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Early use of non-steroidal anti-inflammatory drugs in COVID-19 might reverse pathogenesis, prevent complications and improve clinical outcomes

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ABSTRACT

The pathogenesis of Coronavirus disease 2019 is still obscure and the need for exploration of possible mechanisms to suggest drugs based on knowledge should never be delayed. In this manuscript, we present a novel theory to explain the pathogenesis of COVID-19; lymphocyte distraction theory upon which the author has used, in a preprinted protocol, non-steroidal anti-inflammatory drugs (NSAIDs); diclofenac potassium, ibuprofen and ketoprofen, successfully to treat COVID-19 patients. Furthermore, we agree with a recommendation that glucocorticoids should not be used routinely for COVID-19 patients and suggested to be beneficial only for patients with late acute respiratory distress syndrome. A clinical proof of ibuprofen safety in COVID-19 has been published by other researchers and we suggest that early administration of NSAIDs, including ibuprofen, in COVID-19 is not only safe but it might also prevent COVID-19 complications and this manuscript explains some of the suggested associated protective mechanisms.

1. Introduction

The pathogenesis of Coronavirus disease 2019 (COVID-19), a disease that harvested more than eight hundred thousand lives today, the 27th of August 2020 [COVID-19 Dashboard by the Center for Systems Science and Engineering (CSSE) at Johns Hopkins University], is still not completely understood and a better understanding of the pathogenesis would eventually lead to improvement in the treatment protocols as well as the control of this pandemic [1].

Lymphopenia has been reported to be a common feature associated with severe acute respiratory syndrome coronavirus 2 (SARS CoV-2) causing COVID-19 [2,3], similar to what has been previously reported for the SARS CoV epidemic in 2002–2003 [4]. It is currently well known that both viruses belong to the same genus of beta coronaviruses and share multiple similarities including the same ACE2 receptor to enter the target cells, as well as immune cross reactivity [5]. Furthermore, SARS CoV-2-induced lymphopenia was recently described as an effective and reliable indicator of the severity and hospitalization in COVID-19 patients [6]. Thus, if we may find a possible hypothesis to explain the lymphopenia induced by SARS CoV, it might also help us to explore a potential treatment for SARS CoV-2.

2. SARS CoV-2 might deceitfully distract lymphocytes away from the lungs

It was previously suggested that SARS CoV induced lymphopenia is likely to be caused by indirect mechanisms such as an increase in cortisol levels that occurred as part of the body stress response to this severe respiratory viral infection or by an iatrogenic effect of glucocorticoids used to manage those patients. Moreover, cortisol levels were demonstrated to be significantly higher in lymphopenic patients than in non-lymphopenic patients and to be significantly negatively correlated with monocytes and suppressor CD8⁺ cells, B lymphocytes and helper CD4⁺ cells in SARS CoV patients [4,7]. Interestingly, the adrenal gland was previously shown to express ACE2 receptors and SARS CoV-related inflammation of various organs, including the adrenal gland, has also been reported. Similarly, SARS CoV has been demonstrated to cause architectural disruption and lymphocyte depletion in the spleen and lymph nodes despite no or trace ACE2 expression in examined human tissue specimens, and SARS CoV has also been associated with adrenal glands necrosis and infiltration of monocytes and lymphocytes [8,9]. Relying on the previous mechanisms related to SARS CoV, to be added to our current knowledge that COVID-19 pathogenesis has been shown to be associated with excessive chemokines release; a cytokine storm that has been associated with unfavorable clinical outcomes, including some chemokines attracting lymphocytes and other inflammatory cells to

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infected tissues [10,11]. We suggest that SARS CoV-2, like SARS CoV may cause, both directly and indirectly, progressive inflammation in different body organs and some of these released chemokines, and perhaps others yet to be discovered, are well known to attract lymphocytes to those organs causing lymphopenia encountered with COVID-19. Interestingly, an inadequate Th1-biased T-cell response was suggested to contribute to the immunopathology of SARS-CoV infection [12] and recently, patients complaining from severe COVID-19 outcome have been shown to exhibit a maladapted immune response profile as well as early immune signatures that correlate with divergent disease trajectories [13]. Similarly, after a preprint of this manuscript was published [14], reports of multisystem COVID-19 hyperinflammatory conditions have been released [15,16] and we claim that their pathogenesis is consistent with this hypothesis. More importantly, we suggest that this lymphopenia, if occurred, should be considered a symbol for distraction of lymphocytes to multiple organs instead of being mainly directed to the lungs, the main target organ of COVID-19 and SARS CoV-2-induced lymphopenia has been previously linked with disease severity and prognosis [17]. Interestingly, it might also be considered another reflection of the previously described disturbance of the homeostasis of the interferons' immune response in COVID-19 patients [11,18–20].

3. Potential causes of failure of hydroxychloroquine treatment

Notably, hydroxychloroquine has been previously reported to cause lymphopenia and increase human immunodeficiency virus, viral load which was suggested to be only explained by a biological effect of the drug [21] and a potential likewise relationship with SARS CoV-2 induced lymphopenia should be carefully and thoroughly investigated as it might reason for its inefficacy [22], higher mortality rate in its high dose [23] that eventually might have led to its suspension [24] and formal discontinuation on the 4th of July 2020 upon a recommendation from the Solidarity Trial's International Steering Committee [25].

4. Glucocorticoids role in treatment of COVID-19

Acute inflammation of the adrenal glands increases cortisol secretion, especially early in the COVID-19 clinical course, which further augments lymphopenia and might complete the unfortunate vicious cycle. Moreover, short-duration, high-dose glucocorticoid therapy was not proven effective for early acute respiratory distress syndrome or for severe sepsis. This might be explained by glucocorticoid-induced immunosuppression as well as lymphopenia [26] and when combined with mineralocorticoids, they only showed some benefits in some selected critical cases classified with a poor prognosis, and moderate doses of glucocorticoids were suggested to be beneficial only for patients with late acute respiratory distress syndrome [27]. Furthermore, it has been recommended for patients with rheumatic disease on glucocorticoid therapy to use the minimum possible doses of glucocorticoids during COVID-19 infection [28]. Thus, we would like to agree with the clinical recommendation against the routine use of glucocorticoids in the management of COVID-19 and to confirm they should be only discussed to be administered on a case by case basis [29] and to dispute with some other contradictory reports and encourage more colleagues to present properly performed clinical data to end any remaining controversy [19]. Consistent with this recommendation, dexamethasone has been recently shown to lower COVID-19 28-day mortality only among patients who were receiving respiratory support [30]. However, a study with some limitations has showed that prednisone or methylprednisolone was associated with a significant reduction in COVID-19 hospital mortality and recommended initiation of clinical trials testing corticosteroids during the inflammatory phase of COVID-19 [31]. Similarly, 40–80 mg/d (0.75–1.5 mg/kg/d) of methylprednisolone for 3 days, tapered to 20 mg/d, with a total treatment period of less than 7 days benefited COVID-19 patients with marked radiologic progression and

LDH levels of less than two times the upper limit number and a tailored individualized course was suggested as rescue treatment in more severe or critically ill patients [32]. Moreover, an randomized open-label trial with some limitations showed the use of intravenous dexamethasone plus standard care resulted in a statistically significant increase in the number of ventilator-free days over 28 days in patients with COVID-19 and moderate or severe ARDS, yet with no significant difference in the secondary outcomes of all-cause mortality at 28 days or ICU-free days during the first 28 days [33]. On the other hand, a meta-analysis showed that administration of systemic corticosteroids, compared with usual care or placebo, was associated with lower 28-day all-cause mortality in critically ill patients with COVID-19 [34]. However, important concerns regarding the interpretation of data as well as the limitations of several studies showing potential benefit of glucocorticoids in COVID-19 have been raised and a call to individualize different steroid approaches depending of the host has been repeated [35] and we would like to agree with those concerns. We would also like to suggest trying hydrocortisone sodium succinate 50 mg i.v./6 h [36], which has a more rapid onset than those already tried, for selected critical cases of COVID-19, in situations when potential benefits exceeds the risks.

5. Ibuprofen is currently being proven to be beneficial for COVID-19

Most importantly, based on the suggested pathogenesis of COVID-19 described in this manuscript, we suggest that using non-steroidal anti-inflammatory drugs (NSAIDs), e.g. ibuprofen, might prove beneficial for the early management of COVID-19 trying to ameliorate the suggested inflammatory process leading to lymphopenia and immunosuppression. Theoretically, NSAIDs when used as early as possible during the clinical course of COVID-19 might prevent disease progression or even reverse lymphocytopenia and we suggest it might be added to his newly suggested nitazoxanide/azithromycin protocol for early management of COVID-19 [20] but in a separate arm for nitazoxanide/azithromycin/ibuprofen as well as to add NSAIDs to any other already adopted protocol for early cases of COVID-19 and compare the results against the already used analgesic/antipyretic paracetamol. Interestingly, we have recently provided the first clinical report that has shown this theory to be clinically valid when he has received numerous requests for treatment from Egyptian COVID-19 and both ibuprofen and diclofenac potassium have been shown more superior to the currently used paracetamol not only with regard to its analgesic antipyretic effect but also in significantly improving the lymphocytic count in COVID-19 patients, enhancing their immune response as well as recovery mostly in five days and NSAIDs were the most important component of his illustrated preprinted protocol which is currently under review in a reputed medical journal [37]. We were fully aware that his hypothesis is contradictory to another one that has led to practical avoidance of NSAIDs for COVID-19 patients [38] and we have, since March 2020, prepared a review article disputing that claim and it's been preprinted, sent to the WHO and recently published [39]. Other researchers have also criticized the theoretical basis upon which ibuprofen was avoided in COVID-19 [40,41] and the claims against other drugs mentioned with ibuprofen in that contradictory hypothesis are similarly being revoked [42]. Notably, ibuprofen has been previously hypothesized to be hazardous in another medical argument and later on that hypothesis was proven incorrect [43] and recently a clinical study has shown that ibuprofen use was not associated with worse clinical outcomes, compared with paracetamol or no antipyretic [44]. Similarly, Use of NSAIDs was not associated with 30-day mortality, hospitalization or complications in Danish individuals who tested positive for SARS-CoV-2 [45]. Moreover, ibuprofen has been used successfully and safely for decades to alleviate symptoms of naturally acquired common colds [46] and multiple mechanisms that interfered with the viral pathophysiological effects were suggested [47].

6. Conclusion

Finally, it might be considered a real misfortune that NSAIDs including ibuprofen have been practically avoided to favor the analgesic antipyretic paracetamol with no anti-inflammatory effect. It is also probable that a safe short course of inexpensive and effective drugs like ibuprofen and other NSAIDs could have saved lives, but we have ignored them based on a hypothesis to be confirmed by more studies which are highly encouraged. However, we should learn from unintended mistakes and make sure not to be repeated.

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Declaration of Competing Interest

The authors report no declarations of interest.

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