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Review

COVID-19 and IL-6: Why vitamin D (probably) helps but tocilizumab might not

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ABSTRACT

Interleukin 6 (IL-6), which is involved in the cytokine storm phenomenon, is a therapeutic target in COVID-19, but monoclonal receptor antibody therapeutic agents such as tocilizumab have demonstrated mixed results. Could Vitamin D, which modulates IL-6, be more effective than currently deployed IL-6 antagonists, including tocilizumab, thereby presenting a useful therapeutic option in COVID-19? A narrative review of published trials examining the effect of Vitamin D administration in COVID-19 patients was conducted, and the theoretical basis for the use of tocilizumab as an IL-6 antagonist was compared with the immunomodulatory effect of Vitamin D on IL-6 production. Four of the six included studies reported a positive effect of Vitamin D on outcomes. While tocilizumab non-selectively blocks both anti-inflammatory and pro-inflammatory actions of IL-6, Vitamin D lowers immune cell IL-6 production, potentially reducing pro-inflammatory effects, but does not specifically target IL-6 receptors, avoiding any deleterious effect on the anti-inflammatory actions of IL-6. Vitamin D may have advantages over tocilizumab as an IL-6 immunomodulator, and, given that it is safe if administered under clinical supervision, there is a strong rationale for its use.

1. Introduction

Despite the pending widespread rollout of a vaccine, the novel human coronavirus pandemic which began in late December 2019 (Hui et al., 2020) continues to present an enormous challenge, with no currently approved therapeutic regimen (Tobaiqy et al., 2020). Based upon early reports that many patients with severe COVID-19 produced large quantities of interleukins (referred to as a cytokine storm (Ross et al., 2020), the IL-6 antagonist tocilizumab was trialled as a therapeutic option, but results, while initially promising (Tleyjeh et al., 2020), have not fully met the original high expectations (Stone et al., 2020). The term cytokine storm generally refers to a number of cytokines, including IL-6 as well as Tumour Necrosis Factor - TNF (England et al., 2021). Indeed, the use of TNF antagonists for COVID-19 has been proposed (Feldmann et al., 2020), but, at time of writing, there are no published results using this strategy (England et al., 2021).

Vitamin D, which has immunomodulatory properties (Sassi et al., 2018), was proposed as a potential therapeutic option in the early part of the pandemic (Silberstein, 2020b), supported in part by reports of Vitamin D deficiency resulting in poorer outcomes (see the review by Benskin, 2020). Yet, despite calls for clinical trials of this vitamin (Silberstein, 2020b), in part based upon its modulation of IL-6, a key interleukin implicated in viral replication (Silberstein, 2020a), only a few have been completed at time of writing. This comes as a surprise, given the widespread promotion and multiple trials of the IL-6 antagonist tocilizumab (Tleyjeh et al., 2020). There is clearly a need for prospective trials of Vitamin D in COVID-19, but if its mechanism of action involves IL-6 modulation (Sadeghi et al., 2006; Subramanian et al., 2017), will it prove any better than tocilizumab, which has delivered mixed results (Stone et al., 2020)? This review seeks to determine whether the IL-6 modulating properties of Vitamin D may be more effective than currently deployed IL-6 antagonists, including tocilizumab, thereby presenting a useful therapeutic option in COVID-19.

2. Methods

A limited narrative review of recent clinical trials of therapeutic Vitamin D administration for COVID-19 was performed by searching PubMed and Google Scholar for adult human research studies that included key words “vitamin D” and “Covid-19” and/or “SARS-CoV-2” up to December 31, 2020. A total of 6 studies satisfied the inclusion criteria. As there was heterogeneity in the format of how results were published, analysis was limited to whether administration of Vitamin D resulted in a statistically significant reduction in ICU admission,

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Table 1
Analysis of impact of Vitamin D supplementation on COVID-19 outcome in published controlled trials.

Reference	Location	Measure	Age (years)	N T/C	Vitamin	Duration	Dose	Outcome
Annweiler et al. (2020)	France	Mortality	88 ± 5	16/32	CCC	Single	80,000 IU	P = 0.50
Castillo et al. (2020)	Spain	ICU	53 ± 10	50/26	CCD	≥7 days	0.532 mg	P < 0.001
Ling et al. (2020)	UK	Mortality	74 ± 9	164/162	CCC	Variable	≤40,000 IU/day	P < 0.001
Murai et al. (2020)	Brazil	Mortality	56 ± 15	120/120	CCC	Single	200,000 IU	P = 0.59
Rastogi et al. (2020)	India	Fibrinogen	49 ± 6	16/24	CCC	≥7 days	60,000 IU/day	P = 0.007
Tan et al. (2020)	Singapore	ICU or O_2	62 ± 7	17/26	CCC	≤14 days	1000 IU/day	P = 0.006

The first column lists first author for each study. The fifth column (N) refers to Treated/Controls. The sixth column refers to Cholecalciferol (CCC) or Calcifediol (CCD). The final column details reported statistical effect of Vitamin D on outcome measure.

cytokine levels or mortality.

The theoretical basis for the use of IL-6 antagonist tocilizumab in patients with COVID-19 was also examined, and compared in a narrative format, with the purported effect of Vitamin D on IL-6 and COVID – 19 patient outcomes.

3. Results

There was considerable variation in dosing regimen and outcome measures reported (Table 1). One study - which reported no significant effect of acute Vitamin D treatment on mortality - included a third arm in which patients who underwent 12 months prior maintenance supplementation had significant lower mortality compared to controls (Annweiler et al., 2020). The majority of studies used cholecalciferol, with 3 of these 5 demonstrating a significant effect. The other study reported a significant reduction in Intensive Care Unit admissions following calcifediol administration (Castillo et al., 2020). One study reported a significant reducing effect of cholecalciferol on fibrinogen levels as a nominated inflammatory marker (Rastogi et al., 2020). Another administered a combination of cholecalciferol, magnesium, and vitamin B_{12} and reported a significant reduction in ICU admission and/or O2 requirement (Tan et al., 2020). In summary, although quite diverse, 4 of the 6 studies reported positive outcomes, while a fifth included a third arm with a positive outcome from prior but not acute supplementation.

4. Discussion

Interleukin 6 (IL-6), a cytokine which initiates intracellular signalling (Rose-John, 2012), is produced by a range of cells, including immune, skeletal, vascular smooth muscle and osteoblasts (Jones and Jenkins, 2018). IL-6 is often referred to as having both anti-inflammatory and pro-inflammatory properties, according to the targeted receptors (Rose-John, 2012). Only a limited number of cell types express IL-6 receptors on their surfaces (referred to as membrane bound receptor or IL-6R), including some epithelial cells and hepatocytes (Rose-John, 2012). The binding of IL-6 to receptors on these cells, referred to as classical signalling, has an anti-inflammatory effect (Rose-John, 2012). This contrasts with trans signalling where cells stimulated by, for example, microbial agents (Walev et al., 1996), shed IL-6 receptors, forming a soluble receptor (sIL6-R) which can then bind to any cell in the body (Chalaris et al., 2011). Trans signalling is deemed to be pro-inflammatory, via recruitment of mononuclear cells, inhibition of T-cell apoptosis and T reg cell differentiation (Rose-John, 2012), and undoubtedly play a substantial role in the COVID-19 cytokine storm (Ross et al., 2020).

Tocilizumab is a monoclonal antibody which targets all IL-6 receptors, regardless of whether they are membrane bound or soluble (Tanaka et al., 2012). Clearly tocilizumab and similar non-selective IL-6 antagonists do not discriminate and although administered to modulate pro-inflammatory trans signalling via sIL6-R, will equally block anti-inflammatory classical signalling via membrane bound IL-6R (Tanaka et al., 2012). This might be the explanation for recent mixed results from tocilizumab in COVID-10 patients (Stone et al., 2020).

Contrast this with Vitamin D, which lowers immune cell IL-6 production (Silberstein, 2020a), potentially reducing pro-inflammatory effects, but does not specifically target IL-6 receptors, avoiding any deleterious effect on the anti-inflammatory actions of IL-6. Vitamin D has also been shown to lower TNF levels (Peterson and Heffernan, 2008), representing an additional therapeutic mechanism for countering the COVID-19 cytokine storm. This would appear to work in theory, but what is the evidence of Vitamin D improving COVID-19 outcomes? There is growing evidence that Vitamin D deficiency is associated with greater COVID-19 morbidity and mortality (Brown, 2020), but the evidence for a direct therapeutic effect is still limited. In the results herein described, 4 of the 6 studies reported positive outcomes, while a fifth included a third arm with a positive outcome from prior but not acute supplementation. As noted, the studies were quite diverse in terms of dosing regimens and outcome measures, but do support further investigation. Only one of the trials examined calcifediol, which results in a more rapid increase in serum 25OHD compared to oral cholecalciferol (Quesada-Gomez and Bouillon, 2018), and it, too, described a positive impact on the outcome measure assessed – ICU admission (Castillo et al., 2020).

The addition of L-cysteine as an adjunct to Vitamin D supplementation also merits consideration. This combination reduces oxidative stress more effectively than Vitamin D alone (Jain et al., 2018, 2020) as well as markers of musculoskeletal dyshomeostasis (Parsanathan et al., 2020) and has been proposed as a more effective therapeutic approach than Vitamin D alone (Jain and Parsanathan, 2020).

There is clearly a need for more clinical trials of Vitamin D in COVID-19, including calcifediol, as well as in combination with L-cysteine, but, given that the risk of toxicity is low when administered under professional supervision, there is a strong theoretical rationale for widespread Vitamin D prescription.

5. Conclusions

Both Vitamin D and tocilizumab may have therapeutic roles in COVID-19 by exerting immunomodulatory effects on IL-6, but the former, by reducing immune cell IL-6 production may have advantages over the latter which can block both anti and pro inflammatory action of IL-6. Given that Vitamin D is safe if administered under clinical supervision and deficiency is associated with worse outcomes, there is a strong rationale for its use as a specific therapeutic measure.

Declaration of competing interest

The author declares no conflict of interest.

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