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.

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Imatinib might constitute a treatment option for lung involvement in COVID-19

Dear Editor,

We have read with interest the comprehensive review regarding interleukin-6 (IL-6) and other pro-inflammatory cytokines in the development of coronavirus disease 2019 (COVID-19) pneumonia [1]. The authors insightfully noted that early initiation of anti-viral therapy to reduce viral load of the severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2) could be helpful in preventing the cytokine storm observed in some of these patients.

In this regard, identifying therapeutic options seems critical to control the outbreak caused by SARS-CoV-2. Antimalarial agents and protease inhibitors have been reported as possible treatments [2,3]. Moreover, inhibition of Janus kinase (JAK) and IL-6 pathways have also been suggested as potential therapies, according to recent data [4,5]. Other possible therapies include the use of corticosteroids, intravenous immunoglobulins or synthetic variants of the interleukin-1 (IL-1) antagonist. However, there is a lack of robust evidence regarding these treatments, which often emanates from *in vitro* experiences, murine models or series with a limited number of patients. Therefore, understanding the COVID-19 pathogenesis seems key to getting a better therapy and improving the survival rates [6].

Imatinib is an oral anticancer agent that inhibits the activity of some tyrosine kinases, most prominently the BCR-ABL1 fusion oncoprotein (whose overactivation can lead to chronic myeloid leukemia, CML), c-kit (involved in gastrointestinal stromal tumors development), platelet-derived growth factor receptor (PDGFR), and the native ABL1 kinase, who has a ubiquitous expression and plays important roles in several biological processes [7,8].

In addition to the well-known antitumor effect, imatinib has also shown *in vitro* anti-viral properties against severe acute respiratory syndrome coronavirus (SARS-CoV) and Middle East respiratory syndrome coronavirus (MERS-CoV), which are phylogenetically related to SARS-CoV-2 [9]. In fact, Coleman et al. [10] showed that imatinib can play an inhibitory role over SARS-CoV and MERS-CoV, especially by blocking the early stages of coronavirus (CoV) infection. Sisk et al. [11] also found that imatinib reduced the titers of infectious bronchitis virus (a viral model for studying the role of tyrosine kinase activity during CoV infection) by interfering with virus–cell fusion. Interestingly, ABL1 inhibitors were also shown to have *in vitro* activity against other RNA viruses including coxsackievirus [12], hepatitis C virus [13], or Ebola virus [14], among others, mainly through blocking viral entry or egress from the host cell.

Moreover, evidence suggests that imatinib might modulate the immune response. In fact, this drug has been reported as arthritis suppressor and inhibitor of IL-6 and other pro-inflammatory cytokines according to murine models [15,16]. In this regard, positive effects have been observed lowering inflammation in patients diagnosed with rheumatoid arthritis [17–19], asthma [20] and other chronic inflammatory disorders such as Crohn's disease [21,22] and refractory eosinophilic granulomatosis with polyangiitis [23]. Likewise, imatinib has been linked to improving pulmonary endothelial barrier dysfunction and edema observed in acute lung injury and sepsis [24,25].

Imatinib might play its potentially beneficial immunomodulatory role in COVID-19 patients by several mechanisms. This drug can reduce the transcription factor NF-κB signaling pathway, as demonstrated by Rizzo et al. [26] both *in vitro* (in lipopolysaccharide (LPS)-stimulated human pulmonary artery endothelial cells) and in murine model of acute lung injury. NF-κB is often targeted by pathogens to maintain their life cycle within the host cell and seems to be activated in patients with CoV infection [27,28]. It has also been suggested that imatinib stimulates prostaglandin E2 (which is related to a prominent protective role in the airways) and attenuates cytokine release by activating its receptor EP4, leading to a less pronounced increase of tumor necrosis factor-α (TNF-α), IL1-β and IL-6 in LPS-stimulated blood of patients treated with this drug compared with the cytokine response to LPS in healthy controls [29]. Similar outcomes regarding imatinib reducing TNF-α and IL-6 production in sepsis-induced adult respiratory distress syndrome murine models have been reported [30,31]. These findings could also contribute to explain the observation of a significant down-regulation of NF-κB, IL-6 and other pro-inflammatory cytokines release in lymphomonocytes from CML imatinib-treated patients [32].

Oral absorption of imatinib can be considered optimal, its mean bioavailability reaches 98% and the terminal elimination half-life has been estimated at approximately 18 h [33]. It can be dissolved in water for patients having difficulty swallowing or for those who need a nasogastric tube. Furthermore, this drug is well tolerated and the risk of severe adverse effects is relatively low, especially in short-term administration [34]. It is also recognized that adverse effects, mostly mild to moderate in intensity, will be easily controlled by dose reduction or discontinuation [35]. Additionally, imatinib seems an admissible treatment from an economic point of view and its availability in hospitals is usually high.

In summary, taking into account the potential role of imatinib as antiviral and immunomodulatory agent in addition to an acceptable safety profile, we believe that this drug should be explored as a treatment option for COVID-19 pneumonia.

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