups, the proportion of patients receiving more than 10 mg/day of corticosteroids was approximately 40%.

In the MPA-treated group, 18.4% of patients (n=9/49) were classified as having a severe COVID-19 infection, with 11.1% (n=219/1928) in the not treated with MPA group and 14.3% (n=56/393) in the not treated MPA eligible subgroup having been documented with the same COVID-19 severity. In the age-sex adjusted analyses, MPA-treated patients had an increased risk of presenting a moderate and severe form of COVID-19 compared with patients not treated with MPA: OR for moderate versus mild: 3.57 (95% CI 1.76 to 7.21), p<0.001, and OR for severe versus mild: 8.02 (95% CI 3.35 to 19.20), p<0.001 (table 2). After adjusting for potential confounding factors using the PSOW (online supplemental figure 1), no differences in severity were confirmed in the MPA-treated group compared with the group not treated with MPA: OR for moderate versus mild: 1.18 (95% CI 0.40 to 3.45), OR for severe versus mild: 1.18 (95% CI 0.34 to 4.05) (table 2). Furthermore, MPA-treated patients presented no differences for severity compared with subgroup (OR for moderate vs mild: 0.83 (95% CI 0.27 to 2.50); OR for severe vs mild: 1.20 (95% CI 0.32 to 4.40); table 3). In bootstrapping analyses, the median of PSOW adjusted p values for comparison of severity was 0.70 (2.5th to 97.5th percentiles, 0.13 to 1.00) in overall population and 0.63 (2.5th to 97.5th percentiles, 0.11 to 0.98) in the eligible population.

The median length of hospital stay was 9.0 (IQR 4.0 to 19.0) in the MPA-treated group, 10.0 (IQR 5.0 to 26.0) in patients not treated with MPA and 10.0 (IQR 6.0 to 32.0) in the treatment-eligible subgroup. In the age-adjusted and sex-adjusted analyses, a lower length of hospital stay was found in treated group compared with group of patients not treated with MPA (sHR 0.57 (95% CI 0.33 to 0.98), p=0.040; table 2), but no differences were found in treated group compared with the eligible subgroup (sHR 0.74 (95% CI 0.42 to 1.31); table 3). After adjusting for potential confounding factors by PSOW, no differences were confirmed in the MPA-treated group compared with the group not treated with MPA (sHR 0.87 (95% CI 0.41 to 1.84); table 2) or the eligible subgroup (sHR 0.93 (95% CI 0.42 to 2.05); table 3). In bootstrapping analyses, the median of PSOW adjusted p values for comparison of severity was 0.63 (2.5th to 97.5th percentiles, 0.14 to 0.98) in overall population and 0.64 (2.5th to 97.5th percentiles, 0.15 to 0.98) in the eligible population.

Six (12.2%) patients died in the MPA treatment group, 119 (6.2%) in the group not treated with MPA and 37 (9.4%) in the eligible subgroup. In the age-adjusted and sex-adjusted analyses, MPA-treated patients presented higher risk of death compared with patients not treated with MPA (OR 11.58 (95% CI 4.10 to 32.69), p=0.001; table 2) and eligible subgroup (OR 4.94 (95% CI 1.59 to 15.34), p=0.006; table 3). After adjusting for potential confounding factors by PSOW, no difference in outcomes were detected between the MPA-treated group compared with the group not treated (OR 1.38 (95% CI 0.30 to 6.20); table 2) or the eligible subgroup (OR 1.31 (95% CI 0.28 to 5.95); table 3). In bootstrapping analyses, the median

Table 1 Patient characteristics

	Overall (n=1977)	MPA (n=49)	No MPA (n=1928)	MPA eligible* (n=393)
Age (years)				
18–54	944 (47.7)	36 (73.5)	908 (47.1)	189 (48.1)
55–64	412 (20.8)	7 (14.3)	405 (21.0)	66 (16.8)
65–74	352 (17.8)	5 (10.2)	347 (18.0)	75 (19.1)
≥75	269 (13.6)	1 (2.0)	268 (13.9)	63 (16.0)
Mean±SD	55.3±16.6	44.9±14.6	55.6±16.6	54.9±18.1
Female gender	1317 (66.6)	36 (73.5)	1281 (66.4)	301 (76.6)
Comorbidities††				
Respiratory disease (all)	269 (13.6)	19 (38.8)	250 (13.0)	64 (16.3)
Interstitial lung disease	94 (4.8)	17 (34.7)	77 (4.0)	34 (8.7)
COPD	79 (4.0)	2 (4.1)	77 (4.0)	18 (4.6)
Asthma	115 (5.8)	1 (2.0)	114 (5.9)	18 (4.6)
Cardiac disease (all)	222 (11.2)	9 (18.4)	213 (11.1)	61 (15.5)
Coronary heart disease	183 (9.3)	5 (10.2)	178 (9.2)	49 (12.5)
Stroke	56 (2.8)	5 (10.2)	51 (2.6)	17 (4.3)
Diabetes	195 (9.9)	1 (2.0)	194 (10.1)	39 (9.9)
BMI (kg/m²)				
<30	1342 (75.4)	32 (71.1)	1310 (75.5)	293 (80.1)
30–39.9	389 (21.9)	13 (28.9)	376 (21.7)	65 (17.8)
≥40	49 (2.8)	0 (0.0)	49 (2.8)	8 (2.2)
Mean±SD	26.4±5.5	26.3±5.3	26.4±5.5	25.8±5.5
Hypertension	474 (24.0)	9 (18.4)	465 (24.2)	102 (26.0)
Cancer	71 (3.6)	0 (0.0)	71 (3.7)	25 (6.4)
Smoking	187 (9.5)	4 (8.2)	183 (9.5)	37 (9.4)
Chronic renal failure	94 (4.8)	9 (18.4)	85 (4.4)	40 (10.2)
No. of patients with at least one comorbidity	1343 (68.1)	44 (89.8)	1 299 (67.5)	272 (69.2)
Disease history				
Systemic lupus	134 (6.8)	22 (44.9)	112 (5.8)	112 (28.5)
Systemic sclerosis	76 (3.8)	18 (36.7)	58 (3.0)	58 (14.8)
Others	835 (42.2)	2 (4.1)	833 (43.2)	33 (8.4)
Other vasculitis	143 (7.2)	2 (4.1)	141 (7.3)	49 (12.5)
Inflammatory myopathy	30 (1.5)	2 (4.1)	28 (1.5)	28 (7.1)
Mixed connective tissue disease	12 (0.6)	2 (4.1)	10 (0.5)	10 (2.5)
Eye inflammation	3 (0.2)	1 (2.0)	2 (0.1)	2 (0.5)
Rheumatoid arthritis	643 (32.5)	0 (0.0)	643 (33.4)	0 (0.0)
Primary Sjögren syndrome	56 (2.8)	0 (0.0)	56 (2.9)	56 (14.2)
Vasculitis associate	41 (2.1)	0 (0.0)	41 (2.1)	41 (10.4)
IgG4-related disease	4 (0.2)	0 (0.0)	4 (0.2)	4 (1.0)
Rheumatic disease or AI²D treatments				
Corticosteroid	565 (28.6)	35 (71.4)	530 (27.5)	181 (46.1)
Systemic corticosteroid doses ≥10 mg	211 (37.7)	13 (37.1)	198 (37.7)	80 (44.4)
NSAIDs	167 (8.4)	0 (0.0)	167 (8.7)	12 (3.1)
Colchicine	77 (3.9)	0 (0.0)	77 (4.0)	20 (5.1)
Hydroxychloroquine	181 (9.2)	21 (42.9)	160 (8.3)	129 (32.8)

Continued

Table 1 Continued

	Overall (n=1977)	MPA (n=49)	No MPA (n=1928)	MPA eligible* (n=393)
Methotrexate	687 (34.7)	0 (0.0)	687 (35.6)	64 (16.3)
Leflunomide	73 (3.7)	0 (0.0)	73 (3.8)	3 (0.8)
Salazopyrine	24 (1.2)	0 (0.0)	24 (1.2)	2 (0.5)
Azathioprine	26 (1.3)	0 (0.0)	26 (1.3)	21 (5.3)
IVIGs	9 (0.5)	2 (4.1)	7 (0.4)	7 (1.8)
Biologicals				
Anti-TNF	563 (28.5)	0 (0.0)	563 (29.2)	12 (3.1)
Anti-IL6	75 (3.8)	1 (2.0)	74 (3.8)	4 (1.0)
Anti-IL17a	60 (3.0)	0 (0.0)	60 (3.1)	1 (0.3)
Anti-IL1	15 (0.8)	0 (0.0)	15 (0.8)	1 (0.3)
Anti-CD20	111 (5.6)	1 (2.0)	110 (5.7)	52 (13.2)
Abatacept	45 (2.3)	0 (0.0)	45 (2.3)	1 (0.3)
JAK inhibitor	76 (3.8)	0 (0.0)	76 (3.9)	1 (0.3)
Other biologicals	37 (1.9)	2 (4.1)	35 (1.8)	10 (2.5)

Values are presented as n (percentage) unless otherwise indicated.
*The eligible subgroup included patients who did not receive MPA despite having diseases for which MPA is a recognised therapeutic option.
†3 missing values for comorbidities (in no MPA treatment group) except for BMI where 197 values are missing (treated group: n=4; no MPA treatment group: n=193; eligible subgroup: n=27).
AI^{2}D, autoimmune and autoinflammatory diseases; BMI, body mass index; COPD, chronic obstructive pulmonary disease; IL, interleukin; IVIGs, intravenous immunoglobulins; JAK, janus kinase; MPA, mycophenolic acid; NSAIDs, non-steroidal anti-inflammatory drugs; TNF, tumour necrosis factor.

of PSOW adjusted p values for comparison of severity was 0.60 (2.5th to 97.5th percentiles, 0.13 to 0.98) in overall population and 0.62 (2.5th to 97.5th percentiles, 0.16 to 0.99) in the eligible population.

DISCUSSION

In the present study, we demonstrate that there was no difference among our three study groups in terms of severity, length of hospital stay or death rate from COVID-19. Based on our findings, we claim that the overall excess risk of poor outcome of COVID-19 in patients treated with MPA in an iRMD population after age and sex adjustment is likely due to confounding factors.

When the first alerts about the risk of severe COVID-19 in patients treated with immunosuppressive drugs were published, it was crucial to determine whether this

Table 2 Outcomes of patients treated with MPA and patients that were not treated with MPA

	MPA (n=49)	No MPA (n=1928)	Age-sex adjusted		PSOW adjusted *	
			Effect size (95% CI)	P value	Effect size (95% CI)	P value
Severity				<0.001		0.94
Mild	26 (53.1)	1306 (67.7)	1.00 (ref.)	–	1.00 (ref.)	–
Moderate	14 (28.6)	408 (21.2)	3.57 (1.76 to 7.21)†	<0.001	1.18 (0.40 to 3.45) †	0.77
Severe	9 (18.4)	214 (11.1)	8.02 (3.35 to 19.20)†	<0.001	1.18 (0.34 to 4.05) †	0.79
Length of hospital stay, median (IQR)	9.0 (4.0 to 19.0)	10.0 (5.0 to 26.0)	0.57 (0.33 to 0.98)‡	0.040	0.87 (0.41 to 1.84)‡	0.72
Death	6 (12.2)	119 (6.2)	11.58 (4.10 to 32.69)†	<0.001	1.38 (0.30 to 6.20)†	0.67

Values are presented as n (percentage) unless otherwise indicated. Values, effect size and p values were calculated after handle missing data by simple imputation.
*Effect size and p values calculated using propensity score overlap weighting analyses, using no MPA treatment group as reference.
†OR calculated using multinomial or binary logistic regression models.
‡Sub-HR (sHR) calculated among 645 hospitalised patients using Fine and Gray model with discharge alive as the event of interest and hospital death as the competing event. sHR >1 indicates an increase in length of hospital stay, and an sHR <1 indicates a decrease in length of hospital stay compared with the reference group.
MPA, mycophenolic acid; PSOW, propensity score overlap weighting.

Table 3 Outcomes of MPA-treated patients and MPA-eligible patients

	MPA (n=49)	MPA eligible* (n=393)	Age-sex adjusted		PSOW adjusted†	
			Effect size (95% CI)	P value	Effect size (95% CI)	P value
Severity				0.038		0.88
Mild	26 (53.1)	211 (53.7)	1.00 (ref.)	–	1.00 (ref.)	–
Moderate	14 (28.6)	126 (32.1)	1.39 (0.67 to 2.88)‡	0.37	0.83 (0.27 to 2.50)‡	0.74
Severe	9 (18.4)	56 (14.3)	3.43 (1.33 to 8.83)‡	0.011	1.20 (0.32 to 4.40)‡	0.78
Length of hospital stay, median (IQR)	9.0 (4.0 to 19.0)	10.0 (6.0 to 32.0)	0.74 (0.42 to 1.31)§	0.30	0.93 (0.42 to 2.05)§	0.86
Death	6 (12.2)	37 (9.4)	4.94 (1.59 to 15.34)‡	0.006	1.31 (0.28 to 5.95)‡	0.73

Values are presented as n (percentage) unless otherwise indicated. Values, effect size and p values were calculated after handle missing data by simple imputation.
*The MPA eligible group included patients in the no MPA treatment group who did not receive treatment despite having diseases for which treatment is a recognised therapeutic option.
†Effect size and p values calculated using propensity score overlap weighting analyses, using MPA eligible subgroup as reference.
‡OR calculated using multinomial or binary logistic regression models.
§Sub-HR (sHR) calculated among 205 hospitalised patients using Fine and Gray model with discharge alive as the event of interest and hospital death as the competing event. sHR >1 indicates an increase in length of hospital stay, and an sHR <1 indicates a decrease in length of hospital stay compared with the reference group.
MPA, mycophenolic acid; PSOW, propensity score overlap weighting;

increased risk was related to the molecule itself or to other confounding factors. An analysis of the French iRMD cohort showed that treatment with RTX could be considered an independent risk factor for the development of severe COVID-19,[7] which has since been confirmed by others.[12] Apart from RTX, other commonly prescribed immunosuppressive drugs, and in particular MPA, have been suspected to be linked with poor COVID-19 outcomes, even after gender and age adjusted analyses.[4] Raw data of the French RMD cohort suggested that the course of the COVID-19 infection was less favourable with MPA than that described with other targeted treatments, such as TNFα blockers, with the possibility of severe forms.[6] Analysis of the French cohort data after the addition of nearly 1000 patients confirmed this finding after adjustment for sex and age. An analysis by the GRA in a population of lupus patients showed a similar result after adjustment for sex and age.[12] While the question of specifically protecting at-risk populations through isolation or vaccination arises, it is very important to conclude the direct impact of MPA, which is especially used in fragile patient populations.

In kidney transplant recipients (KTRs), maintenance therapy with MPA was very high, despite high COVID-19 rates (around 85% of patients). In published KTR cohorts, no specific role of MPA has been identified in the course of COVID-19.[13] In a single-centre study, the course of COVID-19 in KTR patients was linked to older age but not to immunosuppression intensity and degree of reduction following COVID-19 diagnosis.[14] In iRMD patients, a large US study showed a higher risk of death with chronic use of immunosuppressants compared with patients treated with MTX.[4] Within this controversial literature, our study is of great interest since we eliminate most of the confounding factors through a PSOW analysis, and no longer find excess risk of death or an outcome of more severe COVID-19 associated with MPA. This method was never applied to data concerning the risk for severe COVID-19. Observational studies must attempt to adjust for differences contrary to randomised clinical trials.[11] In order to replicate the conditions of a randomised trial as closely as possible, we weighted the propensity score to adjust for comparisons between our iRMD patient groups. In addition, the subanalysis of the patient population eligible for this treatment suggests that MPA treatment is not a risk factor for developing severe COVID-19, although larger studies are needed to confirm these findings.

Our results have several limitations, and thus, our results should be considered in the context of overall medical benefit for iRMD patients under consideration for MPA treatment. In our study, the most vulnerable iRMD patients are those with lupus, especially those patients with lupus nephritis,[15] and next, are patients with Systemic sclerosis (SSc), particularly those with ILD.[16] In cases such as these, efficacy of MPA has been demonstrated, and there are limited treatment options available in these disease states.[17] Moreover, RTX is often considered the gold standard for alternative treatment, but RTX has been associated with poor outcomes with COVID-19 in this patient population.[7] It should be emphasised that our analysis was focused on the risk of excess mortality and/or severe COVID-19 outcome in patients treated with MPA. The safety of MPA treatment and the efficacy of the COVID-19 vaccine with concurrent treatment is also a factor that must be considered but is beyond the scope of the current study. Finally, we cannot exclude that differences in outcomes between the study groups are due to lack of adequate statistical power of MPA patients (n=49). Thus, the present results should be interpreted with caution, and future larger studies should be conducted.

In conclusion, MPA use should be continued in patients requiring the treatment for autoimmune disease, without fear of an increased risk of severe COVID-19. However, patients receiving MPA are also the most vulnerable to severe COVID-19, and COVID-19 vaccinations should be a priority with a close follow-up monitoring of the vaccine response.

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