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Letter to Editors

Immunopharmacological management of COVID-19: Potential therapeutic role of valproic acid

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To the editor:

Severe acute respiratory syndrome-coronavirus-2 (SARS-CoV-2) which leads to COVID-19, was first seen in Wuhan province of China in December 2019 and spread globally in a short time. COVID-19 was announced as a pandemic by WHO on March 11th, 2020 and approximately 4 million people infected with the virus and 275.000 died until May 11th, 2020 [1]. Symptoms of COVID-19 may range from mild such as subfebrile fever to severe symptoms such as respiratory and multiorgan failures [2,3]. Acute respiratory distress syndrome (ARDS) is a critical consequence of infection, leading to the most of the death due to COVID-19. A crucial part of COVID-19 patients with ARDS presents an excess pro-inflammatory cytokine release, which may be related to cytokine storm syndrome in the respiratory system [4]. It has been shown that many patients with COVID-19 had increased serum levels of pro-inflammatory cytokines such as IL-6, IL-1β, IL-2, IL-8, IL-17, granulocyte-colony-stimulating factor (G-CSF), granulocyte-macrophage CSF, and TNF-α [5,15]. However, corticosteroids and other immunosuppressant agents have not been encouraged in COVID-19 because of their given deteriorating effects to already vulnerable respiratory tract [6]. At this point, research into novel treatment approaches that focus on direct antiviral effect and immunomodulatory effects has increased to identify the ideal therapeutics for COVID-19.

We recently read with interest the letter by Gómez-Bernal entitled "Lithium for the 2019 novel coronavirus" [7]. The author postulated that a mood-stabilizing agent, lithium, may be considered in the treatment of COVID-19 as it harbors inhibitor functions on the expression of viral RNA. Another mood stabilizer, valproic acid is a wide spectrum anticonvulsant drug which is commonly used in the treatment of epilepsy and bipolar disorder [8]. Despite the mechanism of its actions in different neuropsychiatric disorders is not fully understood, it has been demonstrated that valproic acid has enhancing effects on GABAergic neurotransmission and blockade of voltage-gated sodium channels. It has been indicated that the drug inhibits the production of pro-inflammatory cytokines such as nuclear factor-κB, tumor necrosis factor-alpha, and interleukin-6 in and block the migration of macrophage cells [9]. Moreover, it triggers the apoptosis in CD8+ T lymphocytes via caspase-3 activation, but it does not alter the survival of CD8+ T lymphocytes against viral peptides. It has been suggested that histone deacetylase enzyme inhibitory activity of valproic acid plays a role in its immunomodulatory effects [10]. Regarding the given immunomodulatory effects of valproic acid, it has been suggested that the drug might provide benefits for ARDS due to the exaggerated immune response related to COVID-19.

Most of the clinicians have thought that specific antiviral treatment against COVID-19 is the best choice to struggle with the current outbreak, however, unfortunately, preclinical and clinical research takes a long time to identify effective and safe novel antiviral therapeutical candidates. Therefore, researchers have focused on remodeling or repurposing of current drugs, of which their pharmacological and toxicological properties have been already known and they are in use in clinics at present. It has been demonstrated that valproic acid and its metabolites have direct antiviral activity against several viruses, including Human Immunodeficiency Virus (HIV), Epstein-Barr virus (EBV), and Herpes Simplex virus-1 (HSV-1) [11]. An unpublished molecular repurposing study showed that valproic acid and especially its metabolite, valproic acid Co-A, might be effective against COVID-19 [12]. The authors suggested that valproic acid Co-A has the potential to inhibit RNA dependent RNA polymerase (nsp12) of COVID-19, which inhibits the replication of virus hosted in the human cells. This study consolidates the findings showing the antiviral activity of valproic acid and gives hope for its potential usage in the COVID-19 pandemic.

Although COVID-19 treatment guidelines vary between countries, it commonly consists of polypharmacy primarily based on direct antiviral therapy such as hydroxychloroquine and remdesivir. Thus, drug interaction between valproic acid and current antiviral treatment would be important to consider if the potential usage of valproic acid will be at the clinician's plan. It has been shown that valproic acid might affect the cytochrome P450 enzymes, primarily inhibits CYP2C9 in patients. There is no known adverse interaction between valproic acid and hydroxychloroquine, lopinavir, ritonavir, and azithromycin [13]. Besides, there is no data about remdesivir and valproic acid interaction. Certain studies suggested lopinavir/ritonavir might decrease the blood level of valproic acid [14]. To the best of our knowledge, it does not seem that it

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will induce a serious drug interaction with current therapy.

In conclusion, COVID-19 showed a rapid world-wide invasion in a short time and characterized by a lethal ARDS. Currently, it is unlikely to discover novel therapeutic agents to reduce mortality and morbidity related to COVID-19 in the short term. In the current situation, in our opinion, it would be feasible to examine the potential usage of valproic acid, a drug that we have been using, and well known in the clinical practice for more than 60 years, against COVID-19 pandemic and related ARDS. We suggest that demonstrating the antiviral effects against some viruses and the immunomodulatory effects of this drug would encourage clinicians for blind studies with valproic acid in further studies.

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Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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