Journal of Translational Autoimmunity 8 (2024) 100227

Contents lists available at ScienceDirect

Journal of Translational Autoimmunity

journal homepage: www.sciencedirect.com/journal/journal-of-translational-autoimmunity

Effect of traditional therapeutics on prevalence and clinical outcomes of coronavirus disease 2019 in Chinese patients with autoimmune diseases

Saisai Huang [a,1], Xiaolei Ma [a,1], Juan Cao [b,1], Mengru Du [a], Zhiling Zhao [a], Dandan Wang [a], Xue Xu [a,2,***], Jun Liang [a,*,2], Lingyun Sun [a,2,**]

[a] Department of Rheumatology and Immunology, Nanjing Drum Tower Hospital, Affiliated Hospital of Medical School, Nanjing University , 321 Zhongshan Road, Nanjing, Jiangsu, 210008, China
[b] Department of Geriatrics, Nanjing Drum Hospital, Nanjing Drum Tower Hospital, Affiliated Hospital of Medical School, Nanjing University, 321 Zhongshan Road, Nanjing, Jiangsu, 210008, China

ARTICLE INFO

Handling Editor: Y Renaudineau

Keywords:
COVID-19
Autoimmune diseases
csDMARDs
GCs

ABSTRACT

The impact of the Coronavirus disease 2019 (COVID-19) pandemic on autoimmune diseases (AID) patients has been an important focus. This study was undertaken to characterize the incidence, clinical manifestations and hospitalization among AID affected by COVID-19 and to analyze the association between immunomodulatory medication and these outcomes. Clinical, demographic, maintenance treatment, symptoms and disease course data and outcomes of AID patients with COVID-19 infection were assessed via an online survey tool and printed copy from 1 January till February 28, 2023. A total of 432 patients with AID were enrolled in the study. The results showed the most common conventional synthetic disease-modifying antirheumatic drugs (csDMARDs) was hydroxychloroquine (HCQ). The usage of csDMARDs didn't increase the risk of COVID-19 infection. Patients who warranted hospitalization were significantly older. ILD was associated with higher hospitalization rate. No csDMARDs other than calcineurin inhibitor (CNI) was associated with increased risk of hospitalization. HCQ intake was associated with cough. Compared with no glucocorticoids (GCs) group, high doses of GCs were accompanied with higher proportion of gastrointestinal symptoms and tachycardia, lower proportion of sore throat and ageusia. GCs didn't provoke the COVID-19 infection in patients with AID, but chronic use of oral GCs was significantly more common in those requiring hospitalization, and higher dose of GCs were correlated with higher risk of hospitalization. 97 patients discontinued csDMARDs after infection, which resulted in an elevated risk of hospitalization. Meanwhile, withdrawal of csDMARDs was associated with higher odds of disease flare and lower proportion of remission than maintenance groups. Collectively, our analysis provides the evidence that maintenance treatment of csDMARDs may be more prudent for AID patients during COVID-19 pandemic.

1. Introduction

In December 2019, the first case of severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), the virus that causes coronavirus disease 2019 (COVID-19) was occurred [1]. The clinical manifestations of COVID-19 infection are broad, for most patients, the common symptoms are flu-like illness characterized by fever, fatigue, diarrhea, myalgia and cough [2,3]. However, for some people, this disease can develop into a life-threatening or fatal disease and result in high morbidity and mortality.

Patients with autoimmune diseases (AID) having an inherent immune imbalance, are susceptible to infections due to their underlying disease states as well as the usage of immunosuppressive medications [4–6]. Meanwhile, glucocorticoids (GCs) and some conventional

* Corresponding author.
** ***Corresponding author.
*** **Corresponding author. Department of Rheumatology and Immunology, Nanjing Drum Tower Hospital, Affiliated Hospital of Medical School, Nanjing University , 321 Zhongshan Road, Nanjing, Jiangsu, 210008, China.
E-mail addresses: iamxuxue@163.com (X. Xu), 13505193169@139.com (J. Liang), lingyunsun@nju.edu.cn (L. Sun).
[1] These authors contributed equally.
[2] Lingyun Sun, Xue Xu and Jun Liang are co-corresponding authors.

https://doi.org/10.1016/j.jtauto.2023.100227
Received 15 November 2023; Received in revised form 8 December 2023; Accepted 8 December 2023
Available online 12 December 2023

synthetic disease-modifying antirheumatic drugs (csDMARDs), such as hydroxychloroquine (HCQ), may be effective in COVID-19 treatment [7, 8]. The effect of COVID-19 on AID patients receiving immunosuppressive treatment is elusive so far. It is unknown whether the different immunosuppressants have influences on the virus infection, disease severity and prognosis for AID patients. To address this knowledge gap, we provide a survey of the COVID-19 research among AID patients, to evaluate the possible impacts of csDMARDs treatment on the incidence, clinical manifestations, hospitalization of COVID-19 infection, and disease flare in patients with AID.

2. Materials and methods

2.1. Patients collection

A Chinese-language questionnaire was developed by rheumatologists in Nanjing Drum Tower Hospital. The questionnaire contained 41 questions organized in three broad sections: (1) basic information such as age, sex, education, vaccination et al., (2) symptoms after COVID-19 infection and (3) drugs used in rheumatology. The majority of questions were in the multiple-choice Format. The answers were collected via printed copy and online survey tool from 1 January to February 28, 2023. This study was conducted with the approval of the Institutional Review Board of Nanjing Drum Tower Hospital and in accordance with the declaration of Helsinki. The written informed consent was obtained from all subjects.

Summary and descriptive statistics were used to the questionnaire responses. Absolute and relative frequencies were calculated and depicted in tabular and graphical form. Data are presented as number (nominator) and percentage of all available responses to each question (denominator) throughout the manuscript. The denominator may change in different questions for the following reasons: (1) questions and individual answers could have been skipped, (2) specific subgroup analyses were conducted. Due to the majority of questions were in the multiple-choice format, the sum of nominators from individual questions may exceed the corresponding denominator.

2.2. Statistical analysis

Baseline characteristics and medication use were summarized using mean (range and/or standard deviation) for continuous variables and frequency and proportions for categorical variables, overall and stratified by infection and hospitalization status. The *t*-test was used to compare the means. Pairwise comparisons for categorical variables between groups were made using $\chi 2$ test, logistic regression was used to adjust the comparisons for possible confounding variables. Statistical significance was considered as $p < 0.05$. The software used for statistical analysis were IBM SPSS and GraphPad Prism software.

3. Results

3.1. Characteristics of patients with AID

A total of 432 patients fulfilled our questionnaire, the demographic and clinical characteristics of these patients are shown in Table 1. Most cases were female (369, 85.4 %). 26 cases (6.0 %) were smokers. 347 cases (80.3 %) infected with COVID-19. The most common rheumatic disease was systemic lupus erythematosus (137, 31.7 %), followed by Sjögren's syndrome (85, 19.7 %), rheumatoid arthritis (84, 19.4 %), undifferentiated connective tissue disease (26, 6.0 %), vasculitis (24, 5.6 %). 53 patients (12.3 %)had interstitial lung disease (ILD). To explore the effect of therapeutics on the infection and disease activity of patients with AID during the COVID-19 pandemic, we summarized data on csDMARDs and GCs in these patients, which could have more than one medication. The results showed most common csDMARDs was HCQ (141, 32.6 %), followed by calcineurin inhibitor (CNI) (86, 19.9 %), mycophenolate mofetil/mycophenolic acid (MMF) (66, 15.3 %), methotrexate (MTX) (54, 12.5 %), cyclophosphamide (CTX) (38, 8.8 %). 72.7 % patients with AID were treated with GCs. Of them, 38.7 % cases received GCs dose ≤7.5 mg/day, 22.2 % cases received dose 7.5–15 mg/day, and 12.0 % cases received dose >15 mg/day.

Table 1
Demographic and clinical characteristics of these patients with AID.

	N (%)
Overall	432
Female	369 (85.4)
Smoker	26 (6.0)
Infection with COVID-19	347 (80.3)
Most common autoimmune disease diagnosis[a]	
Systemic lupus erythematosus	137 (31.7)
Sjögren's syndrome	85 (19.7)
Rheumatoid arthritis	84 (19.4)
Undifferentiated connective tissue disease	26 (6.0)
Vasculitis	24 (5.6)
Inflammatory myopathy	16 (3.7)
Axial spondyloarthritis or other spondyloarthritis	12 (2.8)
Systemic sclerosis	11 (2.6)
Mixed connective tissue disease	10 (2.3)
Other	27 (6.3)
Most common csDMARDs prior to COVID-19 diagnosis[b]	
HCQ	141 (32.6)
CNI	86 (19.9)
MMF	66 (15.3)
MTX	54 (12.5)
CTX	38 (8.8)
No csDMARDs	50 (11.6)
GCs	
None	118 (27.3)
≤7.5 mg/day	167 (38.7)
7.5–15 mg/day	95 (22.2)
>15 mg/day	52 (12.0)

Percentages may not sum to 100 due to rounding.
csDMARDs, conventional synthetic disease-modifying antirheumatic drugs; HCQ, hydroxychloroquine; CNI, Calcineurin inhibitor (Tacrolimus, cyclosporine); MMF, Mycophenolate mofetil/mycophenolic acid; MTX, Methotrexate; CTX, Cyclophosphamide, GCs, Prednisone-equivalent glucocorticoids.
[a] Cases could have more than one disease diagnosis. 'Other' rheumatic disease category included (each n < 10): antiphospholipid antibody syndrome; IgG4-related disease; relapsing polychondritis; polymyalgia rheumatica; adult onset still disease.
[b] Cases could have more than one medication.

3.2. Influences of immunosuppressants in prevalence of COVID-19 for AID patients

A $\chi 2$ analysis was conducted to evaluated whether the use of GCs and csDMARDs increase the risk of COVID-19 infection. There was no impact of sex and smoke on the COVID-19 infection in patients with AID. Moreover, GCs and csDMARDs (such as HCQ, CNI, MMF, MTX and CTX) also did not increase the risk of COVID-19 infection, indicating that routine immunosuppressive treatment could not promote AID patients to be more susceptible to COVID-19 infection (Table 2).

3.3. Impacts of immunosuppressants in symptoms of COVID-19 for AID patients

Among the infected patients, fever, cough, and sore throat remained the most common COVID-19 symptomatic presentations. We evaluate the impact of immunosuppressants on the symptoms of COVID-19, the results showed HCQ treatment increased the percentages of cough and ageusia, and CNI reduced the frequency of sore throat and ageusia. MMF intake was associated with ageusia. Patients treated with CTX showed

Table 2
Association between demographic features of patients with AID and COVID-19 infection.

Factors	COVID-19 infection		*P* value[a]
	Yes (N = 347) Frequency (%)	No (N = 85) Frequency (%)	
Gender			
Female	299 (81.0 %)	70 (19.0 %)	0.37
Male	48 (76.2 %)	15 (23.8 %)	
Smoking			
Yes	20 (76.9 %)	6 (23.1 %)	0.65
No	327 (80.5 %)	79 (19.5 %)	
Drugs			
HCQ			
Yes	118 (83.7 %)	23 (16.3 %)	0.22
No	229 (78.7 %)	62 (21.3 %)	
CNI			
Yes	69 (80.2 %)	17 (19.8 %)	0.98
No	278 (80.3 %)	68 (19.7 %)	
MMF			
Yes	57 (86.4 %)	9 (13.6 %)	0.18
No	290 (79.2 %)	76 (20.8 %)	
MTX			
Yes	46 (85.2 %)	8 (14.8 %)	0.32
No	301 (79.4 %)	78 (20.6 %)	
CTX			
Yes	33 (86.8 %)	5 (13.2 %)	0.29
No	314 (79.7 %)	80 (20.3 %)	
GCs			
Yes	251 (79.9 %)	63 (20.1 %)	0.74
No	96 (81.4 %)	22 (18.6 %)	

HCQ, hydroxychloroquine; CNI, Calcineurin inhibitor (Tacrolimus, cyclosporine); MMF, Mycophenolate mofetil/mycophenolic acid; MTX, Methotrexate; CTX, Cyclophosphamide; GCs, Prednisone-equivalent glucocorticoids.
[a] $\chi 2$ test.

lower rate of cough. MTX displayed no impact on the COVID-19 symptoms (Fig. 1).

We then compared the symptoms of those patients who treated with different csDMARDs and GCs. As shown in Fig. 1, cough was significantly more common in the patients treated with HCQ than those with CNI (77.1 % vs. 60.9 %, $P = 0.018$) and CTX (77.1 % vs. 48.5 %, $P = 0.0014$). MMF treated patients showed higher rate of ageusia than those with CNI (36.8 % vs. 14.5 %, $P = 0.037$), MTX (36.8 % vs. 15.2 %, $P = 0.014$) and CTX (36.8 % vs. 15.2 %, $P = 0.028$).

GCs treated patients showed lower rates of sore throat and ageusia, higher rates of gastrointestinal symptoms and tachycardia. Moreover, patients receiving high doses of GCs displayed increased frequencies of gastrointestinal symptoms and tachycardia, but decreased proportions of sore throat and ageusia compared with those with low doses of GCs and no GCs (gastrointestinal symptom, dose >15 mg/day vs ≤ 7.5 mg/day, 22.5 % vs 8.8 %, $P = 0.018$, dose >15 mg/day vs 0 mg/day, 22.5 % vs 5.2 %, $P = 0.0025$) (tachycardia, dose >15 mg/day vs ≤ 7.5 mg/day, 12.5 % vs 2.9 %, p = 0.015, dose >15 mg/day vs 0 mg/day, 12.5 % vs 2.1 %, $P = 0.0122$) (sore throat, dose ≤7.5 mg/day vs 0 mg/day, 48.2 % vs 61.5 %, $P = 0.0012$, dose 7.5–15 mg/day vs 0 mg/day, 36.5 % vs 61.5 %, $P = 0.0012$) (ageusia, dose >15 mg/day vs 0 mg/day, 34.4 % vs 10.0 %, $P = 0.0036$).

In our study, 307 patients were receiving csDMARDs treatment when infected COVID-19, then 97 patients stopped but 210 cases still continued taking them during infection. We further analyzed whether withdrawal of csDMARDs could influence the symptoms of COVID-19. Patients discontinuing csDMARDs showed more clinical symptoms of COVID-19 infection, including fever, shortness of breath, nasal congestion and rhinorrhea (86.6 % vs 64.8 %, $P < 0.0001$, 21.6 % vs 12.4 %, $P = 0.037$, 45.4 % vs 31.9 %, $P = 0.0225$).

3.4. Effects of immunosuppressants in hospitalization of COVID-19 in AID patients

Further analyses were conducted to examine the independent association of GCs and csDMARDs with hospitalization. Of those infected population, 58 participants required hospitalization (16.7 %). We then compared the characteristics of these hospitalized patients with non-hospitalized groups (Table 3). The hospitalized AID patients were older than those non-hospitalized groups (OR 1.064, 95%CI 1.037 to 1.091, $P = 0.035$), but there was no significant difference in gender. ILD was associated with higher hospitalization rate (OR 2.92, 95%CI 1.331 to 6.407, $P = 0.008$).

CNI treatment increased the risk of hospitalization (OR 2.337, 95%CI 1.06 to 5.15, $P = 0.035$). There was no effect of other csDMARDs (MMF, MTX and CTX) on the risk of hospitalization. We also found that treatment with GCs raised the hospitalization rate of AID patients. Moreover, the risk of hospitalization was positively correlated with the dosage of GCs.

97 patients discontinued csDMARDs during COVID-19 infection. Our results showed that withdrawal of csDMARDs resulted in an elevated risk of hospitalization (OR 3.919,95%CI 1.918 to 8.005, $P < 0.001$), but no difference in the length of hospital stays (supplement 1), compared with those maintaining csDMARDs. Meanwhile, withdrawal of csDMARDs lead to an increased risk of disease flare and reduced proportion of remission than the maintenance groups (Table 4).

4. Discussion

Since the early days of 2020, the COVID-19 pandemic has quickly emerged as the most challenging global health crisis in a generation [9]. During the COVID-19 pandemic, in order to guide the treatment of AID patients better, the risk factors and disease outcomes of patients with AID deserve our more attention.

Several large population-based or health-system-based studies showed an elevation risk of COVID-19 hospitalization or death in patients with rheumatic disease [10,11], but the impacts of immunosuppressants on both susceptibility and clinical manifestations as well as hospitalization of patients with AID have been unknown when infected with COVID-19. This manuscript descripts a large collection of COVID-19 cases among AID patients who are receiving different csDMARDs and GCs.

There are conflicting evidences of the associations between GCs and the outcomes of COVID-19. It was reported that there was no relationship between inhaled GCs and COVID-19-related death in people with asthma or chronic obstructive pulmonary disease [12]. Recent studies showed that GCs use was correlated with an elevated risk of COVID-19 infection in patients with inflammatory bowel disease [13]. Similarly, in Korean patients with AID receiving a high dose of systemic GCs also showed an increased risk of positive COVID-19 RNA, severe COVID-19, COVID-19-related death, while patients receiving DMARDs did not exhibit any increased risk of these outcomes [14]. Yves el al found GCs usage were one of the main factors associated with non-response to COVID-19 immunization in immune system disease patients [15]. Other studies had shown extensive use of corticosteroids and tocilizumab resulted in good overall outcome and showed acceptable complication rates [16]. Our result suggested that in China GCs didn't provoke the COVID-19 infection in patients with AID, but chronic oral GCs use and higher dose of GCs were significantly related with an increased risk of hospitalization, which was consistent with a European cohort study that patients treated with a high dose of systemic GCs were prone to hospitalization [17]. The possible explanation might be that GCs might reduce angiotensin converting enzyme (ACE2) expression levels to alter

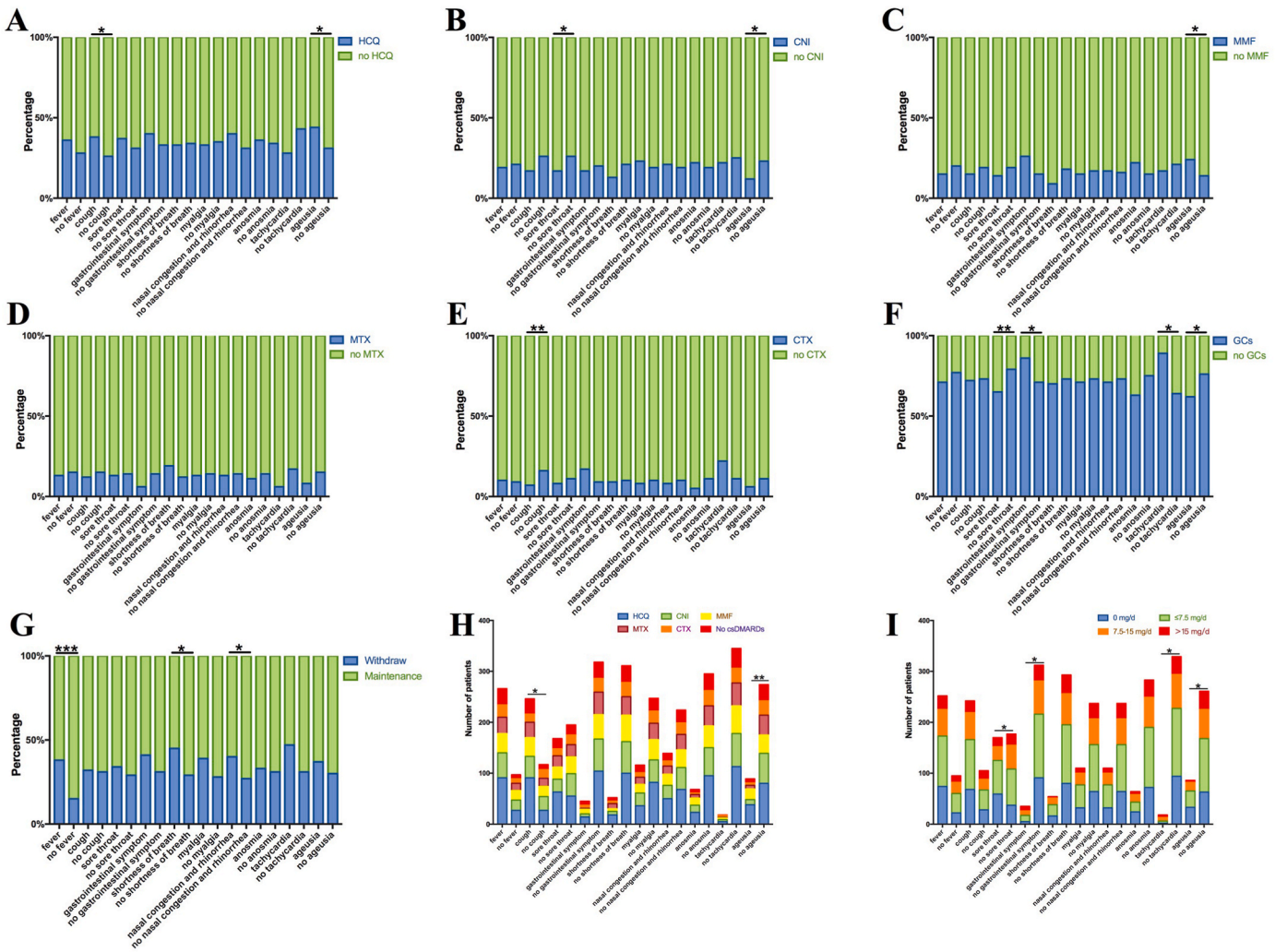

Fig. 1. Association between drugs and symptoms in COVID-19-infected AID*. The influence of HCQ (A), CNI (B), MMF (C), MTX (D), CTX (E), CCs (F) on the symptoms of COVID-19. (G) The symptoms of COVID-19-infected AID in treatment maintenance and withdrawal groups. (H) The symptoms of COVID-19-infected AID in different csDMARDs groups. (I) The symptoms of COVID-19-infected AID in different GCs groups.
*Some symptoms were common in one patient. Some patients could have more than one medication.
*$p < 0.05$, **$p < 0.01$, ***$p < 0.001$.

COVID-19 susceptibility [18]. Meanwhile, GCs were demonstrated to be the first anti-inflammatory medication shown to decrease mortality in severe COVID-19 patients receiving corticosteroids (total n = 1703), compared with those with usual care or placebo [19]. Dexamethasone reduced mortality in patients receiving supplemental oxygen by one-fifth and in patients requiring mechanical ventilation by one-third, but there was no mortality reduction in patients without respiratory support, which suggested that GCs were protective in patients with severe COVID-19-related respiratory failure but may not be helpful in patients with early or mild disease [20]. Despite the therapeutic effect of GCs on severe COVID-19, chronic oral GCs for AID patients, especially higher dose of GCs, significantly aggravated the disease and increased the risk of hospitalization in our study. Therefore, AID patients should be given low doses of GCs or no GCs when the disease is stable, which might help reduce the risk of disease flare and hospitalization rate during or after infection.

Antimalarials alter endosomal pH, inhibit cytokine production and costimulatory molecules, modulate the transport of SARS CoV-2 to endolysosomes, alter glycosylation of the ACE2 receptor, and severely inhibit virus replication [21,22]. Although HCQ has been suggested as a potential treatment for COVID-19 [23,24], the therapeutic effect of HCQ on COVID-19 is controversial. Two observational studies have shown no significant benefit of either HCQ alone or combination with azithromycin on clinical outcomes including mortality [25,26]. We did not observe the protective role of HCQ on COVID-19 infection. CNI, MMF, CTX, MTX were also commonly used for the management of rheumatic disease. In our study, there was no association between COVID-19 infection with those drugs, which was inconsistent with previous studies in Iran that MTX and CTX significantly increased but HCQ decreased the risk of COVID-19 infection in patients with rheumatic disease [27]. This discrepancy may due to the number, race and ethnicity of patients enrolled. In addition, there was a clear correlation of increased hospitalization rate with CNI treatment in AID patients, and the potential mechanism of CNI needed to be further explored.

We also found that csDMARDs and GCs were associated with several clinical symptoms of COVID-19 infection. HCQ intake was associated with cough, and ageusia was more common in MMF groups. High doses of GCs were accompanied with higher proportion of gastrointestinal symptom and tachycardia. The proportion of sore throat and ageusia were obviously higher in no GCs groups. All these symptoms can be ameliorated with symptomatic therapy. It was previously reported that sneezing, malaise and constipation were more frequent in the control group, and vomiting occurred more common in the rheumatic patients [28]. The underlying reasons for the phenomenon are still elusive.

Table 3
Univariate and Multivariate logistic regression analysis of baseline characteristics and medication use between hospitalized and non-hospitalized AID patients with COVID-19 infection.

Variables	Univariate logistic regression			Multivariate logistic regression		
	OR	95%CI	*P* value	OR	95%CI	*P* value
Age, years	1.054	1.032–1.076	<0.001	1.064	1.037–1.091	0.035
Sex						
Female	1					
Male	1.594	0.759–3.346	0.218			
AID category						
SLE	1					
SS	0.911	0.392–2.118	0.828			
RA	0.693	0.271–1.774	0.445			
others	1.831	0.917–3.656	0.086			
ILD	7.6	3.862–14.956	<0.001	2.92	1.331–6.407	0.008
Drugs						
Glucocorticoid						
None	1			1		
≤7.5 mg/day	3.111	1.125–8.607	0.029	2.425	0.834–7.05	0.104
7.5–15 mg/day	5.85	2.057–16.638	0.01	5.712	1.879–17.359	0.002
>15 mg/day	10.92	3.618–32.959	<0.001	9.903	2.892–33.914	<0.001
HCQ	0.566	0.296–1.082	0.085			
CNI	2.344	1.263–4.348	0.007	2.337	1.06–5.15	0.035
MMF	0.372	0.129–1.075	0.068			
MTX	0.642	0.26–1.586	0.337			
CTX	1.858	0.821–4.206	0.137			
csDMARDS withdrawal	2.361	1.32–4.22	0.04	3.919	1.918–8.005	<0.001

AID, autoimmune diseases; SLE, Systemic lupus erythematosus; SS, Sjögren's syndrome; RA, Rheumatoid arthritis; ILD, interstitial lung disease; csDMARDs, conventional synthetic disease-modifying antirheumatic drugs; HCQ, hydroxychloroquine; CNI, Calcineurin inhibitor (Tacrolimus, cyclosporine); MMF, Mycophenolate mofetil/mycophenolic acid; MTX, Methotrexate; CTX, Cyclophosphamide, GCs, Prednisone-equivalent glucocorticoids.

Table 4
The influence of csDMRADs withdrawal on disease activity.

Disease activity	Withdrawal of csDMARDs		*P* value
	Yes (N = 97) Frequency (%)	No (N = 210) Frequency (%)	
No change	60 (61.9 %)	149 (71.0 %)	0.023
Exacerbation	36 (37.1 %)	51 (24.3 %)	
Remission	1 (1 %)	10 (4.7 %)	

csDMARDs, conventional synthetic disease-modifying antirheumatic drugs.

The most controversial issue for rheumatologists is how to achieve a better management when AID patients infected with COVID-19. Some rheumatologists state that patients' immunosuppressants should be maintained, due to the fact that discontinuing or reducing immunosuppressants might increase the risk of disease flare-up and lead to uncontrolled rheumatic disease [29]. Nevertheless, some experts may consider reducing the doses of some drugs, such as prednisolone, cautiously, or even discontinuing the immunosuppressants in the case of COVID-19 infection, in order to better and more quickly control infection [30]. There is a huge unmet clinical need to suggest AID patients responsibly about whether they should remain on their immunomodulatory treatment or not in light of COVID-19 infection. In our study, we made a detailed comparison of clinical symptom as well as the risk of hospitalization between withdrawal and maintenance groups. The result showed fever, shortness of breath, nasal congestion and rhinorrhea were significantly more prevalent in patients withdrawing csDMARDs. It was noteworthy that discontinuation of immunosuppressants notably increased the risk of hospitalization for AID patients compared to those maintenance group, which may be explained by that the cessation of these drugs might lead to disease flare or relapse. Withdrawal of csDMARDs was associated with higher odds of aggravation and lower proportion of remission than those of maintenance groups, but this was a subjective feeling of the patients, specific professional evaluation needs our further exploration. Therefore, for AID patients, continuation of their immunosuppressive treatments might be of greater benefit through prevention of disease flares during the COVID-19 pandemic. More and deeper studies are needed to explore the maintenance or discontinuation treatment in rheumatic disease after COVID-19 infection.

We mainly concerned on the effect of immunosuppressants on the disease activity of AID patients, and put forward several opinions to better manage AID when infected COVID-19. Chronic use of csDMARDs and GCs showed no impact on the susceptibility of COVID-19 in our patients. CNI and high dose of GCs treatment were notably increased the risk of hospitalization for AID patients when infection. We also demonstrated the harmful role of csDMARDs discontinuation in AID patients when infected with COVID-19.

Despite these strengths, the inherent limitations of our study include relatively small sample size, Furthermore, we acknowledge that our cohort is homogenous (subjects derived from a single healthcare system and geographic region) and biased towards patients with SLE. Moreover, the primary data were obtained through questionnaire, and all the restrictions associated with this data gathering method could also apply to our study. Although we assessed the effects of csDMARDs and GCs therapy on the outcomes separately, not all studies presented data in these two groups.

Many mechanistic and clinical observations suggested that biologic disease-modifying antirheumatic drugs (bDMARDs) and targeted synthetic (ts)DMARDs may be useful in controlling specific aspects of the immune overreaction and thus improve the outcomes of severe COVID-19 infection [31,32]. An ongoing effort from our group will evaluate the effect of bDMARDs and tsDMARDs on COVID-19 infection status and outcomes. Other complementary initiatives are currently ongoing and should shed light on some of these knowledge gaps.

In conclusion, this study is the first comprehensive analysis which determined the prevalence, clinical symptoms, hospitalization and the influence of drug withdrawal of COVID-19 in rheumatic disease. Our study suggests that csDMARDs and GCs treatment do not increase the risk of COVID-19 infection. When infected with COVID-19, age and ILD were associated with higher hospitalization rate, CNI and GCs as well as withdrawal of csDMARDs also increase the odds of hospitalization. Our analysis provides the evidence that maintenance of immunosuppressive treatment maybe more beneficial for AID patients during COVID-19 pandemic. Our study contributes to better guide the therapeutic

strategy of patients with AID prior to or after infection, or when infected with virus.

Funding

This study was supported by grants from the National Natural Science Foundation of China (32070883) and funding for Clinical Trial from the affiliated Drum Tower Hospital, Medical School of Nanjing University (2022-YXZX-MY-05, 2022-LCYJ-MS-38), the Puai Medical Research Fund of Beijing Bethune Charitable Foundation (PAYJ-008).

CRediT authorship contribution statement

Saisai Huang: Writing – original draft. **Xiaolei Ma:** Writing – original draft. **Juan Cao:** Data curation. **Mengru Du:** Validation. **Zhiling Zhao:** Investigation. **Dandan Wang:** Writing – review & editing. **Xue Xu:** Writing – review & editing. **Jun Liang:** Writing – review & editing. **Lingyun Sun:** Writing – review & editing.

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.

Data availability

Data will be made available on request.

Acknowledgement

We would like to acknowledge all members of Department of Rheumatology and

Immunology of Nanjing Drum Tower Hospital for survey development and deployment.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.jtauto.2023.100227.

References

[1] S. Muralidar, S.V. Ambi, S. Sekaran, et al., The emergence of COVID-19 as a global pandemic: understanding the epidemiology, immune response and potential therapeutic targets of SARS-CoV-2, Biochimie 179 (2020) 85–100. https://doi:10.1016/j.biochi.2020.09.018.

[2] D. Wang, B. Hu, C. Hu, et al., Clinical characteristics of 138 hospitalized patients with 2019 novel coronavirus-Infected pneumonia in wuhan, China, JAMA 323 (2020) 1061–1069. https://doi:10.1001/jama.2020.1585.

[3] J. Bedford, D. Enria, J. Giesecke, et al., COVID-19: towards controlling of a pandemic, Lancet 395 (2020) 1015–1018. https://doi:10.1016/S0140-6736(20)30673-5.

[4] U. Christen, Pathogen infection and autoimmune disease, Clin. Exp. Immunol. 195 (2019) 10–14. https://doi:10.1111/cei.13239.

[5] A. Sepriano, A. Kerschbaumer, J.S. Smolen, et al., Safety of synthetic and biological DMARDs: a systematic literature review informing the 2019 update of the EULAR recommendations for the management of rheumatoid arthritis, Ann. Rheum. Dis. 79 (2020) 760–770. https://doi:10.1136/annrheumdis-2019-216653.

[6] A. Strangfeld, M. Eveslage, M. Schneider, et al., Treatment benefit or survival of the fittest: what drives the time-dependent decrease in serious infection rates under TNF inhibition and what does this imply for the individual patient? Ann. Rheum. Dis. 70 (2011) 1914–1920. https://doi:10.1136/ard.2011.151043.

[7] D.R. Burrage, S. Koushesh, N. Sofat, Immunomodulatory drugs in the management of SARS-CoV-2, Front. Immunol. 11 (2020) 1844. https://doi:10.3389/fimmu.2020.01844.

[8] B. Russell, C. Moss, A. Rigg, et al., COVID-19 and treatment with NSAIDs and corticosteroids: should we be limiting their use in the clinical setting? Ecancer Med. Sci. 14 (2020) 1023. https://doi:10.3332/ecancer.2020.1023.

[9] A.R. Tuite, V. Ng, E. Rees, et al., Estimation of COVID-19 outbreak size in Italy, Lancet. Inf. Disp. 20 (2020) 537. https://doi:10.1016/S1473-3099(20)30227-9.

[10] S. Akiyama, S. Hamdeh, D. Micic, et al., Prevalence and clinical outcomes of COVID-19 in patients with autoimmune diseases: a systematic review and meta-analysis, Ann. Rheum. Dis. 80 (2021) 384–391. https://doi:10.1136/annrheumdis-2020-218946.

[11] R.H. Haberman, R. Castillo, A. Chen, et al., COVID-19 in patients with inflammatory arthritis: a prospective study on the effects of comorbidities and disease-modifying antirheumatic drugs on clinical outcomes, Arthritis Rheumatol. 72 (2020) 1981–1989. https://doi:10.1002/art.41456.

[12] A. Schultze, A.J. Walker, B. MacKenna, et al., Risk of COVID-19-related death among patients with chronic obstructive pulmonary disease or asthma prescribed inhaled corticosteroids: an observational cohort study using the OpenSAFELY platform, Lancet Respir. Med. 8 (2020) 1106–1120. https://doi:10.1016/S2213-2600(20)30415-X.

[13] D.J. Lukin, A. Kumar, K. Hajifathalian, et al., Baseline disease activity and steroid therapy stratify risk of COVID-19 in patients with Inflammatory Bowel Disease, Gastroenterology 159 (2020), 1541-44.e2, https://doi:10.1053/j.gastro.2020.05.066.

[14] Y.H. Shin, J.I. Shin, S.Y. Moon, et al., Autoimmune inflammatory rheumatic diseases and COVID-19 outcomes in South Korea: a nationwide cohort study, Lancet. Rheumatol. 3 (2021) e698–e706. https://doi:10.1016/S2665-9913(21)00151-X.

[15] Y. Renaudineau, L. Sailler, F. Abravanel, et al., Glucocorticoid use as a cause of non-cellular immune response to SARS-Cov 2 Spike in patients with immune system diseases, J. Autoimmun. 133 (2022), 102912. https://doi:10.1016/j.jaut.2022.102912.

[16] B.M. Luis, M.B. Miguel, D.L. Pedro, et al., Benefits of early aggressive immunomodulatory therapy (tocilizumab and methylprednisolone) in COVID-19: single center cohort study of 685 patients, J. Transl. Autoimmun. 4 (2021), 100086. https://doi:10.1016/j.jtauto.2021.100086.

[17] M. Gianfrancesco, K.L. Hyrich, S. Al-Adely, 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. 79 (2020) 859–866. https://doi:10.1136/annrheumdis-2020-217871.

[18] M.C. Peters, S. Sajuthi, P. Deford, et al., COVID-19-related genes in sputum cells in asthma. Relationship to demographic features and corticosteroids, Am. J. Respir. Crit. Care Med. 202 (2020) 83–90. https://doi:10.1164/rccm.202003-0821OC.

[19] Group WHOREAfC-TW, J.A.C. Sterne, S. Murthy, et al., Association between administration of systemic corticosteroids and mortality among critically Ill patients with COVID-19: a Meta-analysis, JAMA 324 (2020) 1330–1341. https://doi:10.1001/jama.2020.17023.

[20] Group RC, P. Horby, W.S. Lim, et al., Dexamethasone in hospitalized patients with Covid-19, N. Engl. J. Med. 384 (2021) 693–704. https://doi:10.1056/NEJMoa2021436.

[21] E.A. Meyerowitz, A.G.L. Vannier, M.G.N. Friesen, et al., Rethinking the role of hydroxychloroquine in the treatment of COVID-19, Faseb. J. 34 (2020) 6027–6037. https://doi:10.1096/fj.202000919.

[22] M. Wang, R. Cao, L. Zhang, et al., Remdesivir and chloroquine effectively inhibit the recently emerged novel coronavirus (2019-nCoV) in vitro, Cell Res. 30 (2020) 269–271. https://doi:10.1038/s41422-020-0282-0.

[23] X. Yao, F. Ye, M. Zhang, et al., In vitro antiviral activity and projection of optimized dosing design of hydroxychloroquine for the treatment of severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), Clin. Infect. Dis. 71 (2020) 732–739. https://doi:10.1093/cid/ciaa237.

[24] P. Gautret, J.C. Lagier, P. Parola, et al., Hydroxychloroquine and azithromycin as a treatment of COVID-19: results of an open-label non-randomized clinical trial, Int. J. Antimicrob. Agents 56 (2020), 105949. https://doi:10.1016/j.ijantimicag.2020.105949.

[25] Ozuygur Ermis SS, Ergan B, Kacmaz Basoglu O et al, The Efficacy of hydroxychloroquine and azithromycin combination therapy on hospital mortality in COVID 19 pneumonia patients, Turk. J. Med. Sci. https://doi:10.3906/sag-2009-64.

[26] J. Magagnoli, S. Narendran, F. Pereira, et al., Outcomes of hydroxychloroquine usage in United States veterans hospitalized with Covid-19, Méd. 1 (2020) 114–127. https://doi:10.1016/j.medj.2020.06.001.

[27] M. Sahebari, Z. Mirfeizi, Z. Shariati-Sarabi, et al., Influence of biologic and conventional disease-modifying antirheumatic drugs on COVID-19 incidence among rheumatic patients during the first and second wave of the pandemic in Iran, Reumatologia 60 (2022) 231–241. https://doi:10.5114/reum.2022.119039.

[28] S. Moradi, M. Masoumi, S. Mohammadi, et al., Prevalence of coronavirus disease 2019 in rheumatic patients and evaluation of the effect of disease-modifying antirheumatic drugs, Intern. Emerg. Med. 16 (2021) 919–923. https://doi:10.1007/s11739-020-02535-5.

[29] F. Ferro, E. Elefante, C. Baldini, et al., COVID-19: the new challenge for rheumatologists, Clin. Exp. Rheumatol. 38 (2020) 175–180. https://doi:10.55563/clinexprheumatol/r3k9l6.

[30] D.P. Misra, V. Agarwal, A.Y. Gasparyan, et al., Rheumatologists' perspective on coronavirus disease 19 (COVID-19) and potential therapeutic targets, Clin. Rheumatol. 39 (2020) 2055–2262. https://doi:10.1007/s10067-020-05073-9.

[31] P. Richardson, I. Griffin, C. Tucker, et al., Baricitinib as potential treatment for 2019-nCoV acute respiratory disease, Lancet 95 (2020) e30–e31. https://doi:10.1016/S0140-6736(20)30304-4.

[32] R. Karki, B.R. Sharma, S. Tuladhar, et al., Synergism of TNF-alpha and IFN-gamma triggers inflammatory cell death, tissue damage, and mortality in SARS-CoV-2 infection and cytokine shock syndromes, Cell 184 (2021) 149–168. https://doi:10.1016/j.cell.2020.11.025.