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.

Joint Bone Spine 87 (2020) 195–197

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Editorial

Old and new antirheumatic drugs for the treatment of COVID-19

ARTICLE INFO

Keywords:
Covid-19
DMARDs
B-DMARDs
Ts-DMARDs

The coronavirus disease 2019 (COVID-19) is spreading worldwide, with over 350,000 cases. In Italy, 69,176 cases with 6820 deaths were observed at March 24, so the World Health Association recently declared the pandemic feature of the infection [1]. SARS-CoV-2 belongs to the β-Coronaviridiae RNA virus family, which has long been recognized as responsible for infection in pets and respiratory diseases of varying severity in humans (i.e., severe acute respiratory syndrome coronavirus 2, abbreviated as SARS-CoV-2). Hence, the Coronavirus that infects humans can be divided into low and highly pathogenic [2]. SARS-CoV-2 is a new β-Coronavirus, probably a recombinant virus originating from bats. Recombination takes place within the Spike glycoprotein, which recognizes a cell surface receptor, thus allowing transmission between different species [3]. Most viruses enter cells via receptor-mediated endocytosis and in the case of COVID-19 it is assumed that Angiotensin 2 Conversion Receptor (ACE2) could be the receptor used to infect lung cells. ACE2 is highly expressed on pulmonary AT2 alveolar epithelial cells particularly prone to viral infection [4]. In a recent report from China [5], the clinical characteristics of COVID-19 can be reflected in at least three clinical models:

- patients who are asymptomatic;
- patients with mild to moderate disease;
- patients with severe pneumonia who require admission to the intensive care unit (ICU).

The most common symptoms are fever (generally elevated in at least 70% of patients), dry cough, weakness and variable degree of dyspnoea. Dyspnoea develops after a median time of 8 days from the onset of the disease, with a median time of admission to ICU of 5 days from the beginning of dyspnoea. Up to 31% of patients require transfer to an ICU [5–7]. Patients with the worst evolution show a marked increase in plasma cytokines (cytokine storm syndrome), while this report provides no information on acute phase reactants including erythrocyte sedimentation rate (ESR) and C-reactive protein (CRP). However, these reactants have been found at high levels in cytokine storm patients [8].

So far, there is no specific antiviral treatment available for COVID-19 and management is largely supportive. However, in light of the growing understanding of SARS-CoV-2 and COVID-19 biology, several drugs commonly used in rheumatology have been proposed as potential treatments for COVID-19. Chloroquine and Hydroxychloroquine (HCQ) are antimalarial agents with immuno-modulating activities largely used in rheumatology. These agents also exhibit well-known antiviral activity, involving abroad spectrum of viral species [9]. The drugs work by increasing the endosomal pH and inhibiting the Toll-Like Receptor to interfere with viral/cell fusion, as well as interfere with glycosylation of the ACE2, which represents the cellular receptor of the virus [10]. In vitro studies have demonstrated entry and post-entry antiviral activity against SARS-CoV-2 at concentrations obtainable therapeutically for doses used in rheumatology. Furthermore, the immunomodulatory activity of these agents, limiting the systemic immune activation associated with COVID-19, could act in synergy with the antiviral properties [11]. Numerous clinical studies conducted in China on COVID-19 patients have demonstrated the superiority of Chloroquine treatment compared to placebo in inhibiting the exacerbation of pneumonia, improving the imaging data, promoting a negative viral state and reducing the course of the disease in absence of serious adverse reactions [12]. Consequently, several regulatory medical agencies, (Chinese and Italian among them), include Chloroquine and HCQ in the recommendations for treating COVID-19 [13,14]. A recent French study on 36 patients indicated that adding azithromycin to HCQ resulted in further reduction of viral load [15]. Furthermore, the role of HCQ has been emphasized in the treatment of COVID infection during pregnancy [16]. The development of cytokine release syndrome and T cell abnormalities plays a key role in the progression of COVID-19. Under these circumstances, persistent viral stimulation leads to a significant increase in circulating cytokines such as IL-6, IL-10 and TNF-α. The levels of these cytokines are negatively correlated with the absolute lymphocyte count, inducing the exhaustion and apoptosis of T cells which can trigger inflammatory damage to the organs [17].

IL-6 plays a central role in the pathogenesis of SARS-CoV-2-associated cytokine release syndrome and consequently tocilizumab, a humanized monoclonal antibody against the IL-6 receptor, has gained interest as a potential treatment for COVID-19. A retrospective study of 21 patients with severe COVID-19

https://doi.org/10.1016/j.jbspin.2020.03.013

showed that treatment with Tocilizumab 4–8 mg/kg improves oxygen saturation and CT scan abnormalities, lymphocyte count and normalizes CRP levels in most of the patients [18]. The randomized clinical trial (RCT) investigating the safety and efficacy of Tocilizumab in COVID-19 is still ongoing (ChiCTR2000029765). The Chinese recommendations introduced Tocilizumab as an option for patients with extensive and bilateral lung disease or seriously ill patients with elevated IL-6 levels [14]. Based on Chinese data, on March 17, AIFA launched a prospective study on the use of Tocilizumab for COVID-19 disease in a group of patients who show intubated respiratory failure in the first 24 hours, in addition to a study which is collecting data on patients already treated, intubated or not, before the approval of the Registry (TOCIVID). No data are yet available on the introduction of Tocilizumab in COVID-19 patients with earlier stages of respiratory failure, but in the rheumatology literature the major value of early treatment with this drug on the progression of damage due to inflammation has been well documented. Some regional guidelines [13] introduced the dosage of IL-6 with a cut-off greater than 20 pg/mL as a criterion for therapy with Tocilizumab. A study of 188 patients will take place in China from February 10 to May 10. Roche said on Monday March 16 that he had donated 14 million Yuan ($ 2.2 million) to Roactemra in February. Based on these data, a study will start in the United States and France using another anti-IL-6 receptor monoclonal antibody, namely Sarilumab, for COVID-19.

SARS-CoV-2 shares several similarities with SARS-CoV, the coronavirus strain responsible for the 2002 SARS pandemic. Both viruses use Spike (S) proteins to engage their cell receptor, ACE2, for cell invasion [19]. ACE2 expression is upregulated by SARS-CoV-2 infection and stimulation of inflammatory cytokines [20]. In SARS-CoV infection, S proteins can induce shedding of the ectodomain of ACE2, a process closely coupled with the production of TNFα [21]. This loss of ACE2 activity caused by shedding has been associated with lung injury as a consequence of increased activity of the renin-angiotensin system [22]. Although mainly demonstrated for SARS-CoV, the homology between S protein structures suggests that SARSCoV-2 protein S may also exhibit a similar mechanism [23]. Increased TNFα production could consequently facilitate viral infection and cause organ damage. Indeed, anti-TNFα treatment has been suggested as a possible treatment option in COVID-19 [24] and an RCT studying Adalimumab in COVID-19 has recently been registered (ChiCTR2000030089).

Also, IL-1 also plays a pivotal role in cytokine release syndrome, and it may be implicated for interstitial COVID-19 pneumonia. Moreover, data from a phase 3 RCT with Anakinra, an IL-1 inhibitor, in sepsis shows anti-inflammatory benefits in the absence of adverse events [25]. Clathrin-dependent endocytosis is crucial for viral invasion of pneumocytes [26]. This process is promoted by members of the kinase family (NAK), who have been proposed to limit intracellular viral traffic. Tyrosine kinase inhibitors, aimed at members of the NAK family, showed good antiviral activity in vitro [27]. JAK inhibitors, including Baricitinib, Ruxolitinib and Fedratinib, show the ability to inhibit NAK, also limiting systemic inflammatory response and cytokine production through inhibition of the canonical JAK-STAT pathway [28]. Although Baricitinib is the only JAK inhibitor that achieves sufficient plasma concentrations to inhibit NAK members at therapeutic and well-tolerated doses [29], the only drug currently studied in COVID-19 is Ruxolitinib (ChiCTR2000029580). The concerns about these treatments derive from the fact that in the early stages of the innate response to COVID-19, and to viruses in general, the Interferon family plays an important role in the rapid response to the pathogen, and we know the ability of the JAK/STAT system to reduce the response of the IFN system which forms the basis of the higher herpes zoster infection rate observed with these therapies [30]. However, an open-label pilot study (ClinicalTrials.gov: NCT04320277) began on March 24 with the aim of assessing the percentage of patients who need the ICU.

The current state shows that old and new perspectives are opening up for anti-rheumatic drugs in the treatment of this pandemic, and numerous Italian rheumatology groups [31] are struggling to make a contribution in what appears to be a pathology with multidisciplinary aspects. The pathophysiology of some inflammatory rheumatic diseases and the review of drug-related adverse events can help the therapeutic choices during this 21st century pandemic.

Disclosure of interest

The authors declare that they have no competing interest.

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