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Rethinking interleukin-6 blockade for treatment of COVID-19

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ABSTRACT

Interleukin-6 (IL-6) is a pleiotropic cytokine with effects in immune regulation, inflammation, and infection. The use of drugs that inhibit IL-6 biological activity has been proposed as a treatment for patients with Coronavirus Disease 2019 (COVID-19). The rationale for this approach includes commitment to the concept that inflammation is a cause of lung damage in COVID-19 and belief that IL-6 is a pro-inflammatory molecule. Observational data thought to support IL-6 inhibition include elevated circulating IL-6 levels in COVID-19 patients and association between elevated IL-6 and poor clinical outcomes. However, IL-6 has significant anti-inflammatory properties, which calls into question the rationale for employing IL-6 blockade to suppress inflammation-induced tissue injury. Also, studies suggesting a beneficial role for IL-6 in the host response to infection challenge the strategy of using IL-6 blockade to treat COVID-19. In studies of recombinant IL-6 injected into human volunteers, IL-6 levels exceeding those measured in COVID-19 patients have been observed with no pulmonary adverse events or other organ damage. These observations question the role of IL-6 as a contributing factor in COVID-19. Clinical experience with IL-6 receptor antagonists such as tocilizumab demonstrates increase in severe and opportunistic infections, raising concern about using tocilizumab and similar agents to treat COVID-19. Trials of drugs to inhibit IL-6 activity in COVID-19 are ongoing and will shed light on the role of IL-6 in COVID-19 pathogenesis. However, until more information is available, providers should exercise caution in prescribing these therapies given the potential for patient harm.

Introduction

Interleukin-6 (IL-6) is a pleiotropic cytokine with multiple effects in immune regulation, inflammation, and infection [1]. The IL-6 family includes leukemia inhibitory factor (LIF), ciliary neurotrophic factor (CNTF), and oncostatin M, among others [2]. IL-6 binds a polypeptide chain, the IL-6 receptor (IL-6R), which then associates with a membrane glycoprotein, gp130, to initiate intracellular signaling through the JAK-STAT and Ras-MAPK pathways [1,3]. Among its many effects, IL-6 – originally known as B-cell stimulating factor-2 – induces activated B-cell differentiation into antibody-secreting plasma cells. Since self-reacting antibodies are involved in the pathogenesis of some autoimmune conditions such as rheumatoid arthritis (RA) [4], there is strong rationale for IL-6 blockade in these disorders.

Tocilizumab is a humanized anti-interleukin-6 receptor (anti-IL-6R) antibody that reduces IL-6 biological activity by interfering with the ability of IL-6 to engage cell surface IL-6 receptors. Tocilizumab has shown efficacy in the treatment of RA, systemic juvenile idiopathic arthritis (sJIA), and Castleman disease. Recently, tocilizumab has been proposed as a therapy for Coronavirus Disease 2019 (COVID-19) [5]. The rationale for this proposal is the presumed role of excessive inflammation in COVID-19 pathogenesis and belief that IL-6 functions as a pro-inflammatory molecule. There is also a statistical association between elevated circulating IL-6 levels and death in patients with COVID-19. However, numerous *in vitro*, *in vivo,* and clinical data suggest IL-6 is a dubious target for COVID-19 therapy.

Hypothesis

We hypothesize that the use of IL-6 antagonists such as tocilizumab and sarilumab for treatment of COVID-19 will be unsuccessful. A substantial body of evidence demonstrates anti-inflammatory (as opposed to pro-inflammatory) properties for IL-6. Studies also demonstrate an adaptive rather than pathological role for IL-6 in infection. Despite

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elevated levels of circulating IL-6 observed in patients with COVID-19, similarly elevated IL-6 levels are observed in patients with autoimmune diseases without associated acute pulmonary pathology or organ damage. Clinical use of IL-6 antagonists and IL-6 receptor antagonists are associated with increased risk for infections, and IL-6 blockade to treat COVID-19 may thus lead to patient harm.

IL-6 as an anti-inflammatory cytokine

Though often described as a pro-inflammatory molecule, IL-6 has shown anti-inflammatory effects in numerous studies dating back to the 1980s. In a study examining IL-6 effect on production of tumor necrosis factor-α (TNF, the prototype pro-inflammatory cytokine), IL-6 significantly reduced lipopolysaccharide (LPS)-induced release of TNF in leukemia cell lines, reduced TNF release in human peripheral blood mononuclear cells (PBMC), and suppressed LPS-induced TNF in mice [6]. These experiments suggest anti-inflammatory function of IL-6. Studies using intraperitoneal administration of endotoxin into IL-6 knock-out (KO) mice showed higher levels of pro-inflammatory cytokines compared to mice with an intact IL-6 response, and KO mice experienced increased mortality. This demonstrates anti-inflammatory and anti-pathogen IL-6 function *in vivo* [7]. Recent data indicate an inflammation-suppressing effect of IL-6 in lungs. A study comparing wild-type (WT) and IL-6 KO mice showed that IL-6 KO mice exposed to LPS were more susceptible to lung inflammation and injury compared to WT animals [8]. These IL-6 KO mice given exogenous recombinant IL-6 had less severe lung injury and less pulmonary edema than KO mice not given recombinant IL-6 [8].

In humans, IL-6 induces production of established anti-inflammatory molecules. Human volunteers infused intravenously with recombinant IL-6 demonstrated marked increase in blood levels of the endogenous cytokine inhibitors IL-1 receptor antagonist (IL-1Ra) and soluble TNF receptor p55 (TNFsRp55) [9]. In separate studies, IL-6 infusion into human volunteers did not result in production of TNFα or IL-1β. Since TNFα and IL-1β are prototypical pro-inflammatory cytokines, IL-6 does not appear to promote pro-inflammatory activity in humans [10]. Together, these studies indicate IL-6 possesses significant anti-inflammatory (not pro-inflammatory) effects.

IL-6 possesses antimicrobial activity

IL-6 has demonstrated a protective role in the host response to infection. A study published in *Nature* showed IL-6 KO mice had impaired response against vaccinia virus, with a 10–1000-fold increase in viral titers in IL-6 deficient animals. These IL-6 KO mice also demonstrated increased susceptibility to *Listeria monocytogenes* infection, possibly due to reduced bactericidal activity of macrophages [11]. IL-6 KO mice exposed to inhaled *Streptococcus pneumoniae* showed increased number of pulmonary *S. pneumoniae* bacterial colonies and reduced survival time relative to WT mice [12].

A study by Dienz, Rud, Eaton et al. examined the response of WT or IL-6 KO mice to challenge with sublethal doses of H1N1 influenza virus; WT mice recovered from the infection while IL-6-KO mice died [13]. Additional studies in IL-6 KO mice infected with influenza demonstrated enhanced vascular permeability and severe occlusion of alveolar airspaces compared to WT mice; this may represent enhanced acute respiratory distress syndrome (ARDS) in the presence of IL-6 deficiency [14]. These findings were corroborated by Yang, Wang, Yang et al., who showed that IL-6 KO mice infected with intranasal influenza A virus had increased mortality, reduced survival times, higher histological damage scores, and significantly higher viral loads compared to WT mice [15]. They also showed IL-6 enhanced epithelial cell survival and promoted migration and survival of macrophages.

Interestingly, a protective role for IL-6 has been shown in co-infection with influenza virus and *S. pneumoniae* bacteria. Similar to earlier studies, IL-6 was elevated during co-infection and was the most prominent of all cytokines measured. Compared to WT mice, co-infected IL-6 KO mice had higher *S. pneumoniae* bacterial loads, less bacterial clearance, and more severe systemic spread of disease. More serious pathologic changes were seen in IL-6 KO mice, including decreased epithelial barrier function and increased shedding of airway epithelium [16]. Phagocytosis of *S. pneumoniae* was weakened in IL-6 KO mice, and treatment with exogenous IL-6 rescued macrophage function. This study may be especially relevant in the present pandemic, since reports suggest co-infections with other pathogens may be common in COVID-19 [17]. Together, these data highlight a critical role for IL-6 in the host immune response to infection. This suggests blocking IL-6 activity may diminish, not promote, host defense against viral or bacterial lung infections.

Elevated blood levels OF IL-6 IN Covid-19 – IS that a Lot?

In the COVID-19 pandemic, elevated IL-6 levels in COVID-19 are cited as evidence of cytokine storm, and association between increased IL-6 and adverse outcomes provides rationale for use of IL-6 antagonists [5,18–20]. In healthy human volunteers, mean levels of circulating IL-6 have been reported between 2 and 3 pg/mL [21]. In COVID-19, circulating IL-6 levels between 16.4 pg/mL and 627.1 pg/mL were reported in one study [5] and as a mean of 132.32 +/- 278.54 pg/mL in a separate study [22]. A median of 6.98 pg/mL was reported in patients with COVID-19 pneumonia and ARDS [23]. Levels of IL-6 have been shown to correlate positively with mortality; in one study, survivors had a median IL-6 level of 6.3 pg/mL compared to 11 pg/mL in non-survivors [24]. A systematic review and meta-analysis of circulating IL-6 concentrations in COVID-19 has been reported [25]. Nine studies were included that contained between 21 and 552 subjects in each study. Average (mean or median) IL-6 levels in the circulation are reported in total cohorts or in subgroups with better or worse clinical outcome. Average IL-6 levels ranged between 2.4 pg/mL-186 pg/mL when considering subgroups or entire cohorts. Examining IL-6 levels in the total cohorts showed six of the nine studies had average IL-6 levels < 37 pg/mL, and two study average levels were 132.3 pg/mL and 186 pg/mL. Six studies with data permitting comparison between IL-6 and outcome showed a 2.9-fold increase in mean IL-6 in patients with a complicated course compared to patients without a complicated course ($p < 0.001$). A complicated clinical course was defined as hospitalization, intensive care unit admission, development of acute respiratory distress syndrome, invasive mechanical ventilation, renal replacement therapy, or death. This report shows elevated circulating IL-6 concentrations in COVID-19 patients and association between elevated IL-6 levels and disease severity. While elevated IL-6 levels may have prognostic value, correlation between elevated IL-6 and severity of illness does not prove causation.

Perspective is needed when evaluating circulating levels of IL-6 in COVID-19. Rheumatologic literature has shown circulating IL-6 levels in autoimmune conditions well into and surpassing the range observed in patients with COVID-19. A study by Shimamoto, Ito, Ozaki et al. evaluating biomarker association with disease activity in RA patients showed a mean IL-6 level of 51.52 +/- 17.08 pg/mL prior to treatment [26]. Three patients had levels between 100 and 200 pg/mL while two patients had levels between 300 and 500 pg/mL. These observations have been corroborated, with mean IL-6 levels up to 124 pg/mL in some RA cohorts [27]; a minority of patients had IL-6 levels well into the mid-hundreds. Similar IL-6 levels have been reported in patients with other autoimmune and rheumatologic conditions. In patients with anti-neutrophil cytoplasmic antibody (ANCA)-associated vasculitis, a mean IL-6 level of 51.96 pg/mL was measured [28]. In a study involving patients with systemic lupus erythematosus (SLE), the mean IL-6 level was 68.1 +/- 68.00 pg/mL [29]. None of these studies showing increased IL-6 in patients with autoimmune diseases demonstrated association between IL-6 and acute pulmonary disease. There was also no association with acute non-pulmonary organ malfunction. These data

suggest circulating levels of IL-6 observed in patients with COVID-19 do not contribute to acute lung pathology.

Upper limits of circulating IL-6 in COVID-19 infection are miniscule compared to circulating IL-6 levels achieved after exogenous administration of recombinant IL-6 into humans. Recombinant human IL-6 was injected subcutaneously (sc) at 10 μg/kg into healthy volunteers in a study of glucose metabolism. Two-and-a-half hours after IL-6 injection, a mean IL-6 plasma concentration of 4,050 pg/mL was quantified [30]. A separate study in cancer patients given recombinant human IL-6 injected by continuous intravenous infusion at 20 μg/kg/day resulted in mean serum IL-6 levels of 3,000 pg/mL [10]. No adverse pulmonary events were noted in any subjects in these studies, and no hypotension or other severe effects were observed.

Although IL-6 levels in COVID-19 can be elevated beyond levels observed in health, IL-6 concentrations in COVID-19 are often no higher than IL-6 concentrations in patients with rheumatologic conditions such as RA, SLE, or ANCA-associated vasculitis. Exogenous administration of recombinant human IL-6 in human studies can achieve circulating IL-6 concentrations more than an order of magnitude above what is seen in COVID-19, yet no study involving IL-6 injection into humans documents the acute lung injury, organ malfunction, or systemic sepsis reported in COVID-19. Therefore, the severe pulmonary manifestations and organ malfunction in COVID-19 are difficult to attribute to IL-6 biological activity.

IL-6 blockade in humans IS associated with increased risk of infections

Blockade of IL-6 activity, whether occurring naturally or following use of an IL-6 inhibiting drug, has been associated with increased risk of infections. In patients with mutations in the IL-6 receptor (IL-6R), recurrent infections are reported that include skin and soft tissue infections, sinopulmonary infections (including bacterial pneumonias), and systemic infections [31]. Similarly, a patient with endogenous neutralizing autoantibodies against IL-6 suffered recurrences of staphylococcal skin disease [32]. The use of tocilizumab in patients with RA and other autoimmune diseases is associated with serious and opportunistic infections in clinical trials; cumulative safety data suggest that infections are among the most common and serious adverse events. Cellulitis and pneumonia are common manifestations, and bowel perforation is also a risk [33–36]. This effect is not limited to IL-6 receptor antagonists such as tocilizumab or sarilumab; a similar safety profile is observed in patients treated with direct IL-6 inhibitors such as the IL-6-binding monoclonal antibody olokizumab [37,38]. In addition, pharmacokinetic and pharmacodynamic studies report a half-life of up to twenty-one days for tocilizumab, suggesting the risk for infection may persist for weeks after administration [39,40].

Consistent with this risk, a recent review of critically ill adults with COVID-19 admitted to the intensive care unit showed administration of tocilizumab was associated with a higher incidence of secondary bacterial infections, including hospital acquired pneumonia and ventilator associated pneumonia [41]. These clinical observations are an expected consequence of the antimicrobial activities of IL-6 and challenge the concept that IL-6 blockade can be employed to treat a serious infection like COVID-19.

Discussion

Approaches to COVID-19 treatment are developing rapidly. Numerous agents used in patients or proposed for use include hydroxychloroquine, azithromycin, nitazoxanide, lopinavir-ritonavir, remdesivir, corticosteroids, and tocilizumab, among others. As data are presented in the public domain – often without peer review given the urgency of the crisis – providers should exercise caution when using medications “off label” given the extensive side effect profile and questionable efficacy of some of these agents. As an example, several reports suggesting benefits of hydroxychloroquine were retracted or were on retraction watch [42,43]. Subsequent larger and higher-quality reports and publications showed no benefit of hydroxychloroquine in COVID-19 and perhaps harm [44,43]. CDC guidelines now recommend against its use, highlighting the danger of hasty adoption.

IL-6 blocking agents such as tocilizumab are at the forefront of expanding literature on potential therapies for COVID-19 patients. Although a pro-inflammatory “cytokine storm” is often invoked as a rationale for blocking the IL-6 cytokine in COVID-19, IL-6 has significant anti-inflammatory properties. This calls into question the rationale of using IL-6 antagonists as an inflammation-reducing therapy. Studies also indicate IL-6 is crucial in the early host immune response to infection, and thus it is not obvious IL-6 blockade is a sound strategy to treat an infection. Elevated levels of circulating IL-6 in COVID-19 are often no higher than levels observed in patients with autoimmune diseases, and exogenous administration of extremely large doses of IL-6 has not resulted in serious adverse effects, raising doubt that IL-6 is a causative cytokine in COVID-19 pulmonary or systemic injury. Finally, clinical use of IL-6 antagonists in autoimmune conditions is associated with increased risk of severe and opportunistic infections. This observation raises concern that IL-6 blockade, in addition to being unlikely to benefit COVID-19 patients, may also prove harmful.

Healthcare providers worldwide are dedicating significant time and effort to care for those affected by this novel and sometimes life-threatening disease. Use of tocilizumab to treat COVID-19 is already suggested in practice guidelines originating in China and Italy [25]. While these recommendations are well-intentioned and understandable given the current lack of effective treatment specific to COVID-19, we are concerned that clinicians will cite these guidelines as justification to use IL-6 blocking drugs in COVID-19. Ongoing studies [45,46] will add to the knowledge of IL-6 blockade and COVID-19 pathogenesis, and we believe that “off label” use of these therapies for COVID-19 should await scientifically credible, randomized controlled trials given the potential for patient harm.

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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Appendix A. Supplementary data

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