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Medical Hypotheses 140 (2020) 109776

Contents lists available at ScienceDirect

Medical Hypotheses

journal homepage: www.elsevier.com/locate/mehy

Can pioglitazone be potentially useful therapeutically in treating patients with COVID-19?

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A B S T R A C T

The severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) has become a pandemic disease (COVID-19) that has spread globally causing more than 30,000 deaths. Despite the immense and ongoing global effort, no efficacious drugs to fight this plague have been identified and patients admitted to the intensive care units (ICU), for respiratory distress, are managed mostly by means of supportive care based on oxygen maintenance. Several authors have reported that the prevalence of hypertension, diabetes, cardiovascular and cerebrovascular diseases comorbidities were indeed frequent among patients with COVID-19, which suggests that these conditions are likely to aggravate and complicate the prognosis. What the aforementioned diseases have in common is a latent chronic inflammatory state that may be associated with the alteration of laboratory parameters that are typical of the metabolic syndrome and insulin resistance. In severe COVID-19 patients laboratory markers of inflammation such as C-reactive protein, IL-6, D-dimer, serum ferritin and lactate dehydrogenase are elevated in many patients; assessed since the 4th-6th day of illness onset, such increases seem to be predictive of an adverse prognosis. Our hypothesis is that drugs belonging to the family of thiazolidinediones (TZD) such as pioglitazone or rosiglitazone, approved for treating the condition of insulin resistance and the accompanying inflammation, could ameliorate the prognosis of those COVID-19 patients with diabetes, hypertension and cardiovascular disorders comorbidities. TZD are PPARγ agonists that act on nuclear receptors, thereby triggering certain transcription factors. TZD were widely used for type-2 diabetes in the first decade of this century and although concerns have been raised for possible side effects associated with long-term treatment, their use has been recently revaluated for their anti-inflammatory properties in numerous medical conditions.

Introduction

COVID-19: comorbidities

The severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) has become a pandemic disease that has spread globally causing more than 30,000 deaths. Although several treatment trials are under clinical evaluation, no specific and efficacious therapy is available at the moment [1] and patients admitted to the intensive care units (ICU), for respiratory distress, are managed mostly by means of supportive care based on oxygen maintenance [2]. Moreover, the dramatic situation currently facing hospitals in Europe in particular, has hindered any accurate or critical evaluation of the published clinical data and the therapeutical response of treatments utilized during the China's COVID-19 experience [3]. Nevertheless, although initial reports come with certain limitations, it has emerged that patients with previous cardiovascular or metabolic diseases could be at higher risk of developing severe acute respiratory distress syndrome as well as suffering a worsening of their cardiovascular condition. Evaluating 1527 patients, Li et al., [4] reported that 17% had hypertension, 10% diabetes and 16% had cardiovascular and cerebrovascular comorbidities [4]. Moreover, based on a detailed clinical investigation on 140 hospitalized COVID-19 patients Zhang et al. [5] similarly reported a 30% prevalence of hypertension and 12% of diabetes mellitus, though surprisingly asthma and other allergic diseases were not reported by any of the patients. Furthermore, chronic obstructive-pulmonary disease (CODP 1,4%) and present smokers (1,4%) were rare [5]. In addition a *meta*-analysis that aimed to show the prevalence of comorbidities in COVID-19 patients, reported that hypertension (17%), diabetes (8%), cardiovascular diseases (5%) and respiratory system disease (2%) were present and that these comorbidities may be a risk factor for severe patients as compared with non-severe patients [6]. The presence of these conditions suggests there is a frequent incidence of a metabolic syndrome condition and although it is not systematically reported, it does appear that an adverse prognosis is likely when associated with COVID-19. Peng et al., [7] reported that among non-surviving COVID-19 patients, 88% had BMI > 25 kg/m^2. In addition, C-reactive protein was elevated in most COVID-19 patients [7–11]. In particular C-reactive protein was more elevated in those who progressed toward worse condition [12,13].

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https://doi.org/10.1016/j.mehy.2020.109776
Received 1 April 2020; Accepted 21 April 2020

COVID-19: inflammation parameters

Accumulating evidence suggests that a subgroup of patients with severe COVID-19 might have a cytokine storm syndrome [14], thus the identification and treatment of hyperinflammation is recommended in order to reduce mortality [15]. In this regard, the drug tocilizumab (IL-6 receptor blocker) has been approved in patients with COVID-19 pneumonia and elevated IL-6 in China [16]. In particular, SARS-CoV-2 infection increased plasma IL1B, IL1RA, IL7, IL8, IL9, IL10, basic FGF, GMCSF, IFNγ, IP10, MCP1, MIP1A, MIP1B, PDGF, TNFα, and VEGF concentrations, while ICU (intensive care unit) patients at severe stage of disease had higher plasma level of IL2, IL7, IL10, GCSF, IP10, MCP-1, MIP1A and TNFα than non-ICU patients, suggesting a hyper-inflammatory condition also known as a cytokine storm [14,15]. In addition, the specificity of predicting the severity of COVID-19 in adult patients, by assessing IL-6 and D-Dimer concentrations in parallel has been proposed [17]. The mechanisms by which this strong inflammatory response could be linked with the uncontrolled pulmonary inflammation and consequent COVID-19 lethality have been recently discussed [18,19].

COVID-19: neurological implications

The neuro-invasive potential of SARS-CoV-2 in the respiratory failure of COVID-19 patients, has been recently debated [8,20]. Although the evidence of this possibility is based mostly on studies of other Corona viruses [21], the similarities of SARS-CoV2 with the other SARS CoV [22], suggest it is conceivable that the rapid respiratory failure observed in a number of patients could in part be due to the spreading of SARS-CoV-2 to the brain, either through the olfactory nerve or the vagus nerve. However, the hematic or the lymphatic route should also be considered [23]. Once in the brain, the virus may reach the brainstem and the important cardio-respiratory functions located therein, affecting them with unpredictable consequences. This hypothesis is supported by a study reporting that a high number of COVID-19 severely affected patients reported neurological manifestations, headache and impaired consciousness [24,25].

A further consideration that may be worth highlighting is that many patients report losing their olfactory and gustatory senses [26]. Although, to the best of our knowledge, this problem has not been accurately documented, it is well known that a number of viruses such as H3N2 and H5N1 can enter the brain through the olfactory route and at the same time, antiviral antibodies can directly access the olfactory neuron [see [27] for a review]. In addition SARS-CoV-2 shares a notable homological sequence with SARS-CoV and since SARS-CoV has been reported in the brain, it is likely that the hyposmia could be due to the a passage to the brain of the SARS-CoV-2 through the olfactory route [28]. Moreover, it is also possible that the passage of SARS-CoV-2 into the brain could be at least partially responsible for the acute respiratory failure of patients with COVID-19 [24].

COVID-19: treatments

Among the treatments used in COVID-19, it is known that antiviral, antibiotics for secondary sepsis, and sometimes corticosteroids are the most frequently used drugs [3,29]. Nevertheless it appears that the condition that most likely exposes patients to a higher vulnerability has not yet been considered as a therapeutical target [30,31]. On the other hand it seems that in the last stages of pulmonary damage, a state of hyper inflammation sustained by a cytokine storm may overwhelm the immune defence response leading to a multiple organ failure and decease [15].

To handle the elevated levels of IL-6, tests have been carried out using Tocilizumab, a monoclonal antibody that targets IL-6 and it seems that it can improve the prognosis in Covid-19 infected patients with severe respiratory distress [32]. On the other hand, the efficacy of glucocorticoid and other anti-inflammatory drugs that have often been used for handling the condition of COVID-19 patients has been questioned [29]. Moreover, it seems that there is no indication for assessing the condition of overweight, metabolic syndrome or insulin resistance, as a guide to selecting a suitable treatment for such patients [3,30,31].

Hypothesis

In the light of the above, our hypothesis is that the drug pioglitazone could potentially be used to reduce the inflammation and the consequent risk of death that is associated with COVID-19, at least in those patients that have a manifest condition of metabolic syndrome. Pioglitazone belongs to the family of thiazolidinediones (TZDs), i.e. drugs that are commonly used for treating insulin resistance [33]. We know the following facts about insulin resistance: it amplifies inflammation [34], it is associated with several cardiovascular risk factors [35], it is associated with an increase in C-reactive protein, IL-6, and TNF-α [36] and produces a pro-coagulant state with increased fibrinogen and plasminogen activator inhibitor, (PAI-1) [37]. All this raises many concerns regarding the ability of patients with type-2 diabetes to respond properly to the infection with SARS-CoV-2. For these reasons and considering also that inflammatory laboratory markers are elevated in COVID-19 [14], it is of great interest that pioglitazone can produce an anti-inflammatory effect as has been assayed through high sensitive C-reactive protein within short term intervals after starting therapy [38].

Specifically, pioglitazone (30–45 mg/day for three months) can significantly reduce IL-6 and TNFα in insulin resistant individuals without manifest hyperglycaemia matched for age, gender and adiposity [39]. Four months (45 mg/day) treatment with pioglitazone reduced the monocyte gene and protein expression of IL-1b, IL-6, IL-8 and lymphocyte IL-2, IL-6 and IL-8 [40]. It has also been reported that pioglitazone inhibits the secretion of pro-inflammatory cytokines (e.g. IL-1b, IL-6, and IL-8) and can increase the anti-inflammatory ones (e.g. IL-4 and IL-10) in astrocytes stimulated with lipopolysaccharide [41]. It has also been shown to have a potential in decreasing ferritin in a rat model of angiotensin II induced hypertension [42].

Finally we wondered whether pioglitazone can have a direct action on lung inflammation and fibrosis. We found that pioglitazone attenuates lung injury when modulating adipose inflammation in a cecal ligation puncture (CLP) model in mice. In this study, pioglitazone (7 days) significantly reduced TNFα and IL-6 mRNA expression in the peritoneal lavage fluid of CLP group [43]. Additionally, it has been reported that pioglitazone may exert a direct effect on lung inflammation and fibrosis [44], and can reduce the lung fibrotic reaction to silica-exposed rats, which is normally characterized by overproduction of TNFa [45].

As for the hypothesis that either the SARS-CoV-2 or the consequent inflammation response has spread to the brain is concerned, we believe there to be compelling evidence that TZD display central anti-inflammatory properties in neurological disorders and it has been reported that they have a therapeutically usefulness in psychiatric and neurological conditions such as depression [46], in Alzheimer's disease [47], and in animal models of Parkinson [48,49], although in Parkinson's patients, pioglitazone did not significantly altered levels of inflammatory biomarkers at 16 and 45 weeks of treatment with 15 and 45 mg/day [50]. Interestingly, pioglitazone and rosiglitazone treatment attenuated the elevation of inflammatory markers and the decrease in the glutamate transporter (GLT-1) expression, in a primary mixed culture of astrocytes and microglia caused by exposition to viral proteins (i.e.HIV_{ADA} gp120); similarly these results were replicated by in vivo treatment [51].

With regard to the use of TZD in the COVID-19 emergency, concerns will inevitably be raised about the drug's efficacy and patient reaction time after short term administration. Patel et al. [52] showed that pioglitazone is able to suppress neuro-inflammation and maintains

mitochondrial respiration when administered acutely in a model of spinal cord injury in mice. In addition, a sub-chronic treatment with pioglitazone exerted anti-convulsive effects in pentylentetrazole-induced seizures in mice, probably through the induction of constitutive nitric oxide synthase [53]. Pioglitazone showed to have short-term (16 week trial) anti-inflammatory effects by lowering C-reactive protein by 41% and IL-6 by 38% in men with advanced nephropathy [54]. Pioglitazone, administered acutely, is effective in abrogating the dysfunction by attenuating neutrophilia, TNFα, and oxidative stress in an LPS-induced model of acute lung inflammation in guinea pigs [55]. Based on these and other reports, we are confident that pioglitazone could be efficacious after acute or sub-chronic treatment [9,38–44]. On these premises, we are suggesting that the treatment with pioglitazone or other PPARγ agonists does have a rationale in COVID-19 treatment.

Conclusions

Looking at the clinical profile of COVID 19 patients, from one study it emerges that all the progression group had elevated C-reactive protein and decreased albumin levels [12]. A second study shows that in patients hospitalized with COVID-19, among the laboratory markers, D-dimer, IL-6, Serum ferritin, Lactate dehydrogenase, high-sensitivity cardiac troponin were significantly elevated while patient's lymphocyte count was significantly decreased at various time points from illness onset (4 to 19 days) during hospitalization [10]. A third study shows that on admission, 83% of patients had lymphocytopenia while most of the patients had elevated levels of C-reactive protein, and those with severe disease had more prominent laboratory abnormalities [56].Given that pioglitazone is able to reduce many of these inflammatory parameters and considering that the comorbidity of diabetes, hypertension and cardiovascular disorders are indicative of a general inflammation associated with metabolic syndrome and lipid profile alteration, all conditions that can be improved by pioglitazone, we are therefore suggesting that a clinical trial with this drug or with other TZD should be considered as a support therapy in COVID-19. Finally we would like to stress that pioglitazone can be administered in patients that are on statins as it has been reported that the addition of pioglitazone to atorvastatin, further reduces C-reactive protein and other laboratory markers of inflammation [57].

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.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.mehy.2020.109776.

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