Since January 2020 Elsevier has created a COVID-19 resource centre with free information in English and Mandarin on the novel coronavirus COVID-19. The COVID-19 resource centre is hosted on Elsevier Connect, the company's public news and information website.

Elsevier hereby grants permission to make all its COVID-19-related research that is available on the COVID-19 resource centre - including this research content - immediately available in PubMed Central and other publicly funded repositories, such as the WHO COVID database with rights for unrestricted research re-use and analyses in any form or by any means with acknowledgement of the original source. These permissions are granted for free by Elsevier for as long as the COVID-19 resource centre remains active.
COVID-19 in rheumatic disease patients on immunosuppressive agents

Saika Sharmeen, Ahmed Elghawy, Fnu Zarlasht, Qingping Yao

Division of Rheumatology, Allergy and Immunology, Department of Medicine, Stony Brook University Renaissance School of Medicine, USA

ARTICLE INFO

Objective: To analyze clinical characteristics and outcome of COVID-19 patients with underlying rheumatic diseases (RD) on immunosuppressive agents.

Method: A case series of COVID-19 patients with RD on disease modifying anti-rheumatic drugs (DMARDs) were studied by a retrospective chart review. A literature search identified 9 similar studies of single cases and case series, which were also included.

Results: There were 4 COVID-19 inpatients with RD from our hospital, and the mean age was 57 ± 21 years. Two patients had a mild infection, and 2 developed severe COVID-19 related respiratory complications, including 1 patient on secukinumab requiring mechanical ventilation and 1 patient on rituximab developing viral pneumonia requiring supplemental oxygenation. All 4 patients had elevated acute phase reactants, 2 patients had mild COVID-19 with lymphopenia, and 2 patients had severe COVID-19 with normal lymphocyte counts, and high levels of IL-6. None of the patients exhibited an exacerbation of their underlying RD. In the literature, there were 9 studies of COVID-19 involving 197 cases of various inflammatory RD. Most patients were on DMARDs or biologics, of which TNFα inhibitors were most frequently used. Two tocilizumab users had a mild infection. Two patients were on rituximab with 1 severe COVID-19 requiring mechanical ventilation. Six patients were on secukinumab with 1 hospitalization. Of the total 201 cases, 12 died, with an estimated mortality of 5.9%

Conclusion: Patients with RD are susceptible to COVID-19. Various DMARDs or biologics may affect the viral disease course differently. Patients on hydroxychloroquine, TNFα antagonists or tocilizumab may have a mild viral illness. Rituximab or secukinumab could worsen the viral disease. Further study is warranted.

Introduction

Coronavirus 2019 (COVID-19) caused by severe acute respiratory syndrome coronavirus 2 (SARS CoV-2) has been declared a global pandemic since March 2020. This viral outbreak has raised serious concerns among the public and patients with health conditions. In the medical community, Rheumatologists are particularly concerned because their patients represent a population of autoimmune rheumatic disorders who are mostly on immunosuppressive agents and are susceptible to infection. While much has been learnt on COVID-19 in general, little is known of COVID-19 severity and outcomes in patients with rheumatic diseases (RD). Herein, in conjunction with the literature review, we report a case series of patients with RD, who were infected with COVID-19

Patients and methods

A retrospective chart review was conducted in 4 hospitalized patients at Stony Brook University Hospital between early March 2020 and the end of April 2020, including 2 cases that we previously published in the Rheumatologist. These patients had underlying RD on disease modifying anti-rheumatic drugs (DMARDs) prior to developing COVID-19. In our patients, a diagnosis of COVID-19 was made based on clinical grounds and by polymerase chain reaction of samples from nasopharyngeal swabs. In addition, a literature search of PubMed, Scopus, and Web of Science databases was conducted between December 2019 and May 2, 2020 using the terms: “COVID-19” and “rheumatic disease” or “biologic”. The search process and result are depicted in PRISMA (Fig. 1). English language articles that reported single case or case series of COVID-19 in RD were reviewed. Relevant information such as demographic, clinical, therapeutic data, and outcomes of these patients were gathered from the literature. Other relevant literature regarding the virus (SARS), immune response, and cytokine storm, were also searched between 1990 and May 2, 2020. Descriptive statistics was used.

Clinical Significance: Patients with rheumatic disease are susceptible to COVID-19. DMARDs may influence the viral disease course differently.

* Correspondence: Division of Rheumatology, Allergy and Immunology, Department of Medicine, Stony Brook University, Stony Brook, New York 11794, USA
E-mail address: qingping.yao@stonybrookmedicine.edu (Q. Yao).
Results

1 Our data of a case series of COVID-19 in RD

The demographic, clinical, and therapeutic data of 4 cases from our hospital are summarized (Table 1). Of the 4 COVID-19 hospitalized patients with RD, there were 2 men and 2 women with mean age of 57 ± 21 years. The most common symptoms among all 4 patients were fever and cough. Of the 4 patients, 2 patients had a mild infection, and the other 2 developed severe COVID-19 related respiratory complications, including 1 Ankylosing Spondylitis (AS) patient on secukinumab requiring mechanical ventilation and 1 Granulomatous with Polyangiitis (GPA) patient with underlying lung involvement on rituximab, who developed superimposed viral pneumonia requiring supplemental oxygenation. All 4 patients had elevated acute phase reactants, 2 patients had mild COVID-19 with lymphopenia, and 2 patients had severe infection with normal lymphocyte counts and high levels of interleukin (IL)-6. None of the patients exhibited an exacerbation of their underlying RDs. The lupus patient had normal complement levels and negative anti-double stranded DNA antibodies. In this case, acute worsening on chronic renal insufficiency was thought to be secondary to dehydration from diarrhea. The GPA patient did not show disease flare as evidenced by stable renal function and negative antineutrophil cytoplasmic antibody.

Case description

Case 1

A 76-year-old Caucasian woman with Rheumatoid Arthritis (RA) since 2006 presented in March 2020 with complaints of low-grade fevers, minimal dry cough, and headaches of one-week duration. She had been on etanercept 50 mg weekly and methotrexate (MTX) 10 mg weekly for more than 10 years. Additional comorbidities and medications are outlined in Table 1. Laboratory values including erythrocyte sedimentation rate, C-reactive protein, IL-6, and lung imaging studies were normal. A nasopharyngeal swab obtained on admission was positive for SARS-CoV-2 by polymerase chain reaction (PCR) (Viracor Eurofins, Lee’s Summit, Mo.). Her viral symptoms quickly abated without special treatment. She did not receive methotrexate or etanercept during the hospitalization.

Case 2

A 78-year-old Caucasian man presented to our hospital with high fevers (38.9°C) and severe dry cough for the previous 24 hours, along with fatigue, myalgias, shortness of breath, frontal headaches, and light-headedness, in March 2020. His medical history was significant for AS,
for which he received secukinumab 150 mg subcutaneous every four weeks for the previous 16 months. Other information such as comorbidities and medications are outlined in Table 1. On admission, his vital signs were temperature 38.2°C, respiration rate 22 breaths/minute, and blood pressure 179/78 mmHg, with pulse oximeter 98% on room air. The physical exam was within normal limits otherwise. His relevant laboratory findings are listed (Table 1). Despite initial normal chest X-ray, a chest CT performed on admission day 2 showed several small areas of groundglass opacities. Laboratory evaluation with inflammatory markers (Table 1). She tested positive for SARS-CoV-2 and did not receive special treatment except hemodialysis. He was discharged home after 11 days of hospitalization.

Case 4

A 27-year-old Hispanic woman with a diagnosis of GPA two months ago presented with fevers, severe dry cough, and shortness of breath in April 2020. She was treated with high dose steroids and four weekly infusions of Rituximab 2 months ago. Her GPA had been stabilized and she was on prednisone 30mg daily. On presentation, she was tachycardic and tachypneic with respiration rate 17/min, with SO2 100% on room air. Physical examination showed tachycardia but was otherwise normal. He tested positive for SARS-CoV-2 and did not receive special treatment except hemodialysis. He was discharged home after 11 days of hospitalization.

Case 3

A 49-year-old African American man with SLE, lupus nephritis class III/V, and underlying interstitial lung disease (ILD) presented in April 2020 with worsening renal function and hyperkalemia necessitating urgent hemodialysis. The patient had had chronic kidney disease since 2017 and received high doses of prednisone and mycophenolate mofetil until 2019. He only took hydroxychloroquine (HCQ) 200 mg BID. The patient had 10 days of watery diarrhea associated with nausea, vomiting, and decreased oral intake without abdominal pain. He also had low-grade fevers, chills, and generalized myalgias three weeks ago. His vital signs were temperature 36.6 °C, blood pressure 147/89 mmHg, heart rate 133/min, and breathing rate 17/min, with SO2 100% on room air. Physical examination showed tachycardia but was otherwise normal. He tested positive for SARS-CoV-2 and did not receive special treatment except hemodialysis. He was discharged home after 11 days of hospitalization.
positive for SARS-CoV-2 and received 5-day course of HCQ. However, due to poor clinical improvement, she subsequently received one dose of Tocilizumab 400 mg before her inflammatory markers and oxygen requirement improved. She did not require mechanical ventilation.

1 Literature data of COVID-19 in RD

The clinical data and outcomes of published cases are summarized (Table 2). Through the literature search, we identified 9 separate studies of COVID-19 in RD, including 4 single cases (1–4) and 5 case series (5–9). These studies involved 197 cases of various inflammatory RD. Most patients were on conventional and/or biologic DMARDs. The most frequently used DMARDs were tumor necrosis factor (TNF)α inhibitors among the patients. There were 2 cases of RD on rituximab, 1 with GPA having severe COVID-19 requiring mechanical ventilation; the patient received HCQ and lopinavir/ritonavir. The other patient with RA had clinical improvement after receiving HCQ/azithromycin/lopinavir-ritonavir/tocilizumab, and supplemental oxygen. There were 2 tocilizumab users including 1 Systemic Sclerosis patient who was treated at home and 1 RA patient on MTX and HCQ requiring supplemental oxygen, who was discharged 6 days later. Of the 6 secukinumab users, 5 were treated at home, while 1 required hospitalization but was discharged 3 days later. Among the 17 SLE cases, there were 7 ICU admissions and 2 deaths. All patients were on HCQ and 7 were on immunosuppressive agents. The authors did not specify the medications used among those ICU or severe patients (7). In the Global Rheumatology Alliance registry of 110 cases, there were 19 SLE cases; however, their disease severity and DMARD use was not specified. In addition, there were 39 hospitalized patients and 9 deaths (9). In the New York University Langone Health group study of 59 confirmed cases of COVID-19, there were 45 outpatients and 14 inpatients. Of the hospitalized patients, there were 1 ICU patient who had hypertension, BMI >30, mild psoriatic arthritis, and was on MTX prior to infection and 1 death who had coronary artery disease, BMI >40, and severe psoriasis. The remaining patients had mild viral disease course. Based on the total number of the literature cases plus our 4 cases, we estimated the mortality was 5.9% (12/201) among COVID-19 patients with RD.

| Authors          | COVID-19 case no. | Rheumatic disease | DMARD/Biologic             | COVID-19 outcome                          |
|------------------|-------------------|-------------------|----------------------------|-------------------------------------------|
| Mihai, et al     | 1                 | SSc               | Tocilizumab                | Mild, treated as outpatient               |
| Duret, et al     | 1                 | Axial SpA         | Etanercept                 | Mild but required hospitalization          |
| Moutsopoulos    | 1                 | CAPS              | Canakinumab                | Mild, treated as outpatient               |
| Guilpain, et al  | 1                 | GPA               | Rituximab                  | Severe, requiring ICU admission. treated with lopinavir/ritonavir for 3 days HCQ for 10 days Exhusted day 20 Discharged home day 29 |
| Favalli, et al   | 3                 | Sarcoidosis       | Adalimumab                 | Mild                                       |
| Monti, et al     | 4                 | RA                | Etanercept 2               | 14 hospitalized                           |
| Mathian, et al   | 17                | SLE               | Abatacept                  | 7 ICU                                    |
| Haberman, et al  | 59                | Psoriasis 7       | Apremilast 1               | 2 deaths                                  |
|                  |                   |                   | Azathioprine 1             | 45 outpatients                            |
|                  |                   |                   | Hydroxychloroquine 7      | 14 hospitalized                           |
|                  |                   |                   | Leflunomide 1              | 13 treated on regular floor               |
|                  |                   |                   | Mesalamine 5               | 1 ICU                                     |
|                  |                   |                   | Methotrexate 14            | 1 death                                  |
| Gianfrancesco, et al | 110  | RA 40             | Conventional DMARDs 69     | 39 hospitalized                           |
|                  |                   |                   | Biologics 49               | 9 deaths                                  |
|                  |                   |                   | JAK inhibitor 5            |                                           |
|                  |                   |                   | NSAIDs 28                  |                                           |
|                  |                   |                   | Glucocorticoids 27         |                                           |
|                  |                   |                   | Other 5                    |                                           |

DMARDs, disease modifying anti-rheumatic drugs; RD, Rheumatic Disease; RA, Rheumatoid Arthritis; PsA, Psoriatic Arthritis; Axial SpA, Axial Spondyloarthropathy; AS, Ankylosing Spondylitis; CD, Crohn’s disease; UC, Ulcerative Colitis; SLE, Systemic Lupus Erythematosus; GPA, Granulomatous with Polyangiitis; CAPS, Cryopyrin-associated periodic syndrome; HCQ, hydroxychloroquine; NSAIDs, Nonsteroidal anti-inflammatory drugs; JAK inhibitor, Janus kinase inhibitors.
Discussion

During the ongoing COVID-19 pandemic, both healthy individuals and patients with chronic conditions can be infected. We present a cases series of patients with RD, who developed COVID-19. Both our case study and the literature data indicate that patients with systemic autoimmune diseases, particularly those on DMARDs, are susceptible to COVID-19 with an estimated mortality of 5.9%.

Interestingly, we find that these patients in the current study had different clinical outcomes in terms of COVID-19 severity and related complications. For example, both the lupus patient on HCQ and RA patient on etanercept developed mild viral symptoms. The GPA patient on rituximab developed pneumonia requiring supplemental oxygenation via nonrebreather. The AS patient on secukinumab required mechanical ventilation. These two patients with severe disease had significantly higher serum levels of IL-6 that has been shown to correlate with severe COVID-19 and its related disease (10). To address the question of why these patients had different outcomes of the viral illness, several factors need to be considered, including underlying RD, age, gender, comorbidities, DMARD use, as well as the pathogenesis of COVID-19, among others.

Our analysis of these 4 cases has indicated that different DMARDs may affect the COVID-19 course and prognosis differently. To explain the potential effects of various DMARDs, we will first discuss the immunologic mechanisms of COVID-19.

SARS CoV2 is an enveloped RNA virus that consists of four primary structural proteins including a spike (S) glycoprotein, small envelope (E) glycoprotein, membrane (M)glycoprotein, and nucleocapsid (N) protein, along with several accessory proteins (11). The S glycoprotein binds to angiotensin converting enzyme 2 (ACE2), a receptor on cell membranes, followed by fusion of the viral membrane and host cell (12, 13). The cellular serine protease, TMPRSS2, is also required to properly process the SARS-CoV-2 spike protein and facilitate host cell entry (14). The virus entry initially triggers the innate immune response, where Pattern Recognition Receptors (PRR) such as Toll-like receptors (TLRs) recognize pathogen associated molecular patterns (PAMP). The PAMP may be nucleic acids, glycoproteins, lipoproteins and other small molecules that are found in the structural components of viruses. This in turn induces a release of proinflammatory cytokines, which activate transcription factors and JAK-STAT pathways, further releasing a number of proinflammatory cytokines, such as IL-1β, IL-6, interferon (IFN)-γ, IFN-α, TNFα, other cytokines and chemokines. This hyperinflammation can lead to cytokine storm (15). The virus also activates the adaptive immune response, where activated Th1 cells can stimulate cytotoxic CD8+ T cells to destroy virally infected cells. Meanwhile, Th1 cells activate and stimulate B cells to produce antigen-specific antibodies (16, 17). Despite this defense mechanism, like the 2002 SARS-CoV, these viruses have the ability to evade the immune system (18, 19), thus making the development of effective drugs more challenging.

It is reported that a subgroup of COVID-19 patients(15%) developed severe infection and life-threatening complications, in which hyperinflammatory responses or cytokine storm are involved (20). Cytokine storm is defined as a syndrome of excessive immune activation and proliferation of T lymphocytes and macrophages with hypersecretion of proinflammatory cytokines. These mediators include interleukin IL-1β, IL-6, IFN-γ, and TNFα (21–23). Huang et al. described a similar cytokine profile in their patients with COVID-19 and cytokine storm (24). Th17 cells and IL-17 are also involved in the cytokine storm response (25). With what has been learned on the role of cytokine storm, it will be important to use that information to guide and formulate a therapeutic strategy for severe COVID-19 patients. Henderson et. al previously suggested to monitor COVID-19 patients as early as possible with such biometrics as cytopenia, fibrinogen, lactate dehydrogenase, hepatic transaminases, elevated ferritin, CD25, and IL-6 for cytokine storm. They also summarized treatment regimens for cytokine storm in general and their potential utility in severe COVID-19 (26). Among them are IL-6 and IL-1β inhibitors which have been successfully used in alleviating cytokine storm secondary to certain systemic inflammatory RDs (27–30). Tocilizumab, an IL-6 receptor antagonist, has been studied in COVID-19 patients with some success. A study of severe to critical COVID-19 patients in China has shown improved outcome in 15 out of 20 patients (31). Preliminary data from a French study also has provided promising results (32). An Italian prospective open, single-arm, multicenter study of 63 hospitalized adult patients with severe COVID-19 has demonstrated improvement in respiratory and laboratory parameters (33). According to the literature data in our study, two RD patients on tocilizumab developed mild COVID-19 infection, supporting the positive role of IL-6 antagonist. There are still several ongoing clinical trials to investigate the potential role of interleukin antagonists, particularly IL-6 and IL-1β, in the treatment of severe COVID-19 (34–40). JAK inhibitors which indirectly block IL-6 are also being studied in treating this infection (41–44). For a full consideration of using anti-cytokine storm to treat this viral disease, other agents to inhibit the inflammatory mediators may need to be explored. Therefore, it is worthwhile to investigate whether other biologics may have influences in the clinical course of the COVID-19 related respiratory and other complications.

In the present study, our RA patient on etanercept developed mild COVID-19 without complications. Similarly, in the published studies 7 cases were on etanercept and developed mild symptoms, although some patients were hospitalized. Etanercept is a TNFα receptor II antagonist which is known to be associated with a high rate of infections. Unexpectedly, it did not lead to severe COVID-19 in our patient and literature cases, perhaps due to its inhibition of TNFα, a cytokine involved in the viral disease cytokine storm. According to the literature data in our study, TNFα inhibitors including etanercept, adalimumab and infliximab were more frequently used in RD patients, and they seemed to have less severity of the viral illness. TNFα has been reported to be present in the blood and disease tissues of patients with COVID-19 (45). Additionally, it is possible that pretreatment with etanercept could have resulted in a blunted IL-6 response indirectly. In an in vitro study, IL-6 and TNFα were up-regulated by the recombinant S protein of the 2002 SARS-CoV suggesting that TNFα or IL-6 antagonists may potentially reduce the cytokine storm in COVID-19 and its related lung damage (46). These data together suggest that TNFα antagonist may be considered as a treatment strategy for severe COVID-19 in the future.

In case 2, the AS patient developed severe virus-related complications. It is unclear whether secukinumab, a monoclonal antibody to IL-17A, could play a negative role in the case. This is contrasting to an autopsy study of COVID-19 infected cases, which suggested a pathogenic role of Th17 and potential benefit of blocking Th17 (25). In addition, 5 out of the 6 RD patients on secukinumab from the literature data in the current study developed mild COVID-19, and 1 was hospitalized. These data indicate that IL-17A inhibitors influence the viral disease course.

Our patient with SLE had minimal viral symptoms without worsening of his underlying ILD. In an in vitro study, HCQ has been shown to inhibit endosome-lysosome system acidification and to suppress proinflammatory cytokines (47). HCQ is currently being studied in multiple clinical trials (48–60). However, the therapeutic efficacy of HCQ in COVID-19 remains controversial. While some studies showed benefit (47), other studies produced mixed results. Chowdhury et al. surveyed recent literature on clinical trials involving HCQ and Chloroquine. They found 5/7 completed clinical trials showed favorable outcomes, whereas 2/7 trials showed no change compared to control (61). In a French case series of lupus, which was included in our study, HCQ was found to have variable outcomes in the treatment of COVID-19 and its complications (7). Another observational study at the Veterans Affairs hospital showed no benefit of HCQ in severe...
COVID-19 (62). Although HCQ has been used to treat COVID-19, its efficacy will need to be confirmed by the results of the ongoing clinical trials.

Our GPA patient was treated with Rituximab, a monoclonal antibody to CD20, prior to being infected. This drug may have reduced her humoral immune response leading to a more severe disease course. In a prospective study of 200 subjects infected with human coronaviruses, neutralizing antibody has been shown to play a protective role by limiting the infection at a later phase and to prevent re-infection in the future (63). SARS-CoV infection induces IgG production against N protein, which can be detected in serum as early as day 4 after the onset of disease and with most patients being seroconverted by day 14 (64, 65). Hence, B-cell depletion with Rituximab may have altered the antibody response making the patient more vulnerable to the infection. Additionally, SARS-CoV has also been shown to decrease T lymphocytes in 65 patients. Glucocorticoid administration contributed to further decrease in lymphocyte counts (66). As a result, these together hinder the host’s ability to adequately respond to the infection. Similarly, the published case of GPA on Rituximab in the current study also developed severe COVID-19 requiring mechanical ventilation (2). Taken together, these findings suggest that pretreatment with Rituximab, particularly with glucocorticoids, could contribute to a more severe COVID-19 infection and poor outcome.

In summary, RD patients are susceptible to COVID-19. Various DMARDs may affect the viral process differently. Patients on etanercept, HCQ, or tocilizumab may run a mild course of the viral illness. DMARDs may affect the viral process differently. Patients on etanercept. That pretreatment with Rituximab, particularly with glucocorticoids, may have altered the antibody response making the patient more vulnerable to the infection. Additionally, SARS-CoV-2 and other human coronaviruses. Trends Immunol 2020 Apr 2 pii: S1471-4906(20)30057-0 [Epub ahead of print]. doi: 10.1016/j.tit.2020.03.007.

Hoffmann M, Klein-Waéber H, Schroeder S, Kruger N, Herrell T, Ercischen S, et al. SARS-CoV-2 cell entry depends on ACE2 and TMPRSS2 and is blocked by a clinically proven protease inhibitor. Cell 2020;181(2):271–80.e8.

Walls AC, Park YJ, Tortorici MA, Wall A, McGuire AT, Veesler D, Structure, function, and antigenicity of the SARS-CoV-2 Spike glycoprotein. Cell 2020;181(1):92–108.

Tay MZ, Poh CM, Renia L, MacAry PA, Ng LFP. The trinity of COVID-19: immunity, inflammation and intervention. Nat Rev Immunol 2020 Apr 28 [Epub ahead of print]. doi: 10.1038/s41577-020-0341-6.

Li G, Fan Y, Lai Y, Han T, Li Z, Zhou P, et al. Coronavirus infections and immune responses. J Med Virol 2020;92(4):424–32.

Rabi FA, Al Zoubi MS, Kasasbeh GA, Salameh DM, Al-Nasser SD. SARS-CoV-2 and coronavirus disease 2019: what we know so far. Pathogens 2020;9(3): pii: E231. doi: 10.3390/pathogens9030223.

Li X, Geng M, Peng Y, Meng L, Lu S. Molecular immune pathogenesis and diagnosis of COVID-19. J Pharm Anal 2020. Mar 5 [Epub ahead of print]. doi: 10.1016/j.jpha.2020.03.001.

Tortosa AL, Bark RS. SARS coronavirus pathogenesis: host innate immune responses and viral antagonism of interferon. Curr Opin Virol 2012;2(3):264–75.

Astuti I, Yrasafi. Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2): an overview of viral structure and host response. Diabetes Metab Syndr 2020;14(4):407–12.

Mehra P, McAuley DF, Brown M, Sanchez E, Tattersall RS, Manson J, et al. COVID-19: consider cytokine storm syndromes and immunosuppression. Lancet 2020;395(10229):1033–4.

McGonagle D, Sharif K, O’Regan A, Bridgewood C. The role of cytokines in interleukin-6 in COVID-19 induced pneumonia and macrophage activation syndrome-like disease. Autoimmun Rev 2020;20(5):513–9.

Behrens EM, Review Koretzky GA. Cytokine storm syndrome: looking toward the precision medicine era. Arthritis Rheumatol 2017;69(6):1135–43.

Kostik MM, Dubilo MF, Masalova VV, Sniegrewa LS, Kornishina TL, Chikova IA, et al. Identification of the best cut-off points and clinical signs specific for early recognition of macrophage activation syndrome in active systemic juvenile idiopathic arthritis. Semin Arthritis Rheum 2015;44(4):417–22.

Huang C, Wang Y, Li X, Ren L, Zhao J, Hu Y, et al. Clinical features of patients infected with 2019 novel coronavirus in Wuhan, China. Lancet 2020;395(10223):497–506.

Wu D, Yang XO. TH17 responses in cytokine storm of COVID-19: an emerging target of JAK2 inhibitor fedratinib. J Microbiol Infect Dis 2020. Mar 11 pii: S1684-1120(20)30065-7 [Epub ahead of print]. doi: 10.1016/j.jmid.2020.03.005.

Henderson LA, Canna SW, Schultz GS, Volpi S, Lee PY, Kernan KF, et al. On the alert for cytokine storm: immunopathology in COVID-19. Arthritis Rheumatol 2020 Apr 15 [Epub ahead of print]. doi:10.1002/art.41285.

Cromm AA, Honie A, De Benedetti F. Macrophage activation syndrome in the era of biologic therapy. Nat Rev Rheumatol 2016;12(5):259–68.

Ruperto N, Brunner HI, Quartier P, Constantin T, Wulfraat N, Horrell G, et al. Two randomized trials of canakinumab in systemic juvenile idiopathic arthritis. N Engl J Med 2012;367(25):2396–406.

De Benedetti F, Brunner HI, Ruperto N, Kenwright A, Wright S, Calvo I, et al. Randomized trial of tocilizumab in systemic juvenile idiopathic arthritis. N Engl J Med 2012;367(25):2385–95.

Monteagudo LA, Boothe J, Agertn E. Continuous IntraVenous aminolakin infusion to calm the cytokine storm in macrophage activation syndrome. ACR Open Rheumatol 2020 Apr 8 [Epub ahead of print]. doi:10.1002/acr2.11135.

Ma X, Han M, Li T, Lu S, Wu M, Du B, et al. Effective treatment of severe COVID-19 patients with tocilizumab. Proc Natl Acad Sci U S A 2020 Apr 29 pii: 202005615 [Epub ahead of print]. doi: 10.1073/pnas.2005615117.

Genentech’s arthritis drug tocilizumab shows promise in Covid-19 trial [Available from: https://www.clinicaltrialsgreece.com/news/early-trial-toxicity-infection-covid-19/.

Sciascia S, Apra F, Raffa A, Baldovino S, Boaro D, Boero R, et al. Pilot prospective open, single-arm multicentre study on off-label use of tocilizumab in severe patients with COVID-19. Clin Exp Rheumatol 2020 May 1 [Epub ahead of print].
[34] Study to evaluate the efficacy and safety of tocilizumab versus corticosteroids in hospitalized COVID-19 patients with high risk of progression [Available from: https://ClinicalTrials.gov/show/NCT04345445.]

[35] Study of efficacy and safety of canakinumab treatment for CRS in participants with COVID-19-induced Pneumonia [Available from: https://ClinicalTrials.gov/show/NCT04362813.]

[36] Treatment of COVID-19 patients with anti-interleukin drugs [Available from: https://ClinicalTrials.gov/show/NCT04336336.]

[37] Tocilizumab to prevent clinical decompensation in hospitalized, non-critically ill patients with COVID-19 pneumonia [Available from: https://ClinicalTrials.gov/show/NCT04331795.]

[38] Efficacy of early administration of Tocilizumab in COVID-19 patients [Available from: https://ClinicalTrials.gov/show/NCT04346355.]

[39] A study to evaluate the efficacy and safety of Tocilizumab in hospitalized participants with COVID-19 pneumonia [Available from: https://ClinicalTrials.gov/show/NCT04372180.]

[40] A study to investigate intravenous Tocilizumab in participants with moderate to severe COVID-19 pneumonia [Available from: https://ClinicalTrials.gov/show/NCT04363736.]

[41] Stebbing J, Phelan A, Griffin I, Tucker C, Dechle O, Smith D, et al. COVID-19: combining antiviral and anti-inflammatory treatments. Lancet Infect Dis 2020;20(4):400–2.

[42] Safety and efficacy of Ruxolitinib for COVID-19 [Available from: https://ClinicalTrials.gov/show/NCT04340232.]

[43] Safety and efficacy of Baricitinib for COVID-19 [Available from: https://ClinicalTrials.gov/show/NCT04348071.]

[44] Ruxolitinib to combat COVID-19 [Available from: https://ClinicalTrials.gov/show/NCT04354714.]

[45] Wang L, He W, Yu X, Hu D, Bao M, Liu H, et al. Coronavirus disease 2019 in elderly patients: characteristics and prognostic factors based on 4-week follow-up. J Infect 2020; Mar 30 pii: S0163-4453(20)30146-8 [Epub ahead of print]. doi: 10.1016/j.jinf.2020.03.019.

[46] Wang W, Ye L, Ye L, Li B, Gao B, Zeng Y, et al. Up-regulation of IL-6 and TNF-alpha induced by SARS-coronavirus spike protein in murine macrophages via NF-kappaB pathway. Virus Res 2007;128(1-2):1–8.

[47] Zhang W, Zhao Y, Zhang F, Wang Q, Li T, Liu Z, et al. The use of anti-inflammatory drugs in the treatment of people with severe coronavirus disease 2019 (COVID-19): The Perspectives of clinical immunologists from China. Clin Immunol 2020;214(3):108393 [Epub ahead of print]. doi: 10.1016/j.clim.2020.108393.

[48] Multi-site adaptive trials using hydroxychloroquine for COVID-19 [Available from: https://ClinicalTrials.gov/show/NCT04370262.]

[49] The university of the Philippines hydroxychloroquine PEP against COVID-19 trial [Available from: https://ClinicalTrials.gov/show/NCT04364815.]

[50] Hydroxychloroquine vs. Azithromycin for hospitalized patients with suspected or confirmed COVID-19 [Available from: https://ClinicalTrials.gov/show/NCT04329832.]

[51] Hydroxychloroquine and nizoxaxone combination therapy for COVID-19 [Available from: https://ClinicalTrials.gov/show/NCT04361318.]

[52] Efficacy of hydroxychloroquine, telmisartan and azithromycin on the survival of hospitalized elderly patients with COVID-19 [Available from: https://ClinicalTrials.gov/show/NCT04359593.]

[53] Treating COVID-19 with hydroxychloroquine (TEACH) [Available from: https://ClinicalTrials.gov/show/NCT04369742.]

[54] Hydroxychloroquine for the treatment of mild COVID-19 Disease [Available from: https://ClinicalTrials.gov/show/NCT04340544.]

[55] High-dose Hydroxychloroquine for the treatment of ambulatory patients with mild COVID-19 [Available from: https://ClinicalTrials.gov/show/NCT04351620.]

[56] Hydroxychloroquine vs. Azithromycin for outpatients in Utah with COVID-19 [Available from: https://ClinicalTrials.gov/show/NCT04333432.]

[57] Hydroxychloroquine in the prevention of COVID-19 infection in healthcare workers [Available from: https://ClinicalTrials.gov/show/NCT04333225.]

[58] Hydroxychloroquine and azithromycin as prophylaxis for healthcare workers dealing with COVID19 patients [Available from: https://ClinicalTrials.gov/show/NCT04354597.]

[59] Chloroquine, hydroxychloroquine or only supportive care in patients admitted with moderate to severe COVID-19 [Available from: https://ClinicalTrials.gov/show/NCT04362332.]

[60] Hydroxychloroquine for the treatment of patients with mild to moderate COVID-19 to prevent progression to severe infection or death [Available from: https://ClinicalTrials.gov/show/NCT04323631.]

[61] Chowdhury MS, Rathod J, Gernsheimer J. A rapid systematic review of clinical trials utilizing chloroquine and hydroxychloroquine as a treatment for COVID-19. Acad Emerg Med 2020. May 2 [Epub ahead of print]. doi: 10.1111/acem.14005.

[62] Magagnoli J, Narendran S, Pereira F, Cummings T, Hardin JW, Sutton SS, et al. Outcomes of hydroxychloroquine usage in United States veterans hospitalized with Covid-19. medRxiv, 2020 https://doi.org/10.1101/2020.04.16.20065963.

[63] Gorse GJ, Donovan MM, Patel GB. Antibodies to coronaviruses are higher in older compared with younger adults and binding antibodies are more sensitive than neutralizing antibodies in identifying coronavirus-associated illnesses. J Med Virol 2020;92(5):512–7.

[64] Liu W, Fontanet A, Zhang PH, Zhan L, Xin ZT, Baril L, et al. Two-year prospective study of the humoral immune response of patients with severe acute respiratory syndrome. J Infect Dis 2006;193(6):792–5.

[65] Hsieh PE, Huang LM, Chen PJ, Rao CL, Yang PC. Chronological evolution of IgM, IgA, IgG and neutralisation antibodies after infection with SARS-associated coronavirus. Clin Microbiol Infect. 2004;10(12):1062–6.

[66] Gu J, Gong E, Zhang B, Zheng J, Gao Z, Zhong Y, et al. Multiple organ infection and the pathogenesis of SARS. J Exp Med 2005;202(3):415–24.