Editorial

COVID-19: an unexpected indication for anti-rheumatic therapies?

In December 2019, a novel coronavirus, currently defined as Severe Acute Respiratory Syndrome Coronavirus 2 (SARS-CoV-2), was identified as the aetiological agent of a *cluster of pneumonia* in Wuhan, China [1]. Since this outbreak, the novel coronavirus disease (COVID-19) has spread worldwide. By 30 March 2020, COVID-19 had reached pandemic proportions, involving >110 countries and >600 000 cases [2]. Most cases of COVID-19 are self-limiting, but up to 20% of infected patients show a severe or critical disease, including severe pneumonia and multi-organ failure [3]. Systemic immune abnormalities feature in severe COVID-19. Despite peripheral blood showing a reduced lymphocyte number, there is a hyperactivation state of T cells, with an increase of Th17 and a high cytotoxic activity of CD8 [4]. Moreover, patients with severe COVID-19 show increased serum IL-6 levels and reduced number of circulating NK cells. Globally, these clinical and serological abnormalities characterize a cytokine release syndrome (CRS) [5]. During CRS, the systemic activation of immune cells causes the release of a large quantity of cytokines with the aim of limiting viral diffusion and clearing the infection. However, uncontrolled immune system activation can cause terminal organ damage, evolving towards multi-organ failure [6].

So far, there is no available specific antiviral treatment for COVID-19, and management is largely supportive. However, in light of the increasing understanding of SARS-CoV-2 biology and COVID-19 pathophysiology, several drugs commonly used in rheumatology have been proposed as potential COVID-19 treatments (Fig. 1).
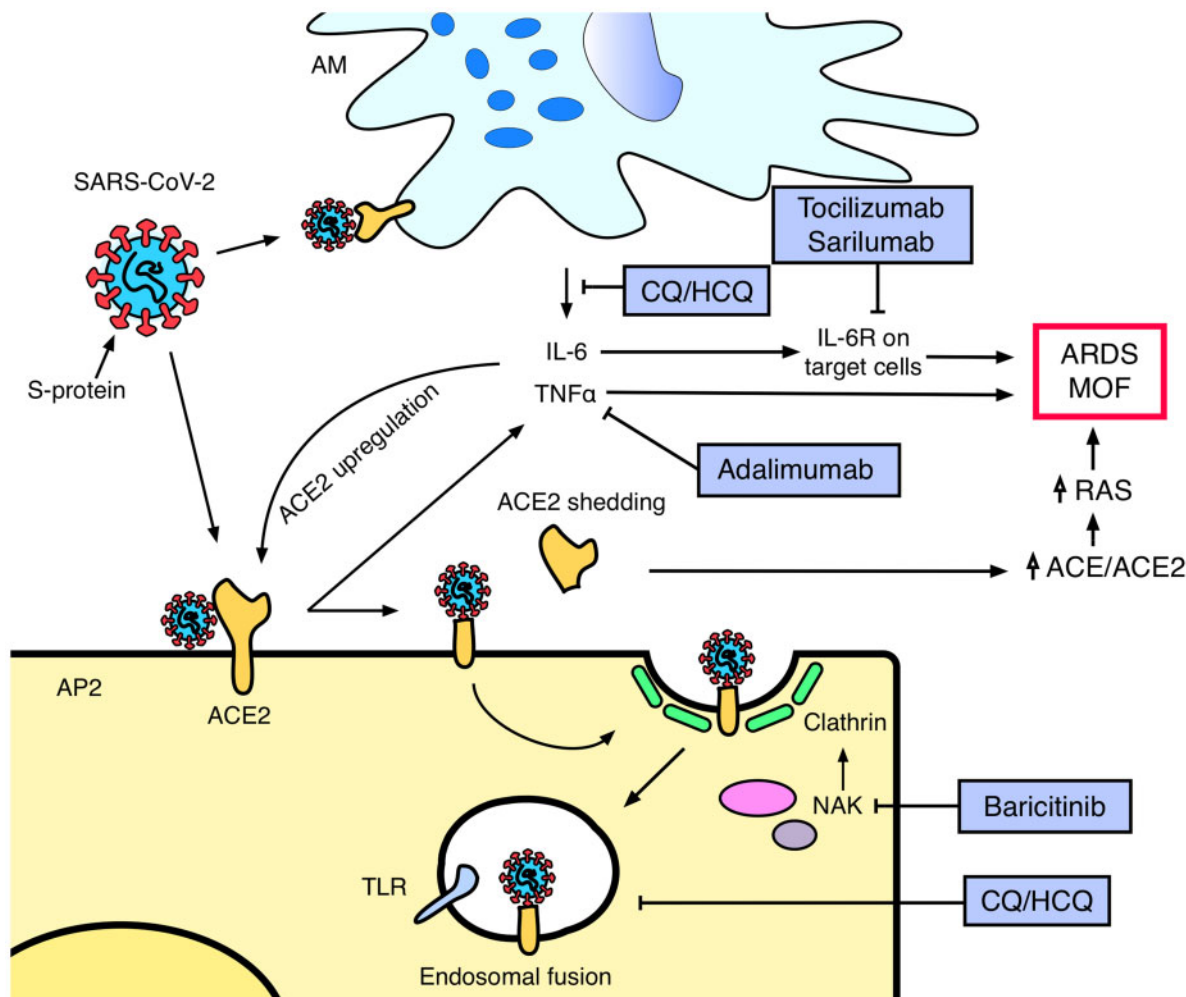
Chloroquine (CQ) and hydroxychloroquine (HCQ) are antimalarial agents with immune-modulatory activities largely used in rheumatology. These agents present also a well-known antiviral activity, involving a broad spectrum of viral species [7]. The drugs act by increasing endosomal pH and inhibiting toll-like receptors, interfering with virus–cell fusion, as well as interfering with the glycosylation of angiotensin-converting enzyme 2 (ACE2), which represents the cellular receptor of the virus [8]. *In vitro* studies demonstrated an antiviral activity against SARS-COV-2 at concentrations achievable at the usual therapeutic doses. Moreover, the immune-modulatory activity of these agents, limiting the systemic immune activation associated to COVID-19, could act synergistically to the antiviral properties [9]. Several clinical trials conducted in China demonstrated superiority of CQ treatment with respect to placebo in improving the evolution of COVID-19 pneumonia and promoting viral clearance [10]. Accordingly, several medical agencies, including Chinese and Italian ones, included CQ and HCQ in the recommendations for treatment of COVID-19 [11, 12]. Recently, a small non-randomized trial evaluating the combination of HCQ and azithromycin in 36 SARS-CoV-2 positive subjects showed a significant efficacy of the combination in clearing the viral nasopharyngeal carriage compared with the control treatment [13]. Azithromycin activates antiviral interferon pathways in bronchial epithelial cells, suggesting an additive effect to its antimalarial action and a potential utility against viral spread [14]. Moreover, HCQ shows a higher antiviral activity compared with CQ on *in vitro* SARS-CoV-2 infected cells [15]. However, the small size and the non-randomized design limit the strength of the studies. Larger randomized clinical trials (RCT) investigating HCQ efficacy, with or without azithromycin, in COVID-19 patients as well as prophylactic treatment in healthcare providers have been announced in several countries, including Australia, Brazil (NCT04321278), Denmark (NCT04322396) and Spain (NCT04304053).

The development of a CRS has a pivotal role in severe COVID-19. The persistent viral stimulation leads to a significant increase of circulating cytokines such as IL-6 and TNFα, which are negatively related to the absolute lymphocyte count and can trigger inflammatory organ damage [16]. IL-6 is central in the pathogenesis of CRS associated to SARS-CoV-2 and consequently tocilizumab, a humanized anti-IL-6 receptor (IL-6R) monoclonal antibody, gained interest as a potential treatment of COVID-19. A retrospective study on 21 patients affected by severe COVID-19 showed that tocilizumab treatment improved the clinical manifestations in most of the patients [17]. Despite the fact that RCTs investigating the safety and the efficacy of tocilizumab in COVID-19 are still ongoing (ChiCTR2000029765; NCT04317092), both Chinese and Italian recommendations led to tocilizumab being introduced as an option for patients with extensive and bilateral lung disease or severely ill patients with elevated IL-6 levels [11, 12]. Similarly, sarilumab, a fully human anti-IL6R antibody, is currently under investigation in severe COVID-19 (NCT04315298).

SARS-CoV-2 shares several similarities with SARS-CoV, the coronavirus strain responsible for the 2002 SARS pandemic. Both viruses use the spike (S)-proteins to engage their cellular receptor, ACE2, for cell invasion [18]. ACE2 expression is upregulated by both SARS-CoV-2 infection and inflammatory cytokine stimulation

Fɪɢ. 1 Antiviral mechanisms of action of anti-rheumatic drugs in COVID-19

ACE: angiotensin-converting enzyme; AM: alveolar macrophage; AP2: alveolar pneumocyte type 2; ARDS: acute respiratory distress syndrome; CQ/HCQ: chloroquine/hydroxychloroquine; IL-6R: interleukin 6 receptor; MOF: multiorgan failure; NAK: numb-associated kinases; RAS: renin–angiotensin system; SARS-CoV-2: Severe Acute Respiratory Syndrome Coronavirus 2; TLR: toll-like receptor.

[19]. In SARS-CoV infection, S-proteins can induce shedding of the ectodomain of ACE2, a process strictly coupled to TNFα production [20]. This loss of ACE2 activity caused by shedding has been associated to lung injury as a consequence of an increased activity of the renin–angiotensin system [21]. Although mainly demonstrated for SARS-CoV, the homology between the structures of S-proteins suggests that also SARS-CoV-2 S-proteins may show a similar mechanism [22]. The increased TNFα production could consequently both facilitate viral infection and cause organ damage. Indeed, anti-TNFα treatment has been suggested as a possible treatment option in COVID-19 [23], and a RCT investigating adalimumab in COVID-19 has recently been registered (ChiCTR2000030089).

Clathrin-dependent endocytosis is crucial for viral invasion of pneumocytes [24]. This process is promoted by members of the numb-associated kinase (NAK) family, which have been proposed as targets to limit intracellular viral traffic. Tyrosine kinase inhibitors, targeting NAK family members, showed good antiviral activity *in vitro* [25]. JAK inhibitors, including baricitinib, ruxolitinib and fedratinib, show the ability to inhibit NAK, limiting also systemic inflammatory response and cytokine production through the inhibition of the canonical JAK–STAT pathway [26]. Among these, baricitinib is the only JAK inhibitor to reach, at therapeutic and well-tolerated doses, plasmatic concentrations sufficient to inhibit NAK members [27]. A RCT investigating baricitinib efficacy in COVID-19 is currently ongoing (NCT04320277).

Severe COVID-19 represents the first example of an infectious disease successfully treatable with immune-modulating therapies. While the ongoing outbreak of COVID-19 requires the urgent development of a vaccine,

this unexpected indication for anti-rheumatic therapies underlines the need to better understand how infectious agents trigger the immune system to produce severe clinical manifestations, especially in the case of pandemics.

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