Pharmaceutical Sciences Asia

Pharm Sci Asia 2022; 49(1), 5-14

DOI:10.29090/psa.2022.01.21.079

Review Article

Are immunosuppressant related to unfavorable outcomes in patients COVID-19 with autoimmune rheumatic disease?: A review of clinical evidence

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ABSTRACT

The impact of immunosuppressant therapy in COVID-19 patients with autoimmune rheumatic disease remains unclear based on previous studies. Here, we reviewed the clinical evidence to evaluate COVID-19 patients with rheumatic disease outcomes, which previously used immunosuppressant therapy to control the disease. We used PubMed and Science Direct database to search literature up to April 2021 for publications with confirmed COVID-19 infection with rheumatic disease. The outcomes of this review were the infection rate of COVID-19 and the rate of hospitalization, ICU admission, and mortality. A total of 16 articles were included in this review. The overall rates of COVID-19 infection in patients with autoimmune rheumatic disease did not differ from the general population. Rheumatic disease patients who previously used hydroxychloroquine showed a similar infection risk of COVID-19 with those who did not use hydroxychloroquine. Furthermore, immunosuppressant therapies were associated with poor clinical outcomes, increase risk of hospitalization, ICU admission, and mortality, particularly in patients with comorbidities. The use of bDMARD, such as TNF-α inhibitor, showed a protective effect to reduce the risk of hospitalization and mortality. The administration of immunosuppressant therapy must be closely monitored in rheumatic disease patients due to unfavorable outcomes. More studies are urgently required to map risk factors of clinical outcomes with the specific immunosuppressant therapy and specific rheumatic disease.

Keywords:
COVID-19, Immunosuppressant, Autoimmune, Rheumatic disease, Outcomes

1. INTRODUCTION

Corona Virus-19 Disease (COVID-19) is caused by severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2), including beta-coronavirus with an RNA core. The disease was first reported from Wuhan, China, in December 2019, and this infection has now been reported worldwide[1,2]. On 11 March 2020, WHO declared COVID-19 as a pandemic. In Indonesia, at the end of February 2021, it was estimated more than one million patients with COVID-19 were confirmed, with 35.014 cases of mortality[3].

A high fatality rate was found in the elderly and comorbidities, especially in patients with chronic respiratory or cardiovascular disease, diabetes, hypertension, and cancer[4]. In addition, a high fatality rate has been reported in transplant patients or with autoimmune disease, especially in those receiving immunosuppressant for long treatment[5]. Since the pandemic, there has been concern about the risk of SARS-CoV-2 infection and complications in patients with autoimmune rheumatic disease[6]. Furthermore, these patients have a higher risk of infection because they are in a state of decreased immunity due to immunosuppressant treatment[7]. In addition, immunosuppressant therapy suppresses the abnormal immune response in COVID-19, which is responsible for severe complications, such as interstitial pneumonia[8]. Additionally, exposure of glucocorticoid and increase of comorbidities among patients with an autoimmune rheumatic disease (obesity, chronic lung disease, diabetes,

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cardiovascular disease) may impact on increasing the high risk of a worse prognosis[9].

Immunosuppressant agents, such as corticosteroids, conventional synthetic disease-modifying anti-rheumatic drugs (csDMARDs), biologic DMARD (bDMARDs), and targeted synthetic DMARD (tsDMARDs), are commonly prescribed to treat numerous autoimmune rheumatic disease, such as rheumatoid arthritis (RA), systemic lupus erythematosus (SLE), etc. as well as for prophylaxis after organ transplantation procedures[10]. The impact of COVID-19 on patients with rheumatic diseases is currently unknown. It is unknown whether patients with rheumatic disease have a worse outcome because of their immunocompromised status or whether they have a better outcome because of anti-rheumatic therapies that reduce hyper-inflammation. In version 2 of the American College of Rheumatology guidance for the management of rheumatic disease in adult patients during the COVID-19 pandemic stated that no specific rheumatic diseases were identified as risk factors for poor outcomes COVID-19. During the pandemic, some studies reported different results regarding clinical outcomes in patients with autoimmune rheumatic disease and COVID-19.

Some studies reported that rheumatic disease was not associated with the risk of SARS-CoV-2 infection and poor clinical outcomes, while other studies are not. However, most of the studies were case reports or case series and survey-based designs. Whether poor clinical outcomes were because of underlying autoimmune disease or immunosuppressant medicines were unclear in previously published studies. Most of the studies did not eliminate the confounding variables such as age, sex, and comorbidities on the clinical outcomes in patients using immunosuppressant. A small number of patients, wide variations of methodology, and lack of generalization to the population were limitations of most studies.

Therefore, we conducted a review to summarize the impact of immunosuppressant therapy in patients with autoimmune rheumatic disease and COVID-19 from the available evidence that described the clinical characteristics and outcomes of COVID-19 patients with autoimmune rheumatic disease.

2. METHOD

This review was performed based on the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines.

2.1. Search strategy

We used PubMed and Science Direct database to comprehensively search articles published up to April 2021 between March and April 2021. We used keywords "autoimmune disease", "COVID-19", "rheumatic disease", "rheumatoid arthritis", "systemic lupus erythematosus", "immunosuppressant", and "immunosuppressive" to search the article in the database. Boolean operator with "OR" and "AND" was used to search articles more specific.

2.2. Study selection and data extraction

All studies involving COVID-19 infected rheumatic patients epidemiological and clinical information were listed. The inclusion criteria in this review were articles focusing on using immunosuppressant therapy to the prevalence of SARS-CoV-2 and clinical outcomes (hospitalization, ICU admission, and mortality) in COVID-19 patients with autoimmune rheumatic disease. Multivariate analysis or logistic regression must be done in the included articles to associate immunosuppressants with clinical outcomes. Studies with a cohort, cross-sectional, and case-control were enrolled in this review. We excluded studies in commentary, review, letter to the editor, case report, and case series. The following information, such as name of authors, study design, sample size, age, sex, type of autoimmune rheumatic diseases, and outcomes, was extracted and summarized in the table.

2.3. Outcomes

The primary outcomes of the included studies were infection rate of SARS-CoV-2, risk of hospitalization, ICU admission, the use of a ventilator, and mortality among patients with rheumatic disease.

3. RESULTS

A total of 16 studies met the inclusion criteria and were included in this present review involving 42.130 patients with autoimmune rheumatic disease. The PRISMA flowchart for article inclusion is shown in Figure 1. The summary characteristic of the included studies is summarized in Table 1. All of the included studies were observational study, either prospective or retrospective.

4. DISCUSSION

This present review has summarized and evaluated the available published literature describing unfavorable outcomes of immunosuppressant therapy in patients with rheumatic disease to the infection risk of COVID-19 and worsen clinical outcomes. Patients with autoimmune rheumatic disease require special attention during the COVID-19 pandemic. They are classified as high risk for infections and other unfavorable effects resulting from their immunocompromised state. About 71% of the patients were female, corresponding to the

Table 1. Summary of characteristics of studies.

Author and country	Study Design	n	Age (Years)	Autoimmune disease	Immunosuppressive drugs	Summary findings
Favalli et al[11] Italy	Cross-sectional	955	Mean: 53.7 Male: 311(32.5%) Female: 644(67.5%)	RA: 531 PA: 203 Spondyloarthritis: 181 Others: 40	bDMARD: 857(89%) tsDMARD: 96(10%) csDMARD: 503(53%) low dose glucocorticoid: 270(28%)	• Overall rate COVID-19 was 0.62% in patients with rheumatic disease, whereas 0.66% in general populations (p-value>0.05). Patients with rheumatic disease who tested positive for COVID-19, stopped their immunosuppressive drugs, including csDMARD and bDMARD.
Macias et al[12] Spain	Cross-sectional retrospective	722 HCQ users: 290 Non HCQ users: 432	**HCQ users:** Median: 56(45-65) Male: 42(16%) Female: 248(84%) **Non HCQ users:** Median: 58(48-60) Male: 82(21%) Female: 350(79%)	**HCQ users:** RA: 144 SLE: 83 Others: 60 **Non HCQ users:** RA: 323 SLE: 11 Others: 98	**Anti-TNF:** HCQ users: 3(1%) Non HCQ users: 54(13%) **Corticosteroids:** HCQ users: 112(39%) Non HCQ users: 149(35%)	• The incidence of COVID-19 in HCQ users was 3.4% and non HCQ users was 3.0% (p-value>0.05). There was no significant differences in patients requiring hospitalization, and death was no observed between two groups.
Jung et al[13] Korea	Retrospective cohort	2066 HCQ users: 649 Non HCQ users:1417	**HCQ users:** Mean: 57.6 Male: 120(18.4%) Female: 529(81.5%) **Non HCQ users:** Mean:60.45 Male: 454(32.0%) Female: 963(67.9%)	RA: 1877 SLE: 299	**HCQ users:** HCQ: 649(100%) Corticosteroids: 591(91%) **Non HCQ users:** HCQ: 329(23.2%) Corticosteroids: 1300(91.7%)	• The incidence of COVID-19 in HCQ users was 2.3% and non HCQ users was 2.2% (p-value>0.05).
Emmi et al[14] Italy	Cross-sectional	458	Median: 56(43-68) Male: 119(26%) Female: 339(74%)	SLE: 117 RA: 24 Spondyloarthritis: 40 Others: 277	Corticosteroids: 263(57.4%) DMARD: 209(45.6%) HCQ: 110(24.0%) Biologics agents: 196 (42.7%)	• There was no significant difference the prevalence of SARS-CoV-2 infection in patients with systemic autoimmune disease (0.22%) compared to those without (0.20%), p-value =0.597.
Marques et al[15] Brazil	Cohort Prospective	334	Median: 45(31-57) Female: 275(81.4%) Male: 59(18.6%)	SLE: 110 RA: 95 Axial spondyloarthritis: 45 SS: 23 PA: 23 Vasculitis: 10 Others: 28	HCQ: 118(34.9%) Oral corticosteroids: 116(34.3%) Anti-TNF: 75(22%) Methotrexate: 68(20.1%)	• Diabetes (PR 1.38), kidney disease (PR 1.36), oral glucocorticoid (PR 1.49), and use of methylprednisolone pulse (PR 1.38) were significantly associated with emergency care. • Age >50 years (PR 1.89), no use of TNF inhibitor (PR 2.51), use of methylprednisolone pulse (PR 2.50) were significantly associated with hospitalization. • Use of oral glucocorticoid (PR 2.24) and use of methylprednisolone pulse (PR 1.65) were significantly associated with ICU admission. • Use of methylprednisolone and cyclophosphamide were significantly associated with mortality (PR 2.86).

CQ: chloroquine; HCQ: hydroxychloroquine; GC: glucocorticoid; DMARD: disease modifying anti rheumatic drug; bDMARD: biologic disease modifying anti rheumatic drug; csDMARD: conventional synthetic disease modifying anti rheumatic drug; tsDMARD: targeted synthetic disease modifying anti rheumatic drug; OR: odd ratio; PR: prevalence risk; CKD: chronic kidney disease; IMB: inflammatory bowel disease; RA: rheumatoid arthritis; SLE: systemic lupus erythematosus; PA: psoriatic arthritis; SS: systemic sclerosis; PMR: polymyalgia rheumatic; MTX: Methotrexate.

Table 1. Summary of characteristics of studies. (cont.)

Author and country	Study Design	n	Age (Years)	Autoimmune disease	Immunosuppressive drugs	Summary findings
Favalli et al[16] Italy	Cross-sectional	2.050	Mean: 57.8 Female: 1.354(66%) Male: 696(34%)	N/A	Prednisone: 1282(62.5%) HCQ: 764(37.2%)	• Patients with rheumatic disease using prednisone or equivalent was significantly associated with increase risk of SARS-CoV-2 infection (OR: 1.23). • The use of bDMARD and tsDMARD reduced risk of SARS-CoV-2 infection (OR: 0.47). Duration of rheumatic disease more than 120 months was significantly associated with reduced risk of SARS-CoV-2 infection (OR: 0.71). • The AUC for overall variables (diasease duration, home lockdown, the use of prednisone, bDMARD, and b/tsDMARD was 0.62).
Veenstra et al[17] USA	Retrospective cohort	213	Mean: 53 Female: 155(72.8%) Male: 58(27.2%)	RA/spondylitis: 72 Psoriasis: 29 IMB: 38 SLE: 33 Others: 45	Biologics: 96(45.1%) DMARDS: 138(64.8%) Multidrug therapy: 40(18.8%) Corticosteroids: 22(10.3%)	• Systemic corticosteroid, multidrug therapy, and azathioprine were significantly associated with increase hospitalization (OR: 5.48), increase risk of COVID-19 (OR: 2.31), and increase the use of ventilator (OR: 16.8), respectively. • Biologic agents (TNF-alpha inhibitor) was significantly reduced hospitalization (OR: 0.42).
Montero et al[18] Spain	Retrospective study	62	Mean: 60.9 Male: 26(42%) Female: 36(58%)	42 hospitalized and 20 ambulatory patients RA: 20 SLE: 9 Others: 33	Glucocorticoid: 30(48%) Dose ≥5 mg: 27(44%) Methotrexate: 12(19%) HCQ: 9(14%) Anti-TNF: 12(19%).	• Male (OR: 7.4), lung disease (OR: 8.9), and glucocorticoid with a dose ≥5 mg/day were significantly associated with more severe COVID-19 infection requiring hospitalization (p-value<0.05). • Comorbidities (obesity, hypertension, and cardiovascular disease) were not associated with increase risk of hospitalization.
Santos et al[19] Spain	Cross-sectional	38	Mean: 75.3 Male: 18(47%) Female: 20(53%)	RA: 16 PMR: 8 SLE: 5 Others: 9	Glucocorticoid: 22(57.8%) csDMARd: 17(44.7%) Methotrexate: 14(36.8%) HCQ: 7(25%)	• The use of immunosuppressive drugs was not associated with mortality (p-value>0.05). Rheumatic disease activity, cardiovascular disease, dyslipidemia, and interstitial lung disease were significantly associated with mortality (p-value<0.05).
Pablos et al[20] Spain	Retrospective study	26.131	Mean: 65 Male: 11.531 Female: 14.600	RA: 10.927 SLE: 2.253 Others: 12.951	csDMARD: 7558 tsDMARD: 5802 bDMARD: 5802	• Generally, patients with rheumatic disease increase the prevalence of COVID-19 1.32 times more likely than general population. However, inflammatory arthritis disease was not associated with a higher incidence of COVID-19.

CQ: chloroquine; HCQ: hydroxychloroquine; GC: glucocorticoid; DMARD: disease modifying anti rheumatic drug; bDMARD: biologic disease modifying anti rheumatic drug; csDMARD: conventional synthetic disease modifying anti rheumatic drug; tsDMARD: targeted synthetic disease modifying anti rheumatic drug; OR: odd ratio; PR: prevalence risk; CKD: chronic kidney disease; IMB: inflammatory bowel disease; RA: rheumatoid arthritis; SLE: systemic lupus erythematosus; PA: psoriatic arthritis; SS: systemic sclerosis; PMR: polymyalgia rheumatic; MTX: Methotrexate.

Table 1. Summary of characteristics of studies. (cont.)

Author and country	Study Design	n	Age (Years)	Autoimmune disease	Immunosuppressive drugs	Summary findings
Nunez et al[21] Spain	Cohort prospective	123	Mean: 59.8 Female: 86	RA: 50 SLE: 8 Others: 65	GC: 61 csDMARD: 104 tsDMARD: 26 bDMARD: 26	• Autoimmune disease (OR: 3.55, *p*-value<0.05) and older age (OR: 1.08, *p*-value<0.05) were significantly associated with hospitalization. GC was not associated with hospitalization.
Zhong et al[22] China	Retrospective study	6.228	Mean: 45.9 Male: 811 Female: 5.417	RA: 2.766 SLE: 1.964 Others: 1.498	Corticosteroid: 1.193 HCQ: 616 Leflunomide : 967 Unknown: 3.919	• Autoimmune patients receiving HCQ have a lower risk of COVID-19 infection than those using DMARD (OR: 0.09, *p*-value: 0.044). • Older age has a risk factor of COVID-19 infection (OR: 1.04, *p*-value=0.0081).
Ferri et al[23] Italy4	Cohort prospective	1.641	Mean: 60 Male: 385 Female: 1256	RA: 695 Systemic sclerosis: 438 SLE : 76 Other : 432	csDMARDS: 62% bDMARD: 53% tsDMARD: 4% others: 40%	• The percentage of autoimmune disease with COVID-19 was higher (1.5%) than those in Italian population (0.34%) (OR: 4.42, *p*-value <0.05).
Zen et al[24] Italy	Cross-sectional	916	Mean: 53.6 Male: 196 Female: 720	SLE: 397 RA: 111 Others: 408	CQ/HCQ: 336 MTX: 139 Mycophenolate: 181 Prednisone >7.5 mg/day: 91	• Out of 148 patients had at least one symptom of COVID-19. Sixty five of them had a naso-pharyng swab, and two patients with positive COVID-19 (0.21%).
Serling-Boyd et al[25] USA	Case control	143 autoimmune disease with COVID-19 688 non autoimmune disease as a control group.	Mean: 60 Female: 108	RA: 44 SLE: 27 Others: 72	bDMARD: 41 csDMARD: 44 HCQ: 30 GC: 51	• There was an increase of the use of mechanical ventilation in patients with autoimmune disease (15%) than those without autoimmune disease (9%) • There was no significant differences between two groups at risk of hospitalization, ICU admission, and mortality
D'Silva et al[26] USA	Case control	52 autoimmune disease patients with COVID-19 104 non autoimmune disease as a control group.	Mean: 62.5 Male: 16 Female:36	RA: 19 SLE: 10 Others: 23	HCQ:9 bDMARD:16 csDMARD:16 GC: 19	• Patients with autoimmune disease required more ICU admission and mechanical ventilation (48%) (OR: 3.22, *p*-value=0.02) compared to those without autoimmune disease (18%).

CQ: chloroquine; HCQ: hydroxychloroquine; GC: glucocorticoid; DMARD: disease modifying anti rheumatic drug; bDMARD: biologic disease modifying anti rheumatic drug; csDMARD: conventional synthetic disease modifying anti rheumatic drug; tsDMARD: targeted synthetic disease modifying anti rheumatic drug; OR: odd ratio; PR: prevalence risk; CKD: chronic kidney disease; IMB: inflammatory bowel disease; RA: rheumatoid arthritis; SLE: systemic lupus erythematosus; PA: psoriatic arthritis; SS: systemic sclerosis; PMR: polymyalgia rheumatic; MTX: Methotrexate.

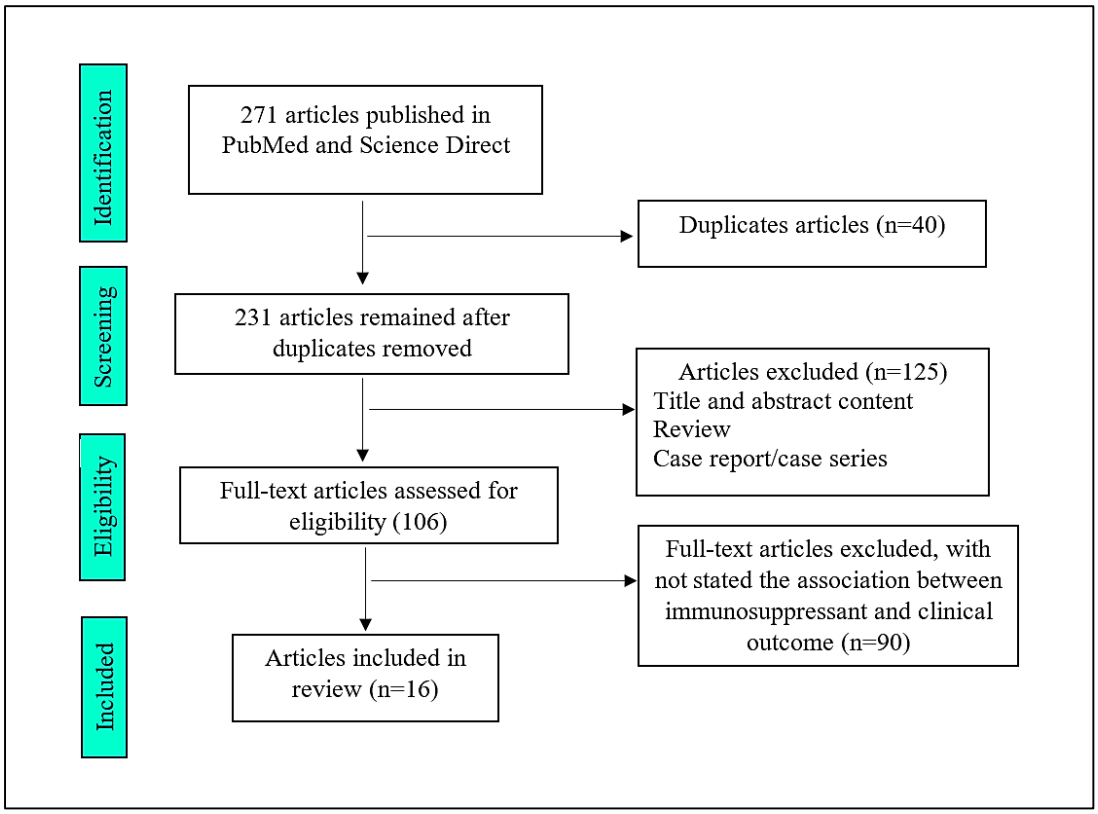

Figure 1. PRISMA flowchart.

natural history of female predominance in autoimmune diseases. Compared to the meta-analysis study by Xu et al, which reported that 64% of patients were female. Because that study involved 31 articles with 1138 patients, a lower number of patients compared to our review[27]. However, our study was consistent with the Global Registry, stating about 76% of patients were female[28]. The number of patients with rheumatoid arthritis in Indonesia is currently estimated at not less than 1.3 million, with calculations based on the prevalence of AR in the world between 0.5-1%[29]. The outcomes of each study were identified as accumulated outcomes without further differentiation by rheumatic disease type[30].

Most studies used hydroxychloroquine as a part of rheumatic disease treatment. The possible antiviral effects of chloroquine and hydroxychloroquine in the pandemic's early phase were interesting aspects that seemed to prevent SARS-CoV-2 endocytosis in alveolar epithelial cells in some *in vitro* studies. These drugs were given Emergency Authorization Used (EAU) by FDA to treat COVID-19 in April 2020. However, in June 2020, both drugs were suspended for COVID-19 management because of harmful effects, QT prolongation in several studies[30-32] including in Indonesia. National Agency of Drug and Food Control of Indonesia announced that hydroxychloroquine was permitted to treat autoimmune rheumatic disease, while chloroquine was not recommended due to harmful toxicity[33]. Due to its antiviral mechanism, hydroxychloroquine has been proposed to prevent SARS-CoV infection. However, this hypothesis was unclear whether the prophylactic effect of hydroxychloroquine could be observed in healthy individuals or patients with a specific disease. In the present review, we found eight studies that reported the overall rate of SARS-CoV-2 infection among autoimmune rheumatic disease ranged from 0.22% to 3.0%, and it was no different with the general population without rheumatic disease. This review was similar to a study in Indonesia, which reported that among 570 autoimmune rheumatic diseases, eleven patients were confirmed SARS-CoV-2 or approximately 1.92%[34].

Furthermore, there was no significant difference in the prevalence of SARS-CoV-2 infection between HCQ users and non HCQ users among patients with rheumatic disease in two studies by Macias et al[12]. (3.4% vs. 3.0%) and Jung et al[13]. (2.3% vs. 2.2%). A lower rate of SARS-CoV-2 infection (0.43%; 27/6228) among patients with rheumatic disease was reported by Zhong et al. in Hubei province, China. In that study, hydroxychloroquine was significantly associated with reduced risk of COVID-19 compared to those taking other DMARDs (OR 0.09, CI 95% 0.21-5.40, *p*-value<0,05)[22]. However, in a study by Zhong et al[22]., the percentage of patients who were taking hydroxychloroquine was lower (26.7%) compared to the study by Macias et al[12]. (40.16%) and Jung et al[13]. (31.4%), respectively. Both studies reported COVID-19 incidence and severity were not significantly different in patients with autoimmune rheumatic disease

treated with or without hydroxychloroquine[12,13].

The study by Machias et al[12]., stated that the overall incidence of COVID-19 was 0.164% (95% CI= 0.16%-0.17%) cases. This figure is within the 95% CI of confirmed COVID-19 found either in patients with or without taking HCQ. This shows that incidence of confirmed SARS-CoV-2 infection among patients with autoimmune rheumatic disease, with or without HCQ, is similar to the incidence of SARS-CoV-2 infection in general population. There was no clinical efficacy associated with the prophylaxis of CQ and HCQ in randomized controlled trials. The efficacy of CQ/HCQ for post-exposure prophylaxis has rarely been studied in randomized control trials with long-term supervision of patients and their contacts. The drug's toxicity, in particular cardiac toxicity, has often outweighed its benefits, in contrast to the treatment of malaria. Patients with COVID-19 who were administered CQ/HCQ did not show any clinical benefit in a recent meta-analysis of 12 studies[35]. Furthermore, both of the two largest randomized controlled trials (RECOVERY[36] and WHO SOLIDARITY[37]) confirmed a lack of clinical benefit of chloroquine and hydroxychloroquine for COVID-19 patients.

Another therapy for autoimmune rheumatic disease, especially in SLE, is a glucocorticoid that can be used with other DMARDs based on the severity of the disease. Rheumatic disease patients administered corticosteroids, especially in high doses, are at risk for severe infection[38]. Glucocorticoids were identified as a significant risk factor for bacterial infection in a cohort study of over 15,000 patients with RA over the age of 65. Glucocorticoid doubled the rate of serious bacterial infections compared to methotrexate use, with a clear dose-response relationship for dosages greater than 5 mg/day and 20 mg/day[39].

Glucocorticoids have been used to manage COVID-19 patients, particularly those with cytokine storm and acute respiratory distress syndrome (ARDS). Several studies have reported slower virus clearance, which may worsen the patient's condition. The Indonesian Rheumatology Association recommends a dose of prednisone as initial therapy of 20 mg/week for mild SLE and 0.5 mg/kg/day for moderate to severe SLE. In the maintenance phase, the recommended dose of prednisone is 7.5 mg/day for all degrees of SLE in combination with other immunosuppressant therapy[40].

This review found four articles discussing the unfavorable effects of corticosteroids in autoimmune rheumatic disease, including increased risk of SARS-CoV-2 infection, hospitalization, and mortality. A study by Favalli et al, reported that prednisone at a dose >2.5 mg/day was significantly associated with the development of SARS-CoV-2 infection[16]. However, a meta-analysis study indicated that prednisone or equivalent for the short term has no impact or little in infection risk. Interestingly, an observational study evaluating a different dose of glucocorticoid (low, medium, and high dose) demonstrated that patients receiving a medium to high dose (≥7.5 mg/day) of prednisolone or equivalent were associated with increased risk of infection and severe infection[41]. However, the odds may differ for each disease treated with glucocorticoid. A study by Fardet et al. reported that the adjusted hazard ratio of infection was varied in patients receiving glucocorticoid. The hazard ratio was 2.01 (CI 95%=1.83-2.19) for cutaneous cellulitis, and 5.84 (CI 95%=5.61-6.08) for lower respiratory tract infection[42].

We found the use of methylprednisolone pulse was significantly associated with emergency care, hospitalization, ICU admission, and mortality, reported by Marques and co-workers[15]. Intravenous methylprednisolone pulse was administered with a dose of 0.5-1 g/day for three consecutive days. It is well assumed that because of their higher potency and the onset of action is faster than oral prednisone, the administration of methylprednisolone pulses is indicated for severe SLE when a rapid effect is crucial. This therapy aims to avoid high-dose and long-term oral prednisone, induce a faster tapering, and reduce the cumulative dose of corticesteroid and adverse effects[43]. A higher infection rate was observed in patients with SLE receiving methylprednisolone with the dose >1500 mg those less than 1500 mg. The infection rate was 9.1% in those who receive methylprednisolone with the dose >1500 mg. Meanwhile, no patients suffered an infection in a <1500 mg[44]. In contrast, the study by Nuñez et al. stated that glucocorticoids were not associated with the risk of hospitalization. However, the study did not mention the dose and duration of glucocorticoid use and the relatively small sample size of 123 patients. In addition, only 54 of the 123 patients underwent treatment at the hospital. From the multivariate analysis results, there was no relationship between the use of glucocorticoids and the risk of hospitalization[21].

Infections represent one of the adverse effects of high-dose corticosteroids, causing an increased risk of morbidity and mortality in patients with SLE. The factors precipitating infection in patients with SLE are disease activity and the administration of immunosuppressant agents, particularly glucocorticoid[45]. Glucocorticoid suppresses cell-mediated immunity by inhibiting IL-1, IL-2, IL-6, dan IFN-gamma. The inhibition of IL-2 reduces T lymphocyte proliferation and inhibits the clonal development expansion of B lymphocytes responsible for producing immunoglobulin. Furthermore, glucocorticoids weaken macrophage activity and impair phagocytosis activity[46]. The Indonesia Rheumatology Association recommended corticosteroids can be given to patients with confirmed COVID-19 who are asymptomatic or with mild-moderate symptoms of infection with the smallest effective dose according to their rheu-

matic disease activity. In COVID-19 patients with signs of severe infection, the determination of the corticosteroid dosage takes into account the clinical conditions and weights risk-benefit ratio for each patient[47].

Surprisingly, five studies reported that the use of bDMARD, particularly TNF-α inhibitor, was significantly associated with a low risk of SARS-CoV-2 infection and hospitalization. TNF-α is a pro-inflammatory cytokine produced by activated monocytes. It involved almost in acute inflammatory reactions, acting as an inducer of inflammation. COVID-19 patients were proposed to have high inflammatory biomarkers, such as IL-6, IL-8, and TNF-α. A blockaded high level of TNF-α has beneficial effects by improving prognosis and reducing organ damage in inflammatory diseases, such as rheumatic disease and COVID-19[48]. A recent study by Del Valle and co-workers indicated that in COVID-19 patients, TNF-α level was high on the first admission. It was a strong and independent predictor of a patient's survival (p-value<0.05). The level of TNF-α gradually decreased after the administration of tocilizumab, an IL-6 inhibitor[49]. Several clinical trials demonstrated that the use of TNF-α inhibitors, including etarnecept, infliximab, and adalimumab, relieves inflammation of the joint, reduces severe joint progression, and improves physical function in patients with advanced rheumatoid arthritis[50-52].

Furthermore, the administration of TNF-α inhibitor in patients with rheumatoid arthritis is more efficacious to promote better symptoms and clinical signs than methotrexate alone. However, The Indonesia Rheumatology Association recommended that the bDMARD administered for rheumatic disease patients with COVID-19 is an IL-6 inhibitor after COVID-19 infection is over. TNF-α inhibitors should be avoided based on this guideline[53].

Several studies in the present review reported comorbidities, including cardiovascular disease, diabetes, chronic respiratory disease, as significant risk factors for hospitalization. Some classical cardiovascular risk factors such as smoking, insulin resistance, dyslipidemia, arterial hypertension, and low baseline of vitamin D influenced cardiovascular comorbidities in patients with rheumatic disease[52-54]. Meanwhile, methotrexate and TNF-α inhibitor were protective factors[55,56]. The development of cardiovascular events among rheumatic disease patients was observed in 10 years and doubled within 12 months[53]. Metabolic syndrome and hypertension were commonly found in patients with rheumatoid arthritis and SLE, with an estimated 14-38% prevalence for metabolic syndrome and 23-66% for hypertension[57,58]. Some studies reported cardiovascular disease (RR: 2.25)[59], hypertension (RR: 2.39)[60], and respiratory disease (OR: 5.15)[61] was associated with mortality on COVID-19 patients with rheumatic disease.

Meanwhile, the study by Montero et al. showed the comorbidities were not associated with hospitalization. It was because of the limited number of patients and the study design was a retrospective study[18]. An effort should be taken to prevent mortality in patients with rheumatic disease. Angiotensin receptor blockers (ARBs) and angiotensin-converting enzyme inhibitors (ACEi) were clinically proven to avoid severity and mortality in COVID-19 patients, particularly with comorbidities[62].

There was some limitation of our review. First, all of the studies did not report the dose and duration of the immunosuppressant therapy to treat rheumatic disease. These aspects will impact the severity and prognosis of patients. Second, some studies have a limited number of patients and with cross-sectional design. Therefore, the results did not reflect the generalized populations directly. Third, the details of the outcomes were unavailable for specific rheumatic disease and specific immunosuppressant therapy. The immunomodulatory effects among immunosuppressant therapy such as csDMARD, bDMARD, tsDMARD may be different.

5. CONCLUSION

The use of immunosuppressant therapy in rheumatic disease patients before the onset of COVID-19 may have unfavorable effects with poor prognosis outcomes. Overall, corticosteroid use, particularly in the moderate to high dose, was associated with poor clinical outcomes. TNF-α inhibitors may be helpful to reduce harmful prognostic factors. Comorbidities in rheumatic disease patients should be closely supervised to minimize the risk for morbidity and mortality. Rheumatologists, pharmacists, and other healthcare teams should collaborate to monitor the prognosis and report the outcomes for a specific rheumatic disease and specific immunosuppressant therapy. This study emphasized further study with larger sample size, multicenter, more detailed treatment, and disease-specific outcomes.

Conflict of interest
All authors declare no conflict of interest in this review

Funding
All authors declare no supporting funding from any agency in this review

Ethics approval
None to declare.

Article info:
Received May 12, 2021
Received in revised form August 9, 2021
Accepted October 28, 2021

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