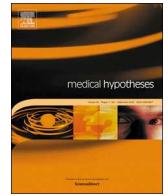




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Letter to Editors

Vitamin D: A simpler alternative to tocilizumab for trial in COVID-19?



A B S T R A C T

There is anecdotal evidence that tocilizumab, an immunosuppressant drug, may be a potential therapeutic option for patients with severe manifestations of coronavirus disease 2019 (COVID-19). Like tocilizumab, Vitamin D appears to modulate the activity of an interleukin (IL-6), which may explain the seasonal variation in prevalence of influenza. While most cases of COVID-19 have, thus far, occurred in the Northern Hemisphere winter, limiting the ability to assess seasonal variation, there remains substantial variation in the severity of this condition that has yet to be explained. A retrospective comparison of Vitamin D levels in previously obtained blood samples between survivors and confirmed fatalities could establish a rationale for implementation of widespread Vitamin D supplementation. This would be far cheaper and simpler than tocilizumab as a therapeutic option to trial.

Background

According to the World Health Organization, by March 26, 2020, coronavirus disease 2019 (COVID-19) had been identified in 462,684 people worldwide, with mortality of approximately 4.5% [1]. While there has been an intense focus upon development of a vaccine and trials of antiviral drugs have commenced, no current effective treatment exists. Dr Guglielmo Gianotti, the director of surgery at Cremona Hospital in Northern Italy (considered to be one of the hardest hit regions in this pandemic) recently stated: “The only drug that we’ve seen that is showing the slightest bit of benefit to patients is the immunosuppressive drug Tocilizumab, which is mainly used for the treatment of rheumatoid arthritis. It’s being trialled at the Pascale Cancer Institute in Naples with very encouraging results.” [2]. Indeed, a trial of tocilizumab for COVID-19 has recently commenced in China [3], and additional trials are set to commence elsewhere [4].

How does tocilizumab work and how might it reduce morbidity and even mortality in patients with COVID-19? There is evidence that some patients with severe COVID-19 experience a cytokine storm with production of large quantities of interleukins, specifically IL-1 and IL-6 [5], and tocilizumab is a potent blocking agent of the IL-6 receptor [6]. While, at time of writing, the evidence for tocilizumab is anecdotal, this drug does offer hope for managing patients with severe pulmonary manifestations of COVID-19. If tocilizumab does prove to be effective, it will come at a substantial cost, both economic, as it is very expensive, and therapeutic, as it can only be delivered by intravenous infusion [7].

Is there a simpler, widely available alternative to tocilizumab that would be readily accessible and not require parenteral administration? One of the notable features of the COVID-19 outbreak was that it began during the Northern Hemisphere winter. Influenza, which also has a high morbidity and mortality, albeit lower than COVID-19, also tends to peak during winter [8]. There have been suggestions that this relates to lower levels of Vitamin D due to reduced sunlight exposure, and a trial of Vitamin D supplementation has been shown to reduce the incidence of influenza A [9]. While there are a number of potential mechanisms by which Vitamin D might assist in preventing influenza, there is also a cytokine storm in this condition, including production of large quantities of IL-1 and IL-6 [10]. Might Vitamin D play a role in modulating

the production of the interleukins, thus reducing the impact of influenza? There is recent evidence that Vitamin D deficiency is associated with increased levels of IL-6 in patients with HIV infections [11], and there is also evidence indicating that Vitamin D supplementation can reduce excess IL-6 levels in diabetic mice [12]. While there have been no published trials of tocilizumab, an IL-6 antagonist, for influenza, it is conceivable that it might have positive effects in this condition, but is there a role for Vitamin D in another condition resulting in excessive IL-6 production, COVID-19?

There is a very wide variation in severity of COVID-19 clinical features, with some patients having minimal if any symptoms, while others become critically ill [13]. While some of this variability might be explained by pre-existing conditions and other factors, such as cigarette smoking and older age [14], there is no current explanation for the variation in severity amongst previously healthy patients and the significant rate of severe infections amongst younger patients. Could the presence of Vitamin D deficiency account for this variability?

Hypothesis

That Vitamin D deficiency might play a role in the variation in severity of COVID-19, such that treatment with Vitamin D would offer a simpler alternative to tocilizumab.

Discussion

There is a high prevalence of Vitamin D deficiency in the general population [15], and especially in some population groups in China [16]. Yet, the demographics of Vitamin D levels amongst patients with confirmed diagnosis of COVID-19 are currently unknown. At time of diagnosis, almost all patients are asked to provide blood samples, and it would seem to be readily feasible to retrospectively determine Vitamin D levels in the specimens. A simple comparison of Vitamin D levels between survivors and confirmed fatalities, taking other factors such as age, pre-existing morbidities and cigarette smoking history into account, could and should be performed. If a significant difference between groups is identified, this would provide a strong rationale for mandating Vitamin D supplementation worldwide. There are current

trials of tocilizumab, an expensive drug that can only be administered intravenously, but, given that Vitamin D appears to have similar modulating effects on an interleukin, it offers a realistic alternative treatment option which may save many lives.

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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