REVIEW ARTICLE

COVID-19, chronic inflammatory rheumatic disease and anti-rheumatic treatments

Dieu-Donné Ouédraogo[1] ⬤ · Wendlassida Joelle Stéphanie Tiendrébéogo[1] · Fulgence Kaboré[1] · Honoré Ntsiba[2]

Abstract

Since December 2019, the pandemic caused by coronavirus disease 2019 (COVID-19) raises a real public health problem. COVID-19 appeared in Wuhan (Hubei province) in China. Drugs that have been used in rheumatology for decades seem to be effective in this infection and are for the most part being studied. The rational use of these anti-rheumatic drugs is based on the cytokinic storm (hyperproduction of IL1, IL6, TNF α) in the body by COVID-19 in its severe form. In this review, the authors make the difference between the infectious and auto-inflammatory part of COVID-19; the disease does not seem to be a risk factor for admission to the intensive care unit for patients suffering from inflammatory rheumatism; however, the poverty of studies on this subject should be noted. The authors also review anti-rheumatic drugs while studying COVID-19 treatment.

Keywords Coronavirus · COVID-19 · Rheumatoid arthritis · Treatment

Introduction

Since December 2019, the pandemic caused by coronavirus disease 2019 (COVID-19) raises a real public health problem [1]. COVID-19 appeared in Wuhan (Hubei province) in China. COVID-19 (SARS-CoV 2) is a coronavirus with nearly 80% common nucleotide with SARS-CoV 1 [2]. It is manifested by fever, dry cough, rhinitis, asthenia, headache, and dyspnea but often by acute respiratory distress syndrome that can lead to death [3–5]. The mortality risk factors appear to be mainly diabetes, high blood pressure, coronary heart disease, chronic obstructive lung disease, and chronic kidney disease [6].

Although hypotheses are made, the pathogenesis of COVID-19 is not clearly elucidated. Choices of treatment are therefore empirical based on previous experience with SARS-CoV1 or Milddle East Respiratory Syndrome (MERS-CoV) [7–9]. Antiretrovirals (Lopinavir/Ritonavir, Remdesivir, Ribavirin) have been tried in treating patients [10–13]. In addition, drugs that have been used in rheumatology for decades seem to be effective in this infection and are for the most part being studied [8, 14–16]. The rational of use of these anti-rheumatic drugs is based on the cytokinic storm (hyperproduction of IL1, IL6, TNF α) in the body by COVID-19 in its severe form [7, 14, 17, 18]. Rheumatologists with their experience in administration of these drugs could help improve their use [16].

COVID-19 therefore raises two major concerns for rheumatologists: do chronic inflammatory rheumatic diseases and their immunosuppressive treatment cause a risk of admission to intensive care units or high mortality in infected patient? Which anti-rheumatic drugs can be used to treat COVID-19?

COVID-19

An infectious part

Coronaviruses (CoVs) are viruses of the subfamily of Orthocoronavirinae from the family Coronaviridae. The name coronavirus, from Latin meaning "virus with a crown," is due to the appearance of virions under an electron microscope, with a fringe of large bulbous projections that resemble the solar corona [19].

Coronaviruses have a viral envelope with a positive RNA genome and a kilobase capsid (shell), which is incredibly large for an RNA virus. They are classified as Nidovirals, since all

✉ Dieu-Donné Ouédraogo
   ouedd@yahoo.fr

1   Department of Rheumatology, University Hospital of Bogodogo, BP: 628, Ouagadougou 09, Burkina Faso

2   Department of Rheumatology, University Hospital of Brazzaville, Brazzaville, Congo

viruses of this order produce a nested set of sub-genomic mRNA during infection. Peak, envelope, membrane, and capsid proteins contribute to the overall structure of all coronaviruses. These RNA viruses are single-stranded (single-stranded) and positive (Baltimore Classification Group IV). They can mutate and recombine.

An auto-inflammatory part

Cytokine dysregulation is a particular interest in patients with COVID-19 infection [14, 17, 18, 20]. The host immune response is by one side essential for the resolution of COVID-19 infection, but it can also be crucial for the pathogenesis of major clinical manifestations of the disease. The angiotensin-converting enzyme 2 (ACE2) has been identified as the host cell-surface receptor for SARS-CoV2 envelope spike glycoprotein [21]. ACE2 is a type I membrane protein expressed on cells in the kidney, heart, gastrointestinal tract, blood vessels, and, importantly, lung AT2 alveolar epithelial cells, which are particularly prone to viral infection [22]. SARS-CoV-2 infection leads to the downregulation of ACE2 expression, thus resulting in excessive production of angiotensin II by the related enzyme ACE. It has been suggested that the stimulation of type 1a angiotensin II receptor (AGTR1A) increases pulmonary vascular permeability, thus potentially explaining the increased lung damage when the expression of ACE2 is decreased [23].

Sarzi-Puttini et al. hypothesized that the decrease in INFγ in COVID-19 may suppress Th1 and favor Th2 [7]. Some of the cytokines seem to be up-regulated especially in patients with more severe disease and T cell depletion. Huang et al. found that IL-2, IL-7, IL-10, G-CSF, IP-10, MCP-1, MIP-1A, and TNF-α levels correlated with disease severity [24]. Diao et al. found that disease severity correlated with TNF-α, IL-6, and IL-10 levels [25], thus documenting TNF-α hyperproduction in the serum of COVID-19 patients.

The regulation of this cytokine storm remains the challenge in the treatment of COVI-19 infection and explains the use of chloroquine and its derivatives, anti-cytokines (anti-IL1, anti-IL6, anti-TNF), and anti-Jak.

Is there an increased risk of COVID-19 infection in patients with chronic inflammatory rheumatic disease?

The corona virus disease 2019 or COVID-19 pandemic is responsible for high mortality in patients with risk factors such as age over 70 years, diabetes, cardiovascular history, chronic respiratory disease, chronic renal failure on dialysis, cancers during treatment, immune deficiency, cirrhosis, obesity, and pregnant women [6]. Inflammatory rheumatism does not appear to be associated with admission to intensive care. Is a

patient with chronic inflammatory rheumatism receiving immunosuppressive treatments not at risk for a severe form of VIDOC-19 infection? To date, little data are available on chronic inflammatory rheumatic diseases and COVID-19 [26].

Rheumatoid arthritis (RA) is associated with an increased risk of infection compared to a general population without RA [27]. This increased risk of infection is correlated with the presence of risk factors that are identical to those reported in COVID-19 [27, 28]. On the other hand, corticosteroids and non-steroidal anti-inflammatory drugs, by inhibiting the inflammatory response, increase the risk of infections, especially bacterial and mycotic infections [28, 29]. Methotrexate treatment does not appear to be associated with an increased risk of infection other than a combination with corticosteroids [30]. In contrast to methotrexate, the biological disease-modifying anti-rheumatic drugs are responsible for an increased risk of infection correlated with advanced age, female sex, treatment with Prednisone at a dose over 7.5 mg/day, and a high number of hospital stays [28].

The particularity of the pandemic of COVID-19 requires specific data for this infection. Monti S et al. studied the clinical course of COVID-19 in a series of patients with chronic arthritis treated with immunosuppressive targeted therapies [31]. The authors have collected information on 320 patients (female 68%, mean age 55 ± 14 years) treated with bDMARDs or tsDMARDs (57% with rheumatoid arthritis, 43% with spondyloarthritis, 52% treated with tumor necrosis factor inhibitors, 40% with other bDMARDs and 8% with tsDMARDs). Thirteen confirmed and/or suspected COVID-19 patients were diagnosed. Only one patient required hospitalization and was 65 years of age. No deaths were observed [31]. Despite the small sample size in this study and the limited data on COVID-19 and inflammatory rheumatism, it seems to be a lower risk of severity and death in this group of patients apart from the usual risk factors (diabetes mellitus, hypertension, obesity…). In this study, it is also reported that in a reference center for the management of patients with COVID-19, out of 700 patients, no severe patient was under biological disease-modifying anti-rheumatic drugs [31]. Until further studies clarify the absence of higher risk in patients with chronic inflammatory rheumatism, increased monitoring of these patients is necessary and application of barrier gestures is useful for all.

Anti-rheumatic treatments as a potential treatment for COVID-19

Chloroquine

Chloroquine (or chloroquinine) is an antimalarial drug of the 4-aminoquinoline family that has been widely marketed in the

form of salts (sulphate or phosphate). It is a medicine used for so long in preventive and curative treatment of malaria. For several decades, chloroquine has been used in rheumatology for its immunomodulating effect, particularly on systemic lupus erythematosus and rheumatoid arthritis. Studies have also shown the antiviral activity of chloroquine in vitro on H5N1 avian influenza [32], Chikungunya [33], Zika [34], Ebola [35], and SARS-Coronavirus 1 [36]. Chloroquine acts by increasing the endosomal pH required for viral/host cell fusion and, as demonstrated in studies on SARS-Cov, it may also interfere with the glycosylation of ACE2 receptors, which may inhibit viral entry into the target cell [36]. A systematic review of the efficacy and safety of chloroquine in the treatment of COVID-19 involving six articles and 23 ongoing clinical trials in China concluded that chloroquine is effective in limiting the replication of SARS-CoV-2 in vitro [37].

Basing on the action of chloroquine on COVID-19 through its in vitro efficacy and on the first results of open studies carried out in Beijing hospitals in Hunan province in central and southern China, in Guangdong province, Prof. Raoult's team proposes that it be used in the treatment of COVID-19 [15]. However, the therapeutic efficacy and safety of chloroquine are still being discussed [38, 39]. For Franck Touret and Xavier de Lamballerie of Inserm 1207 in Marseille, caution must be exercised in view of the previous antiviral failures of chloroquine in vivo and its deleterious effect during acute viral infections [38]. However, chloroquine appears to be effective in COVID-related acute respiratory distress syndrome, improves pulmonary radiological lesions, accelerates the seronegativity of the virus, and shortens the duration of the disease [39]. Chinese experts recommend that patients diagnosed as mild, moderate, and severe cases of COVID-19 pneumonia and without contraindications to chloroquine be treated with 500 mg chloroquine twice a day for 10 days [40].

Since then, chloroquine has been incorporated into treatment protocols for COVID-19 infection in Asia [40] and many other countries.

Hydroxychloroquine

Hydroxychloroquine is a derivative of chloroquine; it differs from chloroquine by having a hydroxyl (OH) group at the end of each chain. It has replaced chloroquine for many years in the treatment of systemic lupus erythematosus and rheumatoid arthritis.

The pharmacological activity of chloroquine and hydroxychloroquine was tested using SARS-CoV-2-infected Vero cells. Physiologically based pharmacokinetic models (PBPK) were implemented for both drugs separately by integrating their in vitro data. Using the PBPK models, hydroxychloroquine concentrations in lung fluid were simulated under 5 different dosing regimens to explore the most effective regimen while considering the drug's safety profile.

Hydroxychloroquine (EC50 = 0.72 μM) was found to be more potent than chloroquine (EC50 = 5.47 μM) in vitro. Based on PBPK models results, a loading dose of 400 mg twice daily of hydroxychloroquine sulfate given orally, followed by a maintenance dose of 200 mg given twice daily for 4 days, is recommended for SARS-CoV-2 infection, as it reached three times the potency of chloroquine phosphate when given 500 mg twice daily 5 days in advance. Hydroxychloroquine was found to be more potent than chloroquine to inhibit SARS-CoV-2 in vitro [41].

This study is confirmed by other authors who suggest that in addition to its anti-viral and immunomodulatory effect, hydroxychloroquine had an anti-inflammatory effect that may mitigate the cytokine storm observed during COVID-19 infection [42].

Zhou et al. propose that hydroxychloroquine (HCQ), which exhibits an antiviral effect highly similar to that of CQ, could serve as a better therapeutic approach. HCQ is likely to attenuate the severe progression of COVID-19, inhibiting the cytokine storm by suppressing T cell activation. They herein strongly urge that clinical trials are performed to assess the preventive effects of HCQ in both disease infection and progression [43]. In the same vein, Gautret P et al. of Professor Raoult's team in an open label non-randomized study of 36 patients infected with COVID-19 showed a significant reduction in viral load at Day 6 of inclusion compared to controls and a lower mean duration of viral carriage than in untreated patients in the literature. Azithromycin added to hydroxychloroquine was significantly more efficient for virus elimination; all patients in Gautret el al study were proposed oral hydroxychloroquine sulfate 200 mg, three times per days during 10 days [44]. Among hydroxychloroquine-treated patients six received azithromycin (500 mg day 1 followed by 250 mg per day, the next 4 days).

In our experience of hydroxychloroquine use in treating systemic lupus erythematosus and some forms of rheumatoid arthritis, 93 patients were included. The average cumulative dose of hydroxychloroquine was 376 g + 405.48 with extremes of 7 g and 2336 g. The average duration of treatment with hydroxychloroquine was 2.83 years + 2.89 years with extremes of 0.08 years and 15 years. Maculopathy was extremely rare (2.1%) [45].

Corticosteroid

Using corticosteroids during COVID-19 infection is highly controversial. Chen et al. reported 19 (19%) patients treated with corticosteroids for 3–15 days and methylprednisolone (1–2 mg/kg per day) and recommend for patients with acute respiratory distress syndrome that this treatment be of the shortest possible duration [3]. For Zhang et al., adverse effects largely dominate the benefit of corticosteroids [14]. Wang et al. reported 62 (44.9%) patients who received corticosteroid

therapy without improvement [46]. Russel et al. reported clinical evidence did not support corticosteroid treatment for COVID-19 lung injury [47]. These studies are supported by others that report no benefit from corticosteroid therapy during COVD-19 infection [48, 49]. For Ling et al. the duration of viral RNA detection from oropharyngeal swabs and fecal samples in the glucocorticoid treatment group was longer than that in the non-glucocorticoid treatment group (15 days vs. 8.0 days, respectively; $t = 2.550$, $P = 0.013$) and the duration of viral RNA detection in fecal samples in the glucocorticoid treatment group was longer than that in the non-glucocorticoid treatment group (20 days vs. 11 days, respectively; $t = 4.631$, $P < 0.001$). So these authors did not recommended glucocorticoids for treating COVID-19, especially for mild disease [36]. For Zheng et al. in severe COVID-19 patients, early and short-term use of low dose of methylprednisolone was beneficial and did not delay SARS-CoV-2 RNA clearance and influence IgG antibody production [50].

Due to the lack of evidences, the interium guideline of WHO does not support routinely give systemic corticosteroids for treatment of viral pneumonia outside of clinical trials [41]. A new randomized controlled trial (RCT) recently registered by Zhou et al. that will compare methylprednisolone via intravenous injection at a dose of 1–2 mg/kg/day for 3 days versus a control group not using glucocorticoid (ClinicalTrials.gov, ChiCTR2000029386) will help to answer some of our questions in the near future.

Tocilizumab

Tocilizumab (TCZ) is a recombinant human IL-6 monoclonal antibody, which specifically binds to soluble and membrane-bound IL-6 receptors (IL-6R), thus blocking IL-6 signaling and its mediated inflammatory response.

Totally, 15 patients with COVID-19 were included in Luo et al. study [51]. Two of them were moderately ill, 6 were seriously ill, and 7 were critically ill. The TCZ was used in combination with methylprednisolone (MP) in 8 patients. Five patients received the TCZ administration twice or more. Although TCZ treatment ameliorated the increased CRP in all patients rapidly, for the 4 critically ill patients who received only single dose of TCZ, 3 of them still dead and the CRP level in the rest 1 patient failed to return to normal range with a clinical outcome of disease aggravation. Serum IL-6 level tended to further spiked firstly and then decreased after TCZ therapy in 10 patients. A persistent and dramatic increase of IL-6 was observed in these 4 patients who failed treatment.

Till now, several clinical trials have been registered on safety and efficacy of tocilizumab in the treatment of severe COVID-19 pneumonia in adult inpatients, including a multicenter, randomized controlled trial for the efficacy and safety of tocilizumab in the treatment of novel coronary pneumonia (NCP) (ChiCTR2000029765), a single arm open multicenter study on tocilizumab (ChiCTR2000030796), and combination of tocilizumab and other drugs (ChiCTR2000030442 and ChiCTR2000030894).

Anti-Jak

One of the known regulators of endocytosis is the AP2-associated protein kinase 1 (AAK1). AAK1 inhibitors can interrupt the passage of the virus into cells and can be helpful in preventing virus infections. JAK inhibitor as well as an AAK1 inhibitor, was suggested a possible candidate for treatment of COVID-19, considering its relative safety and high affinity. Recently Wu et al. reviewed TH17 responses in patients with SARS-CoV-2 and proposed an FDA approved JAK2 inhibitor Fedratinib for reducing mortality of patients with TH17 type immune profiles [20]. Another author proposed Baricitinib as candidat to treat COVID-19 [14].

To date, there are some registered clinical trials of JAK inhibitor: "Study for safety and efficacy of Jakotinib hydrochloride tablets in the treatment of severe and acute exacerbation patients of novel coronavirus pneumonia (COVID-19)" (ChiCTR2000030170); "Severe novel coronavirus pneumonia (COVID-19) patients treated with ruxolitinib in combination with mesenchymal stem cells: a prospective, single blind, randomized controlled clinical trial" (ChiCTR2000029580).

Colchicine

Colchicine has been used safely in a variety of cardiovascular clinical conditions. Among its potential mechanisms of action is the non-selective inhibition of NLRP3 inflammasome, which is thought to be a major pathophysiologic component in the clinical course of patients with COVID-19. GRECCO-19 trial aims to identify whether colchicine may positively intervene in the clinical course of COVID-19 [52]. It will be prospective, cluster randomized, open-labeled, controlled study. Patients with laboratory confirmed SARS-CoV-2 infection (under RT PCR) and clinical picture that involves temperature > 37.5 °C and at least two out of the (i) sustained coughing, (ii) sustained throat pain, (iii) Anosmia and/or ageusia, (iv) fatigue/tiredness, (v) PaO2 < 95 mmHg will be included. (The study has been submitted to clinicaltrials.gov on March 26, 2020.)

Anti-TNF

The hypothesis of anti-TNF use during COVID-19 infection is based on the pathophysiology of the disease [53]. Study evaluating adalimumab in COVID-19 infection has recently been registered in the Chinese Clinical Trial Registry (ChiCTR2000030089).

Conclusion

Chronic inflammatory rheumatism does not seem to be a risk factor for the severity of COVID-19 despite the presence of immunosuppressive therapy. However, the studies are few and do not allow definitive conclusions to be drawn on the subject. Hydroxychloroquine and biological disease-modifying anti-rheumatic drugs (anti-IL6, anti-TNF, anti-IL1) are serious candidates for the treatment of COVID-19. If their efficacy were to be confirmed by the ongoing RCT studies, the next challenge for rheumatologists, infectious diseases specialists, and intensive care physicians would be to determine a window of opportunity, considered to be the best intervention in the best timeframe to increase a better progression of the disease.

Compliance with ethical standards

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