



Systemic autoimmune diseases, anti-rheumatic therapies, COVID-19 infection risk and patient outcomes

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Abstract

As of June 10th 2020 about 7.2 million individuals have tested positive for, and more than 410,000 have died due to COVID-19. In this review we outline the pathophysiology that underpins the potential use of anti-rheumatic therapies for severe COVID-19 infection and summarize the current evidence regarding the risk and outcome of COVID-19 in patients with systemic autoimmune diseases. Thus far there is no convincing evidence that any disease-modifying anti-rheumatic drug (conventional synthetic, biologic or targeted synthetic) including hydroxychloroquine, may protect against severe COVID-19 infection; answers about their possible usefulness in the management of the cytokine storm associated with severe COVID-9 infection will only arise from ongoing randomized controlled trials. Evidence on COVID-19 risk and outcome in patients with systemic autoimmune diseases is extremely limited; thus, any conclusions would be unsafe and should be seen with great caution. At present, the risk and severity (hospitalization, intensive care unit admission and death) of COVID-19 infection in people with autoimmune diseases do not appear particularly dissimilar to the general population, with the possible exception of hospitalization in patients exposed to high glucocorticoid doses. At this stage it is impossible to draw any conclusions for differences in COVID-19 risk and outcome between different autoimmune diseases and between the various immunomodulatory therapies used for them. More research in the field is obviously required, including as a minimum careful and systematic epidemiology and appropriately controlled clinical trials.

Keywords Covid-19 · Autoimmune diseases · Anti-rheumatic drugs · Hydroxychloroquine

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Introduction

Autoimmune diseases are characterized by intrinsic immune alterations, which may lead to chronic inflammation in multiple organ systems. The diseases themselves and many of their treatments are associated with increased risk for severe infections [1–4]. Detailed research on the pathogenesis of these diseases has led to the development of targeted therapies, aimed mainly at cytokines and cells, which play key roles in the chronic inflammatory process.

During the COVID-19 pandemic, the risk and outcomes of patients with autoimmune diseases have become a cause of concern and require proper investigation. On the one hand, this population is, by virtue of the disease and its treatment, potentially vulnerable to suffer severely from COVID-19; on the other hand, many of these patients have been and continue to be exposed to immune modifying therapies which may have the potential to treat some features and improve outcomes of COVID-19 itself.

The initial link came from observations indicating that severe COVID-19 infection, manifested by acute respiratory distress syndrome (ARDS) and/or multi-organ failure, is associated in a proportion of patients with a “cytokine storm” [5–8]. It follows then that certain cytokine-blocking agents may be beneficial in this scenario [9, 10] and several of them are presently being tested in clinical trials internationally. In the meantime, data on the risks and outcomes of COVID-19 infection in patients with autoimmune diseases who are already receiving such agents could be informative but remain scarce [11–13].

In this narrative review, we outline the pathophysiologic mechanisms that underpin the potential utility of anti-rheumatic therapies in the context of severe COVID-19 infection and summarize the current evidence regarding the risks and outcomes of COVID-19 infection in patients with systemic autoimmune diseases.

Rational for the use of anti-rheumatic drugs in the treatment of severe COVID-19 infection

Driven by data indicating that an immune overreaction, a “cytokine storm”, may be a critical component of severe COVID-19 infection [5–7], it has been hypothesized that the use of drugs blocking specific cytokines could be beneficial for some infected patients [9, 10]. Previous observations in patients infected with different viruses such as the influenza virus [14, 15] and other coronaviruses like the SARS-CoV and MERS-CoV [16] suggested that an exaggerated host immune response could participate in tissue injury leading to serious outcomes.

Data regarding the exact nature of host immune responses’ against COVID-19 are now starting to emerge [17]. As is the case with other respiratory viruses, the initial innate antiviral immune responses in the respiratory tract are crucial for effective control of the infection. In the majority of cases (> 80%), these responses are adequate, leading to viral clearance and clinical improvement without significant associated tissue (mainly lung) injury. Data regarding immune responses in recovered patients following mild or moderate illness are limited so far.

On the other hand, in a proportion of patients (~ 20%), severe lung injury is observed which may lead in approximately 5% of patients to ARDS, respiratory and multi-organ failure or even death (~ 1%). In such cases, a dysregulated immune response has been described, usually during the 2nd week of infection, characterized more often by T cell lymphopenia (both CD4 and CD8 cells) [5], enhanced production and release of pro-inflammatory cytokines such as interleukin-6 (IL-6), tumor necrosis factor- α (TNF- α), IL-1 and G-CSF [5–7, 18], decreased production of antiviral type

I and III interferons [17] and T cell exhaustion [17]. This “hyperinflammatory state” which is being referred to as “cytokine storm” shares certain clinical (high fever), laboratory (increased C-reactive protein-CRP, ferritin, serum IL-6 and D-dimer levels) and immunological (macrophage and T cell activation) features with the macrophage activation syndrome or secondary hemophagocytic lymphohistiocytosis (HLH) seen in a subset of patients with infections (bacterial or viral), auto-immune or auto-inflammatory diseases (such as systemic onset juvenile idiopathic arthritis, adult Still’s disease and systemic lupus erythematosus) and after CART cell therapy in patients with leukemia or lymphoma [19–21].

Such observations underpinned the hypothesis that targeting pro-inflammatory cytokines with specific drugs used in autoimmune diseases may control the hyperinflammatory state in COVID-19 infection; however, this approach also raises concerns for a blunted response to viral invasion [22].

Targeted anti-cytokine therapies neutralize individual mediators of inflammation rather than causing a complete shutdown of the innate and adaptive immune responses. Hence, the risk from specific pathogens may differ between therapies. The most commonly used biologic Disease Modifying Anti-Rheumatic Drugs (bDMARDs), i.e. the anti-TNF agents (infliximab, etanercept, adalimumab, golimumab and certolizumab) increase the risk of serious bacterial infections [23] while there is some limited evidence that they may also increase the risk for influenza infection [24]. Humoral immunity may be affected more by some drugs (such as the anti-CD20 monoclonal antibody, rituximab) than other targeted anti-cytokine therapies, such as anti-IL-23, -IL-4/IL-13 or -IL-17A, which have not been associated with a significant increase in the risk of viral infections.

So far there have been few studies assessing the role of cytokine-targeted (mainly IL-1 and IL-6) therapies in patients with COVID-19 infection [25–29] but none of them were randomized controlled studies.

However, drugs with the potential to inhibit multiple cytokines may be riskier. These include the more recently developed targeted synthetic (ts)DMARDs, mainly the JAK inhibitors. These drugs target JAK1 and JAK3, affecting the function of several cytokines that are involved in antiviral responses (including type I interferons, IL-2, IL-15, IL-21 and IFN γ) and could theoretically inhibit viral clearance [30]. The flip side of this is that JAK2 inhibition may block SARS-CoV-2 entry and pro-inflammatory cytokines that depend on JAK signaling (including IL-17, IL-6 and GM-CSF) [31, 32].

The majority of patients with autoimmune diseases, however, still receive the older conventional synthetic (cs) DMARDs and/or variable doses of glucocorticoids that may also have significant effects in the context of COVID-19 infection. Hydroxychloroquine has been suggested as a potential therapeutic agent for prophylaxis or therapy of

COVID-19 infection but the results so far have been conflicting [25, 33–39]. There is concern regarding the use of moderate- to high-dose glucocorticoids in COVID-19 infection [40, 41] and so far these are only recommended for mechanically ventilated patients with ARDS [42]. There are no data so far for other commonly used csDMARDs, such as methotrexate, azathioprine, cyclosporine and mycophenolate mofetil.

In summary, whereas on the one hand b- or ts-DMARDs may theoretically increase the risk and severity of viral infections, there are, on the other hand, mechanistic and clinical observations suggesting that they may be useful in controlling specific aspects of the immune overreaction and thus improve the outcomes of severe COVID-19 infection. Indicative answers for both questions may arise from well-conducted observational studies in patients with autoimmune diseases receiving DMARD therapy compared with the general population. A definitive answer for the latter question could only be provided as a result of appropriately conducted randomized controlled trials (RCTs) in patients with severe COVID-19 infection [43].

Current data on COVID-19 infection in patients with rheumatic diseases

A literature search in the electronic databases PubMed, Scopus and Web of Science was performed until May 29th, using the terms “COVID-19” and “rheumatic diseases”, “disease-modifying anti-rheumatic drugs”, “biologics”, “rheumatoid arthritis”, “systemic lupus erythematosus”, “spondyloarthropathies”, “psoriatic arthritis”, “ankylosing spondylitis”, “vasculitis”, “scleroderma”, “JAK inhibitors”, “glucocorticoids” or “corticosteroids” in order to identify relevant publications of patients with rheumatic diseases and COVID-19 infection. Articles were initially selected by their title and abstract and then the full text was searched for the appropriate relevant content. References from the selected articles were also manually searched for relevant articles.

In Table 1, we summarize data from all published studies and case series which described COVID-19 infection in patients with autoimmune diseases. There is significant heterogeneity both in the general characteristics as well as the autoimmune disease characteristics and treatments of the patients included in these cohorts.

The largest series with detailed data so far is from New York [44]. It reports data on the outcome of 86 patients with autoimmune/inflammatory diseases who had either confirmed (59 patients) or suspected (27 patients) COVID-19 infection (Table 1) [44]. The majority were females (57%) at a rather young age (mean 46 years). Most common diagnoses included spondyloarthritis (SpA) and/or psoriasis (PSO), inflammatory bowel diseases (IBD), rheumatoid

arthritis (RA) or a combination of these diseases. Compared to other patient cohorts, comorbidities were rather uncommon (hypertension: 13%, COPD: 5%, diabetes: 6%). Most patients were on biologics or JAK inhibitors (72%) with few receiving glucocorticoids (9%). Hospitalization was required for 14 (16%), ICU admission or mechanical ventilation in 1 patient (7%) while there was only 1 death at arrival in the ER (7%). The rate for hospitalization was not different from that of the general population of New York (26%).

An observational study from France monitored the clinical course of COVID-19 infection in 17 patients with systemic lupus erythematosus (SLE) who were on long-term hydroxychloroquine therapy (median 7.5 years) (Table 1) [45]. Comorbidities were common in this group including obesity (59%) and chronic kidney disease (47%). All but one patient had clinically quiescent SLE, with a SLEDAI score equal to 0. Twelve (71%) patients were receiving glucocorticoids (usually at doses < 10 mg/day) and seven (41%) were receiving additional immunomodulatory drugs. Hydroxychloroquine and glucocorticoids were maintained at the same dose, while immunosuppressive drugs were discontinued or reduced. Fourteen patients required hospitalization (82%), half of them ($n=7$) in the ICU and finally 2 patients (14%) died. Although this study is also limited by small numbers, the authors concluded that hydroxychloroquine does not appear to prevent severe COVID-19 infection. Regarding the severity of COVID-19 in SLE patients, no safe conclusion can be drawn, but the high incidence of other comorbidities may confound these observations.

In the relatively early phase of the outbreak in N. Italy, Monti et al. performed a survey in patients with chronic arthritis in their outpatient clinic to investigate potential infections with COVID-19 or high-risk contacts (Table 1) [46]. The authors gathered information from 320 patients (57% with RA, 43% with SpA, 52% treated with anti-TNFs, 40% with other bDMARDs and 8% with tsDMARDs). They identified 4 confirmed and 4 suspected COVID-19 infections while another 5 reported high-risk contacts but remained asymptomatic for the 2-week observation period. Three patients (one with confirmed and two with suspected COVID-19) were on hydroxychloroquine. All patients with symptoms of infection had their anti-rheumatic therapy temporarily withdrawn at the time of symptom onset. No significant relapses of the rheumatic disease occurred; none of the patients with a confirmed or highly probable COVID-19 developed severe respiratory complications or died and only one patient with confirmed infection, aged 65, required admission to hospital and received low-flow oxygen supplementation for a few days. All patients with confirmed COVID-19 received at least one antibiotic course, and the hospitalized patient also received antiviral therapy and hydroxychloroquine. The authors also reported that among 700 patients admitted for severe COVID-19 during

Table 1 Anti-inflammatory treatment and outcomes of patients with confirmed or suspected COVID-19 infection

	Haberman et al. [44]	Mathian et al. [45]	Monti et al. [46]	Global Rheumatology Alliance [48]	Total <i>n</i> (%)
Patients	86	17	8	600	711
Definite COVID-19	59	17	4	548	628 (88%)
Suspected COVID-19 diseases	27		4	52	83 (12%)
RA	20		6	230	256 (36%)
SpA (PsA, AS, PSO)	34 ^a		2	122	158 (22%)*
IBD (UC/CD)	37 ^a				37 (5%) ^a
SLE		17		85	102 (14%)
Other				198	198 (29%)
bDMARDs	58		6	205	269 (38%)
Anti-TNF	40		4	119	163
IL-17 blocker	6			16	22
IL-23 blocker	3				3
IL 12/23 blocker	6			3	9
Rituximab	1			27	28
Anti-IL6R	1			16	17
Anti-CTLA4			2	17	19
Vedolizumab	1				1
JAK inhibitors	6		2	26	34 (5%)
csDMARDs	20	7	5	344	376 (53%)
Methotrexate	17	2	3	NR	
Azathioprine	1				
Leflunomide	1		1		
MMF		5			
Sulfasalazine	1		1		
Hydroxychloroquine	8	17	3	130	158 (22%)
Glucocorticoids	8	12		189	209 (29%)
Hospitalized patients	14	14	1	277	306 (43%)
deaths	1	2	0	55	58 (8%)

n number, *RA* rheumatoid arthritis, *SpA* Spondyloarthritis, *PsA* psoriatic arthritis, *AS* ankylosing spondylitis, *PSO* psoriasis, *IBD* inflammatory bowel disease, *UC* ulcerative colitis, *CD* Crohn's disease, *SLE* systemic lupus erythematosus, *bDMARDs* biologic disease modifying anti-rheumatic drugs, *IL-17* interleukin-17, *csDMARDs* conventional synthetic DMARDs, *MMF* mycophenolate mofetil, *NR* not reported

^aSome patients had more than 1 disease

one month at their hospital, which was a referral center for COVID-19, none was receiving either bDMARDs or tsDMARDs [46].

An initiative driven by the Global Rheumatology Alliance aims to continuously collect data internationally for patients with rheumatic diseases infected with COVID-19. Initially data for 110 patients were reported [47] and more recently its updated form containing data for 600 patients (548 with confirmed and 52 with presumptive diagnosis of COVID-19) were published (Table 1) [48]. The most common diseases were RA (38%), SpA (20%), SLE (14%) and other diseases (33%, including vasculitis, Sjogren's syndrome etc.). Medications included csDMARDs in 48%, bDMARDs in 29%, tsDMARDs in 4% and glucocorticoids in 27%. Common comorbidities included hypertension in 33%, lung disease

in 21%, diabetes in 12%, cardiovascular disease in 11% and chronic renal insufficiency in 7%. Of the 600 infected patients, 46% were admitted to hospital and 9% died. By multivariable logistic regression analysis, age > 65 years (odds ratio—OR 2.56), certain comorbidities (hypertension or cardiovascular diseases, lung disease, diabetes and chronic renal disease, ORs 1.86–3.02) and high glucocorticoid dose (≥ 10 mg/day, OR 2.05) were associated with a higher risk for hospitalization. On the other hand, previous use of anti-TNF agents was associated with a lower hospitalization risk (OR 0.40) [48]. These results should be interpreted with caution since selection bias may have played a significant role here with inclusion of more severe cases.

Case reports of patients with autoimmune/rheumatic diseases who were infected with COVID-19 are also

increasingly appearing in the literature. A brief report from Italy described the incidence of COVID-infection and outcome among 123 patients with autoimmune/inflammatory diseases [49]. Most patients, ~60% were receiving csDMARDs, 20% bDMARDs, while 64% were also receiving relatively low dose glucocorticoids (average 5.3 mg of prednisolone daily). Only one registered patient (0.81%) developed a confirmed COVID-19 infection; this incidence was similar to that of COVID-19 infection in the area (0.62% at that time).

An interesting case of a 52-year-old woman with granulomatosis with polyangiitis for 32 years, who developed severe COVID-19 infection while on therapy with rituximab and glucocorticoids has been reported [50]. The patient had ear, nose and throat, orbital, lung, joint and skin involvement, anti-proteinase 3 (PR3) antibodies and had been heavily pretreated (with cyclophosphamide—total dose of 41 g, anti-TNF, mycophenolate mofetil, methotrexate, leflunomide, rituximab and steroids). Few months before the pandemic she received four infusions of weekly rituximab (375 mg/m²) and a maintenance dose of rituximab (500 mg) was administered in March 2020, while still under prednisone 15 mg daily. She was diagnosed with COVID-19 having presented with bilateral interstitial pneumonia 4 days after her last rituximab dose. She received lopinavir/ritonavir for 3 days but required mechanical ventilation, for ARDS, 18 days after symptom onset. Hydroxychloroquine was started following intubation and the authors report rapid clinical improvement with no need for mechanical ventilation after 2 days and no need for oxygen supplementation after 7 days, while nasopharyngeal RT-PCR became negative and the patient was discharged. The authors hypothesized that glucocorticoids and rituximab may have limited the cytokine storm and delayed the worsening of clinical status of the patient.

A very brief discussion of a few cases of COVID-19 infection in patients with autoimmune/inflammatory diseases from the UK has also been published, without any details reported [51]. These cases include a 23-year-old male with Crohn's disease on infliximab with mild disease who did not require hospitalization, a female with ulcerative colitis (of unspecified age) on tofacitinib and steroids who also did not require hospitalization and a 53-year-old female with Crohn's disease on adalimumab who was hospitalized but did not require mechanical ventilation.

Conclusions

As of June 10th 2020 about 7.2 million individuals have tested positive for, and more than 410,000 have died from COVID-19 [52]. Despite these numbers, data regarding the risk of infection and the severity and outcome of the disease in patients with systemic autoimmune diseases

remain extremely limited. The estimated prevalence of systemic autoimmune/inflammatory diseases in the general population ranges between 2 and 3% [53]. Assuming an equal risk for COVID-19 infection and death with the general population, one would have expected at least 5000 deaths of such patients so far. Were data on them to have been collected systematically through international collaborations, these are useful numbers for detailed analyses of risk with potentially powerful clinical messages. One should take into account though that the percentages of patients with systemic autoimmune disease who receive immunosuppressives may be lower within the elderly population which is more vulnerable to severe outcomes. Moreover, since males seem to have higher death rates than females [54], the female preponderance in systemic autoimmunity could be a protective factor.

Based on the available data at present, any conclusions would be unsafe and should be seen with great caution. Analysis of the published data presented in this review suggest the following: (A) there is thus far no convincing evidence that any of the DMARDs (conventional synthetic, biologic or targeted synthetic) including hydroxychloroquine, used in the management of systemic autoimmune diseases may protect against severe COVID-19 infection; (B) answers about the possible usefulness of DMARDs in the management of the cytokine storm and its sequelae during severe COVID-9 infection will only arise from the currently ongoing RCTs; (C) the risk of COVID-19 infection in patients with systemic autoimmune diseases does not seem to be much higher than in the general population with similar comorbidities [46, 49]; (D) the severity of COVID-19 infection (in terms of requirement for hospitalization, ICU admission or death) does not appear to be particularly dissimilar in this population compared with the general population, although data from large series of patients are not available yet; (E) it is impossible at this stage to draw any conclusions for differences in COVID-19 risk and outcome between different autoimmune diseases and between the various immunomodulatory therapies used for them.

More research in the field is obviously required, including as a minimum careful and systematic epidemiology, basic laboratory research and well-designed and appropriately controlled clinical trials.

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References

- Listing J, Gerhold K, Zink A (2013) The risk of infections associated with rheumatoid arthritis, with its comorbidity and treatment. *Rheumatology (Oxford)* 52:53–61
- Mehta B, Pedro S, Ozen G, Kalil A, Wolfe F, Mikuls T, Michaud K (2019) Serious infection risk in rheumatoid arthritis compared with non-inflammatory rheumatic and musculoskeletal diseases: a US national cohort study. *RMD Open* 5:e000935
- Tektonidou MG, Wang Z, Dasgupta A, Ward MM (2015) Burden of serious infections in adults with systemic lupus erythematosus: a national population-based study, 1996–2011. *Arthritis Care Res (Hoboken)* 67:1078–1085
- Schmidt J, Smail A, Roche B, Gay P, Salle V, Pellet H, Duhaut P (2016) Incidence of severe infections and infection-related mortality during the course of giant cell arteritis: a multicenter, prospective, double-cohort study. *Arthritis Rheumatol* 68:1477–1482
- Chen G, Wu D, Guo W, Cao Y, Huang D, Wang H, Wang T, Zhang X, Chen H, Yu H, Zhang X, Zhang M, Wu S, Song J, Chen T, Han M, Li S, Luo X, Zhao J, Ning Q (2020) Clinical and immunological features of severe and moderate coronavirus disease 2019. *J Clin Invest* 130:2620–2629
- Huang C, Wang Y, Li X, Ren L, Zhao J, Hu Y, Zhang L, Fan G, Xu J, Gu X, Cheng Z, Yu T, Xia J, Wei Y, Wu W, Xie X, Yin W, Li H, Liu M, Xiao Y, Gao H, Guo L, Xie J, Wang G, Jiang R, Gao Z, Jin Q, Wang J, Cao B (2020) Clinical features of patients infected with 2019 novel coronavirus in Wuhan, China. *Lancet* 395:497–506
- Wu C, Chen X, Cai Y, Xia J, Zhou X, Xu S, Huang H, Zhang L, Zhou X, Du C, Zhang Y, Song J, Wang S, Chao Y, Yang Z, Xu J, Zhou X, Chen D, Xiong W, Xu L, Zhou F, Jiang J, Bai C, Zheng J, Song Y (2020) Risk factors associated with acute respiratory distress syndrome and death in patients with coronavirus disease 2019 pneumonia in Wuhan, China. *JAMA Intern Med* 180(7):934–943. <https://doi.org/10.1001/jamainternmed.2020.0994>
- Cure E, Kucuk A, Cumhur CM (2020) Cyclosporine therapy in cytokine storm due to coronavirus disease 2019 (COVID-19). *Rheumatol Int* 40:1177–1179
- Feldmann M, Maini RN, Woody JN, Holgate ST, Winter G, Rowland M, Richards D, Hussell T (2020) Trials of anti-tumour necrosis factor therapy for COVID-19 are urgently needed. *Lancet* 395:1407–1409
- Mehta P, McAuley DF, Brown M, Sanchez E, Tattersall RS, Manson JJ (2020) COVID-19: consider cytokine storm syndromes and immunosuppression. *Lancet* 395:1033–1034
- Fragoulis GE, Evangelatos G, Arida A, Bournia VK, Fragiadaki K, Karamanakos A, Kravvariti E, Laskari K, Panopoulos S, Pappa M, Tektonidou MG, Sfikakis PP (2020) Treatment adherence of patients with systemic rheumatic diseases in COVID-19 pandemic. *Ann Rheum Dis*. <https://doi.org/10.1136/annrheumdis-2020-217935>
- Venerito V, Lopalco G, Iannone F (2020) COVID-19, rheumatic diseases and immunosuppressive drugs: an appeal for medication adherence. *Rheumatol Int* 40:827–828
- Georgiev T (2020) Coronavirus disease 2019 (COVID-19) and anti-rheumatic drugs. *Rheumatol Int* 40:825–826
- Beutel G, Wiesner O, Eder M, Hafer C, Schneider AS, Kielstein JT, Kuhn C, Heim A, Ganzenmuller T, Kreipe HH, Haverich A, Tecklenburg A, Ganser A, Welte T, Hoepfer MM (2011) Virus-associated hemophagocytic syndrome as a major contributor to death in patients with 2009 influenza A (H1N1) infection. *Crit Care* 15:R80
- Kash JC, Tumpey TM, Proll SC, Carter V, Perwitasari O, Thomas MJ, Basler CF, Palese P, Taubenberger JK, Garcia-Sastre A, Swayne DE, Katze MG (2006) Genomic analysis of increased host immune and cell death responses induced by 1918 influenza virus. *Nature* 443:578–581
- Hirano T, Murakami M (2020) COVID-19: a new virus, but a familiar receptor and cytokine release Syndrome. *Immunity* 52:731–733
- Vardhana SA, Wolchok JD (2020) The many faces of the anti-COVID immune response. *J Exp Med* 217:e20200678
- Ruan Q, Yang K, Wang W, Jiang L, Song J (2020) Clinical predictors of mortality due to COVID-19 based on an analysis of data of 150 patients from Wuhan, China. *Intensive Care Med* 46:846–848
- Lee DW, Gardner R, Porter DL, Louis CU, Ahmed N, Jensen M, Grupp SA, Mackall CL (2014) Current concepts in the diagnosis and management of cytokine release syndrome. *Blood* 124:188–195
- La RP, Horne A, Hines M, von Bahr GT, Machowicz R, Berliner N, Birndt S, Gil-Herrera J, Girschikofsky M, Jordan MB, Kumar A, van Laar JAM, Lachmann G, Nichols KE, Ramanan AV, Wang Y, Wang Z, Janka G, Henter JI (2019) Recommendations for the management of hemophagocytic lymphohistiocytosis in adults. *Blood* 133:2465–2477
- Henderson LA, Canna SW, Schulert GS, Volpi S, Lee PY, Kernan KF, Caricchio R, Mahmud S, Hazen MM, Halyabar O, Hoyt KJ, Han J, Grom AA, Gattorno M, Ravelli A, de Benedetti F, Behrens EM, Cron RQ, Nigrovic PA (2020) On the alert for cytokine storm: immunopathology in COVID-19. *Arthritis Rheumatol* 72:1052–1063
- Ritchie AI, Singanayagam A (2020) Immunosuppression for hyperinflammation in COVID-19: a double-edged sword? *Lancet* 395:1111
- Singh JA, Cameron C, Noorbaloochi S, Cullis T, Tucker M, Christensen R, Ghogomu ET, Coyle D, Clifford T, Tugwell P, Wells GA (2015) Risk of serious infection in biological treatment of patients with rheumatoid arthritis: a systematic review and meta-analysis. *Lancet* 386:258–265
- Dirven L, Huizinga TW, Allaart CF (2012) Risk factors for reported influenza and influenza-like symptoms in patients with rheumatoid arthritis. *Scand J Rheumatol* 41:359–365
- Greek Rheumatology Society and Professional Association of Rheumatologists (ERE-EPERE) (2020) Recommendations regarding COVID-19 infection in rheumatic patients in Greece. *Mediterr J Rheumatol* 31:6–7
- Capra R, De RN, Mattioli F, Romanelli G, Scarpazza C, Sormani MP, Cossi S (2020) Impact of low dose tocilizumab on mortality rate in patients with COVID-19 related pneumonia. *Eur J Intern Med* 76:31–35
- Cavalli G, De LG, Campochiaro C, Della-Torre E, Ripa M, Canetti D, Oltolini C, Castiglioni B, Tassan DC, Boffini N, Tomelleri A, Farina N, Ruggeri A, Rovere-Querini P, Di LG, Martinenghi S, Scotti R, Tresoldi M, Ciceri F, Landoni G, Zangrillo A, Scarpellini P, Dagna L (2020) Interleukin-1 blockade with high-dose anakinra in patients with COVID-19, acute respiratory distress syndrome, and hyperinflammation: a retrospective cohort study. *Lancet Rheumatol* 2:e325–e331
- Xu X, Han M, Li T, Sun W, Wang D, Fu B, Zhou Y, Zheng X, Yang Y, Li X, Zhang X, Pan A, Wei H (2020) Effective treatment of severe COVID-19 patients with tocilizumab. *Proc Natl Acad Sci USA* 117:10970–10975
- Dimopoulos G, de Mast Q, Markou N, Theodorakopoulou M, Komnos A, Mouktaroudi M, Netea MG, Spyridopoulos

- T, Verheggen RJ, Hoogerwerf J, Lachana A, van de Veer-donk FL, Giamarellos-Bourboulis EJ (2020) Favorable Anakinra responses in severe COVID-19 patients with secondary hemophagocytic lymphohistiocytosis. *Cell Host Microbe* 28:117–123. <https://doi.org/10.1016/j.chom.2020.05.007>
30. Favalli EG, Biggoggero M, Maioli G, Caporali R (2020) Baricitinib for COVID-19: a suitable treatment? *Lancet Infect Dis*. [https://doi.org/10.1016/S1473-3099\(20\)30262-0](https://doi.org/10.1016/S1473-3099(20)30262-0)
 31. Richardson P, Griffin I, Tucker C, Smith D, Oechsle O, Phelan A, Stebbing J (2020) Baricitinib as potential treatment for 2019-nCoV acute respiratory disease. *Lancet* 395:e30–e31
 32. Stebbing J, Phelan A, Griffin I, Tucker C, Oechsle O, Smith D, Richardson P (2020) COVID-19: combining antiviral and anti-inflammatory treatments. *Lancet Infect Dis* 20:400–402
 33. Gautret P, Lagier JC, Parola P, Hoang VT, Meddeb L, Mailhe M, Doudier B, Courjon J, Giordanengo V, Vieira VE, Dupont HT, Honore S, Colson P, Chabriere E, La SB, Rolain JM, Brouqui P, Raoult D (2020) Hydroxychloroquine and azithromycin as a treatment of COVID-19: results of an open-label non-randomized clinical trial. *Int J Antimicrob Agents*. <https://doi.org/10.1016/j.ijantimicag.2020.105949>
 34. Gautret P, Lagier JC, Parola P, Hoang VT, Meddeb L, Sevestre J, Mailhe M, Doudier B, Aubry C, Amrane S, Seng P, Hocquart M, Eldin C, Finance J, Vieira VE, Tissot-Dupont HT, Honore S, Stein A, Million M, Colson P, La SB, Veit V, Jacquier A, Deharo JC, Drancourt M, Fournier PE, Rolain JM, Brouqui P, Raoult D (2020) Clinical and microbiological effect of a combination of hydroxychloroquine and azithromycin in 80 COVID-19 patients with at least a 6-day follow up: a pilot observational study. *Travel Med Infect Dis* 34:101663
 35. Geleris J, Sun Y, Platt J, Zucker J, Baldwin M, Hripscak G, Labella A, Manson D, Kubin C, Barr RG, Sobieszczyk ME, Schluger NW (2020) Observational study of hydroxychloroquine in hospitalized patients with Covid-19. *N Engl J Med* 382:2411–2418
 36. Kim AHJ, Sparks JA, Liew JW, Putman MS, Berenbaum F, Duarte-Garcia A, Graef ER, Korsten P, Sattui SE, Sirotich E, Ugarte-Gil MF, Webb K, Grainger R (2020) A rush to judgment? Rapid reporting and dissemination of results and its consequences regarding the use of hydroxychloroquine for COVID-19. *Ann Intern Med* 172:819–821
 37. Bogdanos DP, Daniil Z, Zakynthinos E, Gourgoulianis K, Sakas LI (2020) When there is a pandemic there is no time to waste: should we have hydroxychloroquine in our armoury against COVID-19 infected patients? *Mediterr J Rheumatol* 31:94–97
 38. Mahevas M, Tran VT, Roumier M, Chabrol A, Paule R, Guillaud C, Fois E, Lepeule R, Szwebel TA, Lescure FX, Schlemmer F, Matignon M, Khellaf M, Crickx E, Terrier B, Morbieu C, Legendre P, Dang J, Schoindre Y, Pawlotsky JM, Michel M, Perrodeau E, Carlier N, Roche N, de Lastours V, Ourghanlian C, Kerneis S, Ménager P, Mouthon L, Audureau E, Ravaut P, Godeau B, Gallien S, Costedoat-Chalumeau N (2020) Clinical efficacy of hydroxychloroquine in patients with covid-19 pneumonia who require oxygen: observational comparative study using routine care data. *BMJ* 369:m1844
 39. Tang W, Cao Z, Han M, Wang Z, Chen J, Sun W, Wu Y, Xiao W, Liu S, Chen E, Chen W, Wang X, Yang J, Lin J, Zhao Q, Yan Y, Xie Z, Li D, Yang Y, Liu L, Qu J, Ning G, Shi G, Xie Q (2020) Hydroxychloroquine in patients with mainly mild to moderate coronavirus disease 2019: open label, randomised controlled trial. *BMJ* 369:m1849
 40. Bhimraj A, Morgan RL, Shumaker AH, Lavergne V, Baden L, Cheng VC, Edwards KM, Gandhi R, Muller WJ, O'Horo JC, Shoham S, Murad MH, Mustafa RA, Sultan S, Falck-Ytter Y (2020) Infectious Diseases Society of America guidelines on the treatment and management of patients with COVID-19. *Clin Infect Dis*. <https://doi.org/10.1093/cid/ciaa478>
 41. Russell CD, Millar JE, Baillie JK (2020) Clinical evidence does not support corticosteroid treatment for 2019-nCoV lung injury. *Lancet* 395:473–475
 42. Alhazzani W, Moller MH, Arabi YM, Loeb M, Gong MN, Fan E, Oczkowski S, Levy MM, Derde L, Dziera A, Du B, Aboodi M, Wunsch H, Cecconi M, Koh Y, Chertow DS, Maitland K, Alshamsi F, Belle-Cote E, Greco M, Laundry M, Morgan JS, Kesecioglu J, McGeer A, Mermel L, Mammen MJ, Alexander PE, Arrington A, Centofanti JE, Citerio G, Baw B, Memish ZA, Hammond N, Hayden FG, Evans L, Rhodes A (2020) Surviving sepsis campaign: guidelines on the management of critically ill adults with coronavirus disease 2019 (COVID-19). *Crit Care Med* 48:e440–e469
 43. Mikuls TR, Johnson SR, Fraenkel L, Arasaratnam RJ, Baden LR, Bermas BL, Chatham W, Cohen S, Costenbader K, Gravallese EM, Kalil AC, Weinblatt ME, Winthrop K, Mudano AS, Turner A, Saag KG (2020) American College of Rheumatology guidance for the management of adult patients with rheumatic disease during the COVID-19 pandemic. *Arthritis Rheumatol*. <https://doi.org/10.1002/art.41301>
 44. Haberman R, Axelrad J, Chen A, Castillo R, Yan D, Izmirly P, Neimann A, Adhikari S, Hudesman D, Scher JU (2020) Covid-19 in immune-mediated inflammatory diseases—case series from New York. *N Engl J Med* 383:85–88
 45. Mathian A, Mahevas M, Rohmer J, Roumier M, Cohen-Aubart F, Amador-Borrero B, Barrelet A, Chauvet C, Chazal T, Delahousse M, Devaux M, Euvrard R, Fadlallah J, Florens N, Haroche J, Hie M, Juillard L, Lhote R, Maillot T, Richard-Colmant G, Palluy JB, Pha M, Perard L, Remy P, Riviere E, Sene D, Seve P, Morelot-Panzini C, Viallard JF, Viot JS, Benameur N, Zahr N, Yssel H, Godeau B, Amoura Z (2020) Clinical course of coronavirus disease 2019 (COVID-19) in a series of 17 patients with systemic lupus erythematosus under long-term treatment with hydroxychloroquine. *Ann Rheum Dis* 79:837–839
 46. Monti S, Balduzzi S, Delvino P, Bellis E, Quadrelli VS, Montecucco C (2020) Clinical course of COVID-19 in a series of patients with chronic arthritis treated with immunosuppressive targeted therapies. *Ann Rheum Dis* 79:667–668
 47. Gianfrancesco MA, Hyrich KL, Gossec L, Strangfeld A, Carmona L, Mateus EF, Sufka P, Grainger R, Wallace Z, Bhana S, Sirotich E, Liew J, Hausmann JS, Costello W, Robinson P, Machado PM, Yazdany J (2020) Rheumatic disease and COVID-19: initial data from the COVID-19 Global Rheumatology Alliance provider registries. *Lancet Rheumatol* 2:e250–e253
 48. Gianfrancesco M, Hyrich KL, Al-Adely S, Carmona L, Danila MI, Gossec L, Izadi Z, Jacobsohn L, Katz P, Lawson-Tovey S, Mateus EF, Rush S, Schmajuk G, Simard J, Strangfeld A, Trupin L, Wysham KD, Bhana S, Costello W, Grainger R, Hausmann JS, Liew JW, Sirotich E, Sufka P, Wallace ZS, Yazdany J, Machado PM, Robinson PC (2020) 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* 79:859–866
 49. Favalli EG, Agape E, Caporali R (2020) Incidence and clinical course of COVID-19 in patients with connective tissue diseases: a descriptive observational analysis. *J Rheumatol*. <https://doi.org/10.3899/jrheum.200507>
 50. Guilpain P, Le BC, Foulongne V, Taourel P, Pansu N, Maria ATJ, Jung B, Larcher R, Klouche K, Le Moing V (2020) Rituximab for granulomatosis with polyangiitis in the pandemic of covid-19: lessons from a case with severe pneumonia. *Ann Rheum Dis*. <https://doi.org/10.1136/annrheumdis-2020-217549>
 51. Price E, MacPhie E, Kay L, Lanyon P, Griffiths B, Holroyd C, Abhishek A, Youngstein T, Bailey K, Clinch J, Shaikh M, Rivett

- A (2020) Identifying rheumatic disease patients at high risk and requiring shielding during the COVID-19 pandemic. *Clin Med (Lond)*. <https://doi.org/10.7861/clinmed.2020-0149>
52. WHO Coronavirus Disease (COVID-19) Dashboard. <https://covid19.who.int/>. Accessed 07 June 2020
53. Shapira Y, Agmon-Levin N, Shoenfeld Y (2010) Geoepidemiology of autoimmune rheumatic diseases. *Nat Rev Rheumatol* 6:468–476
54. de Groot NG, Bontrop RE (2020) COVID-19 pandemic: is a gender-defined dosage effect responsible for the high mortality rate among males? *Immunogenetics* 72:275–277

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