The Egyptian Journal of Hospital Medicine (October 2022) Vol. 89 (2), Page 6589- 6595

Role of Hydroxychloroquine in Rheumatoid Arthritis and Systemic Lupus Erythematosus Patients during COVID-19 Pandemic

Noha H. Elnagdy[1], Ali Sobh[2], Mohamed Elegezy[3], Mohamed Mofreh[4], Ahmed Hazem El-nagdy[5], Mohamed Tohlob[6], Marwa H. Elnagdy[7], Ahmed E. Abdulgalil[8]

[1]Department of Physical Medicine, Rheumatology and Rehabilitation,
[2]Department of Pediatrics-Mansoura University Children's Hospital,
[3]Department of Endemic medicine, [4]Department of Clinical Pathology,
[6]Department of Chest Medicine, [7]Department of Medical Biochemistry and Molecular Biology,
[8]Mansoura nephrology and dialysis unit, Faculty of Medicine, Mansoura University, Egypt.
[5]Department of Microbiology, Faculty of Dentistry, Horus University, Damietta Elgadeda, Egypt
***Corresponding Author: Noha H. Elnagdy, Email**: n.elnagdy86@mans.edu.eg,
Phone no:00201116118771, **Orcid id**: 0000-0002-2135-3599

ABSTRACT

Background: Antimalarial drugs including Hydroxychloroquine (HCQ) and chloroquine have been demonstrated to be associated with anti-inflammatory actions in different connective tissue diseases (CTD) as rheumatoid arthritis (RA) and Systemic Lupus Erythematosus (SLE). One of the points of interest was the emergent antiviral effect of these drugs against Covid-19 infection. However, this antiviral effect is still debatable. **Objective:** The objective was to study HCQ effects on the severity and outcome of COVID-19 infection in patients with RA and SLE.

Patients and Methods: A total of 94 cases diagnosed as RA and SLE with COVID-19 infection were comprised in the study and were categorized into 2 groups: the first group included patients who were receiving HCQ treatment before infection, and the second group included patients who were not receiving HCQ before. Clinical, laboratory, and radiological findings as well as the outcome of patients were assessed to compare the severity of COVID-19 infection in both groups. **Results:** Demographic data showed higher female predominance. Fever, cough, rhinorrhea, and myalgia were observed in both groups with no significant variation except for rhinorrhea. D-dimer was significantly increased in the first group. Decreased oxygen saturation, need for mechanical ventilation, radiological changes suggestive of COVID-19 infection, and acute kidney injury (AKI) were more observed in the HCQ group with statistical significance. **Conclusion:** HCQ administration was not associated with less severe infection or better outcomes in RA and SLE patients infected with COVID-19.

Keywords: Hydroxychloroquine, Rheumatoid Arthritis, Systemic Lupus Erythematosus, COVID-19.

INTRODUCTION

Coronaviruses are viruses that can affect both animals and humans. They may be associated with a variety of respiratory disorders such as severe acute respiratory syndrome (SARS), Middle East respiratory syndrome (MERS), and COVID-19 which is induced by SARS-CoV-2 [(1)]. Although the infection with SARS-CoV-2 might be without manifestations, multiple vital organs have been proven to be affected. The respiratory system is the most common site to be affected [(2)]**.** Pneumonia is one of the most serious manifestations of this viral infection and may be life-threatening [(3)].

Various treatment strategies have been used since the beginning of the pandemic including HCQ which is a commonly utilized DMARD in the context of RA and SLE management [(4,5)]**.** The use of HCQ was based on its different mechanisms of action including decrement of replication of the virus in vitro, inhibition of production of cytokines and costimulatory molecules, alteration of cell pH, affecting the lysosomal activity and signaling pathways as well as autophagy [(6)]**.**

The fact that HCQ has a very high concentration in the lung that it may reach a hundred times more than its concentration in the blood, led to the belief in its possible therapeutic effect concerning COVID-19- associated pneumonia management [(7)]. Therefore, the US Food and Drug Administration emergently approved it for the management of cases of COVID-19 [(8)]. However, results from the SOLIDARITY trial, demonstrated that the usage of HCQ wasn't accompanied by either benefit or harm in the management of COVID-19- infected patients. Also, results from later randomized controlled trials, such as the RECOVERY trial, showed that HCQ wasn't beneficial in hospitalized COVID-19 patients [(9)]**.** It has been concluded that the evidence about the efficacy and safety of HCQ regarding COVID-19 management was feeble and conflicting [(10)]**.**

Infection with COVID-19 might be very extensive in cases with CTD. Despite the lower possibility of severe COVID-19 infections in patients receiving HCQ and/or glucocorticoid therapy with low- to medium-dose, immunosuppressive agents should be used with extra caution due to their dysregulated immune response [(11)]**.**

The beneficial role of HCQ in CTD patients infected with COVID-19 is questionable [(12)]. Also, the effect of HCQ on the severity of infection and its effect on outcome in this group of patients is controversial**.** We carried out the present study to assess whether HCQ use influences the severity and outcome of COVID-19 infection among cases with RA and SLE.

Received: 1/7/2022
Accepted: 7/9/2022

PATIENTS AND METHODS

Study design and overview

This observational retrospective study was done in Mansoura University hospitals over the period from January to December 2021 after obtaining approval from the Institutional Review Board (IRB) of Mansoura University. Entire cases included in the study, or their caring relatives were well informed about the study.

The study comprised patients diagnosed with RA or SLE with confirmed SARS-COV2 infection. RA diagnosis was done according to ACR/EULAR 2010 RA classification criteria [13]**.** However, the diagnosis of SLE was done according to ACR classification criteria for SLE [14]. Patients were categorized into two groups: the first group comprised 53 cases who were receiving HCQ treatment (200-400 mg/d) for at least 3 months before infection, and the second group included 41 patients who were not receiving HCQ before.

Data were collected from hospital medical records of RA and SLE cases infected with COVID-19 with no disease activity at the time of infection. These patients presented to our hospital with symptoms suggesting COVID-19 infection. These symptoms included fever higher than 37·5°C, cough, dyspnea, anosmia, rhinorrhea, fatigue, myalgia, arthralgia, headache, nausea, abdominal discomfort, emesis, or diarrhea. For these cases, COVID-19 IgM and IgG were done by chemiluminescent immunoassay using an automated assay (iFlash 1800-YHLO Biotech Co., Ltd., Shenzhen, China). The level of SARS-CoV-2 IgM or IgG Abs (AU/ml) was measured in an automated manner based on RLU and a built-in calibration curve, and 10.0AU/ml was regarded as the positive cut-off; reactive result (≥10.0AU/mL) denotes possible infection by SARS-CoV-2 virus, and non-reactive results (<10.0AU/mL) denote the absence of SARS-CoV-2. COVID-19 diagnosis was confirmed if rhino-pharyngeal swabs were positive for SARS-CoV-2 RNA.

Collected data included the onset and duration of symptoms, contact with infected cases, laboratory investigations (including hemoglobin, total leucocytic count, neutrophilic count, lymphocytic count, ESR, CRP, ferritin, D-dimer, SGPT, SGOT, and serum creatinine), radiological findings at the time of infection, hospitalization, need for oxygen, ICU admission, mechanical ventilation, and survival.

Patients with disease activity at the time of COVID infection, and other types of respiratory diseases including pneumonia induced by other micro-organisms, bronchial asthma, history of immune deficiencies, or age less than 18 years were excluded from this study.

The relation between HCQ intake and SARS-CoV-2 infection severity decreased SPO2, need for mechanical ventilation, ICU admission, AKI, and mortality among cases with RA or SLE was assessed in both groups.

Ethical approval:

The study protocol was approved by the IRB of Mansoura University (no: R.21.03.1233). Entire cases comprised in the study, or their caring relatives were well informed about the study, and written informed consent was obtained from all participants in the study. This work has been carried out following The Code of Ethics of the World Medical Association (Declaration of Helsinki) for studies involving humans.

Statistical analysis

Data were fed to the computer and analyzed by utilizing IBM SPSS Corp. Released in 2013. IBM SPSS Statistics for Windows, Version 28.0. Armonk, NY: IBM Corp. Qualitative data were defined by utilizing numbers and percentages and compared by utilizing Chi-Square, Fischer exact, and Monte Carlo tests as appropriate. Quantitative data were defined by utilizing median for non-normally distributed data and mean, SD for normally distributed data after testing normality using the Kolmogorov-Smirnov test. The Significance of the obtained results was judged at the (0.05) level. Student t-test and Mann-Whitney U test were utilized to compare 2 independent groups as a parametric and non-parametric test, respectively.

RESULTS

Socio-demographic features and history of patients in both groups are shown in **Table (1)**. There was female predominance in both groups. Systemic hypertension was statistically significant in HCQ group in comparison with the 2nd group (P=0.015). From the 53 cases receiving HCQ, 33 were RA and 20 were SLE. While cases not taking HCQ were 27 RA and 14 SLE. Rhinorrhea was statistically significant among patients not receiving HCQ (p=0.015) **(Table 2). Table (3)** showed laboratory findings of the studied groups. There was statistical significance as regard D-dimer (p=0.019) and serum creatinine (p=0.01) which were more elevated in cases receiving HCQ.

Table (1): Socio-demographic characteristics and history of patients in both groups:

	Cases on HCQ		Cases without HCQ		Test of significance
	N=53	%	n=41	%	
Age/years median(min-max)	35 (18-75)		22 (18-78)		z=2.34 p=0.02*
BMI (kg/m2) mean±SD	26.32±5.28		24.19±5.82		t=1.81 p=0.073
Sex					
male	9	17	11	26.8	χ^2=1.34
Female	44	83	30	73.2	p=0.247
Consanguinity					
-ve	47	88.7	37	90.2	χ^2=0.06
+ve	6	11.3	4	9.8	p=0.807
Smoking					
non-smoker	52	98.1	41	100	FET=0.782
smoker	1	1.9	0	0	P=1.0
Hypertension					
-ve	30	56.6	33	80.5	χ^2=5.97
+ve	23	43.4	8	19.5	p=0.015*
DM					
-v	48	90.6	38	92.7	χ^2=0.133
+ve	5	9.4	3	7.3	p=0.715
Chronic Lung Disease					
-ve	45	84.9	36	87.8	χ^2=0.163
+ve	8	15.1	5	12.2	p=0.686
Diagnosis of cases					
RA	33	62.3	27	65.9	χ^2=7.72
SLE	20	37.7	14	34.1	p=0.021*

χ^2=Chi-Square test, FET: Fischer exact test, *statistically significant, z: Mann Whitney U test.

Table (2): Clinical presentation of the studied cases.

	Cases on HCQ		Cases without HCQ		Test of significance
	n=53	%	n=41	%	
Fever	38	71.7	27	65.9	χ^2=0.370 p=0.543
Cough	45	84.9	31	75.6	χ^2=1.29 p=0.256
Rhinorrhea	12	22.6	19	46.3	χ^2=5.88 p=0.015*
Anosmia	12	22.6	4	9.8	χ^2=2.72 p=0.099
Vomiting	14	26.4	8	19.5	χ^2=0.614 p=0.433
Diarrhea	12	22.6	9	22.0	χ^2=0.006 p=0.936
Abdominal pain	12	22.6	12	29.3	χ^2=0.534 p=0.465
Myalgia	34	64.2	29	70.7	χ^2=0.453 p=0.501
Hepatitis	5	9.4	1	2.4	χ^2=1.89 p=0.169
Myocarditis	3	5.7	2	4.9	χ^{2FET}=0.028 p=1.0
Guillain barre syndrome	0	0.0	1	2.4	χ^{2FET}=1.31 p=0.436

χ^2=Chi-Square test, FET: Fischer exact test, *statistically significant

Table (3): Laboratory findings of the studied cases.

	Cases on HCQ (n= 53)	Cases without HCQ (n= 41)	Test of significance
HB (gm/dl) mean±SD	10.01±1.37	10.39±1.27	t=1.38 p=0.173
TLC Median (Min-Max)	4.8(1.5-27)	6.5(1.5-21)	z=1.40 p=0.161
Neutrophils Median (Min-Max)	2.9(0.6-15.0)	4.1(0.7-16)	z=1.03 p=0.303
Lymphocytes Median (Min-Max)	1(0.3-8.8)	1.22(0.2-6.9)	z=0.038 p=0.970
CRP Median (Min-Max)	24(0-113)	20(0-106)	z=1.29 p=0.195
ESR Median (Min-Max)	35(13-100)	38(6-100)	z=0.103 p=0.918
Ferritin Median (Min-Max)	150(5-677)	162(27-420)	z=0.015 p=0.988
D dimer Median (Min-Max)	120(6.3-1100)	76(8-800)	z=2.35 p=0.019*
SGOT Median (Min-Max)	32(11-2792)	29(11-84)	z=1.01 p=0.312
SGPT Median (Min-Max)	31(17-406)	31(13-68)	z=0.286 p=0.775
Serum creatinine Median (Min-Max)	1.1(0.4-10)	0.8(0.4-5.8)	z=2.57 p=0.01*

*Statistically significant, Z: Mann Whitney U test, t: Student t-test.

Our results showed statistical significance in SPO2 and radiological changes suggestive of COVID-19 infection in cases receiving HCQ (p=0.027 and p=0.03 respectively). Also, AKI was statistically significant. Only one case not receiving HCQ died in comparison to 10 cases receiving HCQ **(Table 4).** The relation between diagnosis and outcome among HCQ cases is shown in **Table 5**. The need for oxygenation was significantly higher among SLE patients receiving HCQ than patients with RA.

Table (4): COVID-19 and outcome status among the studied cases.

	Cases on HCQ		Cases without HCQ		Test of significance
	n=53	%	n=41	%	
COVID-19 contact	31	58.5	14	34.1	χ^2=5.19, p=0.019*
Hospitalization	17	32	7	17.1	χ^2=1.16, p=0.281
ICU	10	18.9	3	7.3	χ^2=1.94, p=0.164
OXYGEN	14	26.4	4	9.8	χ^2=4.14, p=0.04*
Mechanical ventilation	10	18.9	2	4.9	χ^2=4.06, p=0.04*
Radiological findings (CORAD)	N=39		n=18		
II	1	2.6	3	16.7	
III	3	7.7	0	0.0	χ^{2MC}=8.87
IV	5	12.8	6	33.3	p=0.03*
V	30	76.9	9	50.0	
Multisystem affection	2	3.8	1	2.4	FET=0.133 P=0.715
Multiorgan failure	3	5.7	1	2.4	FET=0.589 P=0.629
Sepsis	6	11.3	4	9.8	χ^2=0.06, p=0.807
AKI	14	26.4	3	7.3	χ^2=5.69, p=0.017*
Outcome					
Alive	43	81.1	40	97.6	χ^2=6.04
Dead	10	18.9	1	2.4	p=0.014*
O2 saturation (Mean±SD)	89.72±10.33		93.71±5.40		t=2.24, p=0.027*
Respiratory Rate (Mean±SD)	23.85±7.32		22.07±6.65		t=1.21, p=0.228
hospitalization stay /days (Mean±SD)	13±4.8		9.57±3.21		t=1.44 p=0.166

χ^2=Chi-Square test, FET: Fischer exact test, MC: Monte Carlo test, t: Student t-test, *statistically significant.

Table (5): Relation between diagnosis and outcome among HCQ group cases:

	RA (33 cases) no (%)	SLE (20 cases) no (%)	Test significance
Hospitalization	8 (24.2%)	9 (45%)	P=0.235
ICU admission	5 (15.2%)	5 (25%)	P=0.303
Need oxygenation	5 (15.2%)	9 (45%)	P=0.034*
Mechanical ventilation	5 (15.2%)	5 (25%)	P=0.346
Death	5 (15.2%)	5 (25%)	P=0.346

DISCUSSION

Our study included 94 patients suffering from CTD (RA and SLE) who were infected with COVID-19 and were divided into 2 groups: the first group included 53 cases who were receiving HCQ, and the second group included 41 cases who were not receiving HCQ. The main presenting symptoms in the HCQ group were cough in 45 patients (84.9%) and fever in 38 patients (71.7%), while cough was the main presenting symptom in the second group (75.6 %). These findings are in line with the findings of studies by **Ye *et al.*** *2021* [(11)] and **Pham *et al***. 2021 [(15)] which showed that fever and cough were the most common symptoms in both groups of their studies. Rhinorrhea was significantly presented among 2nd group cases (P=0.015), this finding is similar to what was reported by **Pham *et al***. 2021[(15)] in their study.

No significant difference was demonstrated among both groups as regards lymphopenia nor inflammatory markers (CRP, ferritin) (P=0.970 & P=0.195& P=0.988) correspondingly. D-dimer median was significantly elevated in HCQ group 120 (6.3-1100) ng/ ml in comparison to 2nd group 76 (8-800) ng/ ml (P=0.019), these characteristics were comparable to **Wang *et al.*** 2020 [(3)] who reported similar findings in COVID19 patients including fever (98.5%), fatigue (69%), dry cough (59%) and lymphopenia (0.8×10^9/L with IQR (0.6-1.1)). These clinical and laboratory alterations noticed with COVID-19 infection suggest the presence of coagulation activation, cellular immune deficiency, and myocardial, hepatic, and renal injury.

There was a statistically significant increase in serum creatinine level among cases of HCQ group 1.1(0.4-10) mg/dL in comparison to 2nd group 0.8(0.4-5.8) mg/dL (P=0.01). Fourteen patients (26%) developed AKI in the HCQ group vs 3 patients (7%) in the 2nd group (P=0.017). These results are similar to the results reported by **Pham *et al***. 2021 [(15)] who found that percentage of patients who developed AKI in the HCQ group (64%) was higher than that of patients who developed AKI in the control group (32%).

Regular intake of HCQ didn't prevent COVID-19 pneumonia. In our study, we detected worse radiological findings in HCQ groups. Radiological abnormalities were observed in most of the patients in both groups in the form of bilateral ground glass opacities which were subpleural mostly at lower lobes with very high suspicion of COVID-19 (CORAD 4 & 5) in 90 % of the patients who showed radiological abnormalities in HCQ group vs 80% of the patients (CORAD 4 & 5) who showed radiological abnormalities in the 2nd group (p=0.03), which gave an idea that HCQ didn't protect from the progression to COVID-19 pneumonia. These findings are comparable to **Fredi *et al***. 2020 [(16)] whose findings indicated that cases with rheumatic and musculoskeletal diseases didn't seem to have a milder form of COVID-19 pneumonia in comparison with controls. In contrast to these findings are those of **Chen *et al***. 2020 [(17)] study which showed that a larger percentage of patients had improved pneumonia in the HCQ treatment group (80%) compared with the control group (55%). This discrepancy could be owing to the smaller number of patients in **Chen *et al*** study and that our patients are more immune-compromised.

The mean of oxygen saturation was significantly lower in the HCQ group than in the 2nd group (P=0.027). Also, The average duration of hospital stay was longer in the HCQ group than 2nd group, which copes with what was recorded in the RECOVERY trial [(9)] in which cases in the HCQ group were associated with a prolonged duration of hospital stay in comparison with the usual-care group (16 days Versus 13 days) and a minimal possibility of discharge alive within 28 days (59.6% versus 62.9%) and more than what was reported by **Wang *et al***. *2020* [(3)] as the average period of hospital stay was 10 days (IQR, 7.0-14.0).

The results of our study showed that CTD patients who were receiving HCQ before infection (first group) were not secure from COVID-19 infection. Also, our study showed that there was more severe respiratory deterioration in this group where nearly half of the patients complained of dyspnea in comparison to about a fifth of the patients in 2nd group (P=0.03), also, 14 patients needed oxygen therapy and 10 patients were mechanically ventilated in HCQ group in comparison to 4 patients who needed oxygen and 2 patients who were mechanically ventilated in 2nd group (P=0.04 & P=0.03). These findings are matched with the RECOVERY trial [(9)] which showed a higher possibility of progression to invasive mechanical ventilation or death in the HCQ group.

Ten patients from the HCQ group died vs 1 patient from the 2nd group (P=0.014). These results are in agreement with the RECOVERY trial [(9)] which reported that among hospitalized patients with COVID-19, those who received HCQ didn't have a minimal

incidence of death at 28 days in comparison with cases receiving usual care. In addition, this trial showed that the percentage of patients with cardiac arrhythmias in the HCQ group was higher with raised concerns about the prolongation of the QTc interval. **Rentsch *et al***. 2021 [(18)] also stated that HCQ didn't reduce the mortality rate in patients who were receiving HCQ before the COVID-19 outbreak for treatment of CTD. The findings of these studies together with our results give an impression that HCQ does not lower the possibility of mortality among cases with CTD who were receiving it before infection with COVID-19.

Beyond its well-known usage as an antimalarial medication, HCQ is primarily used as an immunomodulatory for CTD including SLE and RA where it interferes with the formation of lysosomal antigens by antigen-presenting cells, inhibits T-cell recruitment, and reduces the release of pro-inflammatory cytokines comprising IL-6 and TNF. HCQ is a powerful immune modulator and hasn't been associated with a higher possibility of infection. The overall effect of this immune modulation is beneficial for managing auto-immune diseases. HCQ is also not regarded as an immunosuppressive drug [(6)].

Although several researches have shown that long-term utilization of HCQ doesn't raise the possibility of infection, the immunologic effects that make HCQ an essential medication for the management of autoimmune diseases may have non-desirable adverse effects in COVID-19 patients. There may be a negative effect on antiviral innate and adaptive immune responses that need to be taken into account and researched as part of the consequences of such immune modulation on patients with COVID-19.

Our study demonstrated no valuable effects of HCQ in CTD cases infected with COVID-19 infection. This is consistent with several trials such as the **Rentsch *et al*.** study [(18)], **Pham *et al.*** study [(15)], and RECOVERY trial [(9)]. Our study had some limitations. The serum of patients wasn't acquired to assess the viremia. Viral load is possibly relevant to assess the severity of coronavirus infection. In addition, interactions between HCQ and other DMARDS require additional research to ascertain their impacts on patients' immunological states and their effect on humoral and cellular immunity.

CONCLUSION

HCQ administration was not associated with less severe infection or better outcomes in RA and SLE patients infected with COVID-19.

Acknowledgements

No acknowledgements are to be declared.

Conflict of interest

The authors declare that no conflict of interest.

Funding

The authors declare that no funding from any source was used in this study.

Author contribution: Authors contributed equally to the study.

ABBREVIATIONS

- **ACR**: American colleague of rheumatology
- **AKI:** Acute kidney injury
- **CTD**: Connective tissue diseases
- **DMARD**: Disease-modifying antirheumatic drugs
- **EULAR:** European Alliance of Associations for Rheumatology
- **HCQ**: Hydroxychloroquine
- **MERS**: Middle East respiratory syndrome
- **RA**: Rheumatoid arthritis
- **SARS**: Severe acute respiratory syndrome
- **SLE**: Systemic Lupus Erythematosus

REFERENCES

1. **Ortiz-Prado E, Simbaña-Rivera K, Gómez-Barreno L *et al.* (2020):** Clinical, molecular, and epidemiological characterization of the SARS-CoV-2 virus and the Coronavirus Disease 2019 (COVID-19), a comprehensive literature review. Diagn Microbiol Infect Dis., 98(1):115094. https://doi.org/10.1016/j.diagmicrobio.2020. 115094
2. **Renu K, Prasanna P, Gopalakrishnan A (2020):** Coronavirus pathogenesis, comorbidities and multi-organ damage - A review. Life Sci., 255:117839. https://doi.org/10.1016/j.lfs.2020.117839
3. **Wang D, Hu B, Hu C *et al.* (2020):** Clinical Characteristics of 138 Hospitalized Patients With 2019 Novel Coronavirus-Infected Pneumonia in Wuhan, China. JAMA., 323(11):1061-9. https://doi.org/10.1001/jama.2020.1585
4. **Lee T, MacKenzie L, McDonald E *et al.* (2020):** An observational cohort study of hydroxychloroquine and azithromycin for COVID-19: (Can't Get No) Satisfaction. Int J Infect Dis., 98:216-7. https://doi.org/10.1016/j.ijid.2020.06.095
5. **Wang M, Cao R, Zhang L *et al.* (2020):** Remdesivir and chloroquine effectively inhibit the recently emerged novel coronavirus (2019-nCoV) in vitro. Cell Res., 30(3):269-71. https://doi.org/10.1038/s41422-020-0282-0
6. **Meyerowitz E, Vannier A, Friesen M *et al.* (2020):** Rethinking the role of hydroxychloroquine in the treatment of COVID-19. FASEB J., 34(5):6027-37. https://doi.org/10.1096/fj.202000919
7. **Yao X, Ye F, Zhang M *et al.* (2020):** 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(15):732-9. https://doi.org/10.1093/cid/ciaa237
8. **U. S. Food and Drug Administration (2020):** Fact sheet for healthcare providers emergency use authorization (EUA) of hydroxychloroquine sulfate supplied from the strategic national stockpile for treatment of COVID-19 in certain hospitalized patients. https://dailymed.nlm.nih.gov/dailymed/fda/...
9. **RECOVERY Collaborative Group (2020):** Effect of hydroxychloroquine in hospitalized patients with Covid-

19. New England Journal of Medicine, 383(21):2030-40. https://doi.org/10.1056/NEJMoa2022926

10. **Hernandez A, Roman Y, Pasupuleti V *et al.* (2020):** Update Alert: Hydroxychloroquine or Chloroquine for the Treatment or Prophylaxis of COVID-19. Ann Intern Med., 173(4):W78-W9. https://doi.org/10.7326/L20-0945
11. **Ye C, Zhong J, Cai S *et al.* (2021):** COVID-19 infection in patients with connective tissue disease: A multicity study in Hubei province, China. MedComm., 2(1):82-90. https://doi.org/10.1002/mco2.56
12. **Lane C, Weaver J, Kostka K *et al.* (2020):** Safety of hydroxychloroquine, alone and in combination with azithromycin, in light of rapid wide-spread use for COVID-19: a multinational, network cohort and self-controlled case series study. Cold Spring Harbor Laboratory, 2020:1-29. https://doi.org/10.1101/2020.04.08.20054551
13. **Radner H, Neogi T, Smolen J *et al.* (2013):** Performance of the 2010 ACR/EULAR classification criteria for rheumatoid arthritis: a systematic literature review. Annals of the Rheumatic Diseases, 73(1):114-23. https://doi.org/10.1136/annrheumdis-2013-203284
14. **Tan E, Cohen A, Fries J *et al.* (1982):** The 1982 revised criteria for the classification of systemic lupus erythematosus. Arthritis & Rheumatism: Official Journal of the American College of Rheumatology, 25(11):1271-7.https://doi.org/10.1002/art. 1780251101
15. **Pham K, Torres H, Satlin M *et al.* (2021):** Failure of chronic hydroxychloroquine in preventing severe complications of COVID-19 in patients with rheumatic diseases. Rheumatology Advances in Practice, 5(1):rkab014.
16. **Fredi M, Cavazzana I, Moschetti L *et al.* (2020):** COVID-19 in patients with rheumatic diseases in northern Italy: a single-centre observational and case-control study. Lancet Rheumatol., 2(9):e549-e56. https://doi.org/10.1016/S2665-9913(20)30169-7
17. **Chen Z, Hu J, Zhang Z *et al.* (2020):** Efficacy of hydroxychloroquine in patients with COVID-19: results of a randomized clinical trial. BMJ., 2020:1-11. https://doi.org/10.1101/2020.03.22.20040758
18. **Rentsch C, DeVito N, MacKenna B *et al.* (2021):** Effect of pre-exposure use of hydroxychloroquine on COVID-19 mortality: a population-based cohort study in patients with rheumatoid arthritis or systemic lupus erythematosus using the OpenSAFELY platform. The Lancet Rheumatology, 3(1):e19-27.