Letter to the Editor

COVID-19/SARS-CoV-2

It is time to consider an anti-inflammatory therapy based on the pathophysiology of COVID-19 infection during the right time window?

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The main chest computed tomography (CT) imaging features of COVID-19 have been previously described [1–4]. Based on chest CT scans (e.g. the reverse halo sign), linear consolidations, and other signs indicate an organising pneumonia pattern [3]. Pathological characteristics such as pulmonary oedema and hyaline membrane formation are of great importance for timely and appropriate administration of corticosteroids in critically ill COVID-19 patients. Pathological evidence has revealed the pulmonary tissue pathology, where an acute fibrinous (in the initial stage) and organising pneumonia (AFOP) can be described based on the intra-alveolar fibrin deposits in some critically ill COVID patients. This indicates a cortico-sensitive pathology [5]. Autopsy series have further indicated that the predominant histological pattern in severe COVID-19 patients is organising pneumonia (OP), not diffuse alveolar damage (DAD) [6]. Thus, an insight into the empirical corticosteroid therapy of COVID-19 might be reconsidered based on the histological pattern of lung injury and cytokine storm-associated hyperinflammation. Despite multiple targeted therapeutic approaches and/or use of anti-viral agents, no specific effective therapeutic strategy is available for COVID-19. On the other hand, various clinical trials of potential therapies as well as vaccines are ongoing. While the hyperinflammatory phase with cytokine storm is linked to the histological pattern of severe COVID-19 [4], patchy inflammatory cell infiltration has also been demonstrated at the early stage of COVID-19 pathology [7].

COVID-19 therefore shows 2 classic phases of the immune response: a protective immune defence against the virus and inflammation-driven tissue/organ damage. Hence, immune-boosting strategies such as potentiation of serum immunity or pegylated IFN-α and antiviral strategies may be suggested in the early or non-severe stage of COVID-19. On the other hand, immunosuppression/immunomodulatory strategies (e.g. corticosteroids, immunomodulators, inflammatory cytokine antagonists such as tocilizumab [8] or anakinra, decrease of lung inflammatory cell infiltration, etc.) in the inflammation-driven damaging phases can be considered [9]. Therefore, anti-inflammatory approach at the wrong time (in the early phase) may be potentially linked to deleterious effects, or may not even be beneficial for consolidated and irreversible tissue damage.

This indicates that the cytokine storm condition in COVID-19, which is associated with the severe pathology, can be targeted by the anti-inflammatory strategy. Virus-induced immunopathological events have been

shown to be associated with COVID-19 pneumonia, suggesting a timely tailored therapy based on the pathophysiology of COVID-19. Additionally, AFOP pattern reveals an open question regarding the use of corticosteroid therapy.

While there is no doubt that antiviral strategy has a special place in fighting COVID-19, an anti-inflammatory regimen (e.g. corticosteroids, etc.) may be hypothetically considered as a tailored combination therapy in preventing further injury and improving the treatment success rate among COVID-19 patients during this extremely short time window.

Short-term administration of low-dose corticosteroids may show beneficial effects in the treatment of COVID-19 patients, especially severe patients, by considering their wise and timely use as well as gradual tapering [10–15]. Based on the sensitivity of the AFOP pattern to glucocorticoids, however, questions about the uncertain risks, type of pulmonary lesion, and the appropriate timing remain to be answered in terms of COVID-19. Compelling evidence so far suggests the benefit of steroids (methylprednisolone, and dexamethasone in patients with severe COVID-19) [16, 17]. The application of corticosteroids has been suggested in the multinational Surviving Sepsis Guidelines for patients requiring mechanical ventilation [18]. Based on this, the WHO has updated its guidelines to suggest steroid use (e.g. dexamethasone) for severe COVID-19 associated with hypoxemic respiratory failure [19]. Reliable evidence on the beneficial effects of immunomodulating drugs such as anti-tumour necrosis factor (TNF) drugs anti-IL6, and anti-IL-1 are scarce in the clinical setting and require further in-depth investigations in clinical trials.

In the early stages of the COVID-19 pandemic it was reported that azithromycin alone as a macrolide or in combination with hydroxychloroquine may be beneficially effective in the management of COVID-19 patients with a potential safety signal [20, 21], because of its immunomodulatory and postulated antiviral properties [22, 23]. Additionally, the efficacy of azithromycin for improving the phagocytic function of macrophages has been described in chronic obstructive pulmonary disease (COPD) [24].

With immunomodulatory properties, macrolides mitigate anti-inflammatory cytokines and increase the levels of immunoglobulins [25]. Preclinical and clinical findings on macrolides in respiratory infections as well as preliminary evidence from COVID-19 signifies the potential beneficial effects of azithromycin in combating COVID-19 [26–28]. An EC_{50} of 2.12 µM against COVID-19 has been proven for azithromycin in *in vitro* screening [27].

A limited number of clinical studies suggested that administration of hydroxychloroquine may enhance the early clinical recovery of COVID-19 patients. The efficacy of hydroxychloroquine has been demonstrated for 62 moderately ill patients [29]. In contrast, the findings of a RECOVERY trial by Horby *et al*. revealed findings against the beneficial effect of hydroxychloroquine administration on a population of 4674 COVID-19 patients [30].

In a French clinical trial, the high efficacy of the combination of hydroxychloroquine with azithromycin has been reported as 100% among COVID-19 patients virologically cured at day 6, whereas 57.1% of patients benefited from only hydroxychloroquine [31]. In contrast, no beneficial effect or rapid viral clearance of this combination have been found at the same dose scheme for the severe COVID-19 in an uncontrolled observational study [32]. Additionally, no beneficial effects of this combination or hydroxychloroquine alone have been found for either postexposure prophylaxis or COVID-19 under randomised, controlled trials [33–35], while in-hospital mortality was not found to be different among COVID-19 patients receiving hydroxychloroquine, azithromycin, or their combination, as compared to patients receiving no treatments [36]. On the other hand, other investigations indicated the need for caution, especially regarding patients with underlying arrhythmia due to QT prolongation or torsades de pointes (TdP) [21, 37]. In a systematic review, early administration of hydroxychloroquine has been indicated to be effective in the outpatient setting for COVID-19 [38], while no beneficial effect has been revealed for the use of hydroxychloroquine as a readily available drug in patients with mild to moderate COVID-19 [39]. The WHO discontinued the therapeutic arms of the Solidarity trial on 4 July 2020 based on the results because of a lack of beneficial effects, which was in agreement with the findings from the RECOVERY trial of COVID-19 [40].

However, ongoing trials on hydroxychloroquine can answer the controversy because hydroxychloroquine was not linked to a lower death at 28 days among hospitalised patients with COVID-19 when compared to those who received the usual treatment, as reported by the RECOVERY Collaborative Group [41].

Non-steroidal anti-inflammatory drugs (NSAIDs) are capable of disrupting the resolution of the inflammatory process. In this regard, naproxen may be considered for patients suffering from severe COVID-19 in inflammation-driven damaging phases, due to its triple effects including anti-inflammatory, anti-influenza virus [42], and antiplatelet properties. No conclusive evidence so far suggests its risk for severe adverse events (e.g. death) in patients with COVID-19 [43], while a cautionary approach is suggested for patients with non-severe symptoms [44]. Nonetheless, pending further investigation, its benefits and risks will be established in the near future.

Increasing evidence demonstrates the association of COVID-19 with coagulopathy and thrombosis risk, especially in severely ill patients [45–48], where providing the role of D-dimer or scoring systems is of great importance for stratifying patients' risk.

Emerging evidence suggests that statins play a positive role in the improvement of outcomes among COVID-19 patients (e.g. reduction of the risk of mortality and its severity) due to their pleiotropic features (e.g. anti-inflammatory and anti-thrombotic features, etc.). Therefore, de novo use of statins has been suggested for COVID-19 patients without underlying comorbidities [49, 50], but determination of the benefit/risk of statins requires further studies under clinical conditions [51].

Although corticosteroids worsen the glycaemic control in diabetic patients, their use may be considered after balancing glucose levels by using glucose-lowering therapies. The corticosteroid therapy for diabetic patients with COVID-19 requires consideration of the probability of uncontrolled glucose levels. However, management of diabetic patients is challenging for decreasing the risk of complications and death. On the other hand, certain inflammatory markers in COVID-19 patients might be linked to poor glycaemic control; thus, euglycaemia is important in diabetic patients during COVID-19 circumstance [52].

Thrombotic event monitoring for COVID-19 inpatients is of great importance, and patients with bleeding episodes should be managed.

Antithrombotic therapy (antiplatelet or anticoagulant administration) for preventive, prophylaxis, and treatment approaches can also be recommended based on the clinical manifestation and the severity of COVID-19 in patients with signs of coagulopathy. There are rationales behind antiplatelet, corticosteroid, and anti-cytokine treatments to stabilise the endothelium and platelets [53].

COVID-19 disease is a challenging issue for patients suffering from inflammatory autoimmune systemic diseases (ASD), and a study by Ferri et al. indicated a higher occurrence of COVID-19 infection among patients with ASD in Italy, indicating the need to provide preventive/management strategies [54]. Susceptibility of individuals with rheumatic disease to COVID-19 has been reported by an observational study in Hubei province, China [55]. Conversely, another study indicated that autoimmune rheumatic disease was not related to a considerable risk of COVID-19 disease or its severity among adults and paediatrics [56]; such findings indicate the need for clarification of the susceptibility of patients with ASD to COVID-19 and the possible interactions between COVID-19 and ASD. Therefore, the possibility of the risks/benefits of anti-rheumatic therapy needs clarification, but the use of low-dose corticosteroids and bDMARDs has been recommended at various times for COVID-19 patients [57].

Given the lack of specific antivirals for COVID-19, a tailored and accessible anti-inflammatory treatment regimen including azithromycin, prednisolone, naproxen, and statins may be envisaged. This is to target the inflammation-driven damaging phases of COVID-19 pathology through appropriate assessment of the risk/benefit ratio. Furthermore, the use of antivirals with high lung distribution profiles may be an effective strategy to decrease viral loads of SARS-CoV-2 [58].

Lopinavir/ritonavir and remdesivir are among the drugs with poor lung distributions, and thus are considered to be inadequate for the inhibition of SARS-CoV-2 [59, 60].

However, well-designed randomised clinical trials are of great importance to pave the way for assessing the risks/benefits of such drugs. We conclude that in our opinion the use of expensive antiviral drugs, often with unproved efficacy, may deprive a large population of COVID-19 patients in the world (particularly in less developed countries) from appropriate treatment. On the other hand, an anti-inflammatory approach using widely accessible drugs could be effective if applied during the right time window of COVID-19 pathology, and hence we recommend this approach.

Conflict of interest

The authors declare no conflict of interest

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