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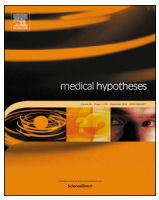

# Is there a role for insulin-like growth factor inhibition in the treatment of COVID-19-related adult respiratory distress syndrome?

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A B S T R A C T

Adult respiratory distress syndrome (ARDS) is the leading cause of death associated with SARS-CoV-2 infection and COVID-19. IGF-1 has been implicated in ARDS, yet its role in relation to COVID-19-related lung injury has not been investigated. We hypothesize that blockage of the IGF-1 receptor (IGF-1R) mitigates lung injury and decreases the risk of death in patients COVID-19-related ARDS. Patients with fibroproliferative ARDS have been shown to have increased IGF-1 and IGF-1R staining in lung tissue specimens. Rising levels of IGF-1 in bronchioalveolar fluid (BAL) and increased IGF-1 mRNA expression in lung tissues (but declining serum IGF-1 levels) have been found in late stage ARDS compared with early lung injury. Blockage of IGF-1R decreases lung tissue damage and increases survival in bleomycin-induced as well as H1N1 influenza-related lung injury in animal models. Teprotumumab is a monoclonal antibody directed against the IGF-1R that was FDA-approved in 2020 for the treatment of Graves' orbitopathy. In order to determine if teprotumumab may reduce lung injury and death related to ARDS in the setting of COVID-19, preliminary clinical data is needed. IGF-1 levels in serum and BAL fluid must be measured in patients with COVID-19-related ARDS. Histopathology from lung samples from patients with COVID-19-related ARDS must be examined for increased expression of the IGF-1R. Once these are ascertained, and if the data support IGF-1 involvement, a randomized, placebo-controlled phase 2A trial of teprotumumab therapy in the setting of COVID-19-related ARDS and non-COVID-19-related ARDS designed to generate initial data on short-term efficacy, safety, dosing and administration should be performed.

## Background

Adult respiratory distress syndrome (ARDS) is the leading cause of death associated with SARS-CoV-2 infection and COVID-19 [1]. Prior to the COVID-19 pandemic, there were an estimated 120,000 cases of ARDS per year in the United States with an overall 30% associated mortality [2,3]. With over 600,000 and 140,000 deaths due to COVID-19 worldwide and in the United States, respectively, according to the Johns Hopkins Coronavirus Resource Center website (https://coronavirus.jhu.edu/map.htm) referenced on July 20, 2020, an effective treatment modality for ARDS is even more critical.

Elevated levels of plasma IL-1B, IL-1RA, IL-2, IL-4, IL-6, IL-7, IL-8, IL-9, IL-10, IL-17, basic FGF, GCSF, GMCSF, IFNγ, IP10, MCP-1, MIP-1A, MIP-1B, PDGF, TNFα, and VEGF have been found in hospitalized patients with COVID-19 [1,4,5]. In addition, higher levels of IL-2, IL-7, IL-10, GCSF, IP-10, MCP1, MIP1A, and TNFα are associated with ICU patients compared with non-ICU patients with COVID-19 [4]. Increased serum IL-6 has been associated with increased mortality in this infection and investigation is underway to determine the utility of the IL-6 inhibitor tocilizumab for the treatment of COVID-19-related ARDS [1,5].

The role of insulin-like growth factor-1 (IGF-1), however, has not yet been investigated in the setting of COVID-19. IGF-1 receptors (IGF-1R) exist on practically every human cell and their activation is critical for cell growth, differentiation, and apoptosis. Recent studies have uncovered that IGF-1 is also important for inflammation and immune regulation in the lung as well as in the orbit [6–8]. In inflammation, stimulation of the IGF-1R activates the PI3K/AKT signaling pathway, inducing AKT activation and the downstream IL-17-mediated inflammatory pathway [7,9]. Co-stimulation of IGF-1R and the thyrotropin receptor on the orbital fibroblast is critical for the development of Graves' orbitopathy [9,10]. Inhibition of IGF-1 with teprotumumab, a recently FDA-approved monoclonal antibody against the IGF-1R, rapidly improves the inflammation and proptosis associated with Graves' orbitopathy [6].

## Hypothesis

IGF-1 and IGF-1R is likely upregulated in lung tissues of patients with ARDS related to COVID-19, contributing to tissue injury and fibrosis. Paradoxically, serum levels of IGF-1 will likely decline in more severe cases. Blockage of IGF-1R may mitigate lung injury and decrease the risk of death in patients COVID-19-related ARDS.

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## Supporting evidence

In the lung, Krein and colleagues found enhanced staining of IGF-1 and IGF-1R in specimens of patients with fibroproliferative ARDS compared to controls [11]. Schnapp demonstrated that IGF-1 is elevated in bronchoalveolar lavage (BAL) fluid from patients with early ARDS and provides a pro-survival signal for lung fibroblasts, but not lung epithelial cells [12]. This group later found that blockage of IGF-1R with an anti-IGF-1R monoclonal antibody (A12) led to decreased lung fibrosis, increased fibroblast apoptosis, and significantly increased survival compared to administration of a control antibody in a mouse model of bleomycin-induced lung injury [13]. They also found that late administration (day 14 after injury) of A12 also decreased lung fibrosis. Administration of A12 did not affect survival in control (no bleomycin injury) mice. The researchers found elevated levels of IGF-1 mRNA expression beginning within one day after bleomycin administration, peaking at day 7, and then decreasing, although never returning to baseline within the 28 days of the experiment. Similarly, Piñeiro-Hermida demonstrated that IGF1-R deficiency, using mice with a post-natally-induced IGF-1R gene deletion, was associated with improved survival, reduced vascular fragility and permeability, and less inflammatory cell lung infiltrate in bleomycin-induced lung injury [14].

A study by Ahasic and colleagues in 2012 found results, which at first glance, appear to be in opposition to the contributory role of IGF-1 and IGF-1R to the pathogenesis of ARDS. In this cross-sectional study of patients in the critical care unit with risk factors for developing ARDS, the researchers found that serum IGF-1 and IGF binding protein-3 (IGFBP3) were lower in patients with ARDS than in "controls" (patients with risk factors, but without ARDS). In addition, they found that serum IGF-1 and IGFBP3 levels were lowest in ARDS patients who ultimately did not survive. From these data, the researchers suggest that *increased* IGF-1 (rather than blockage of the IGF-1R) may be "protective in critical illness and development of ARDS." A limitation of this study is that the "controls" are not true healthy individuals without lung disease, but patients in the critical care unit with severe medical illness and significant risk factors for the development of ARDS. In addition, the study did not evaluate levels of IGF-1 in the lung (e.g., BAL fluid) in these patients.

A paper by Andonegui, et al. helps rectify the apparent disparities between Ahasic's findings and those of the previous studies discussed [8]. Andonegui showed that free IGF-1 appears to be high in the serum and low in the lung epithelial lining fluid early in acute lung injury (ALI)/early ARDS (patients with ALI/ARDS $<$ 24 h) but then shifts to high levels of IGF-1 in the epithelial lining fluid/low levels in the serum during late-stage, fibroproliferative ARDS (patients with ARDS $>$ 5 days). This increase in IGF-1 in the epithelial lining fluid in fibroproliferative ARDS appears to be both serum leak (consumption effect) into the lung tissue and production by local cells. In addition, fibroproliferative ARDS lung biopsy specimens showed high levels of IGF-1 mRNA, whereas IGF-1 mRNA was not detected in any of the control lungs biopsies. The lower serum levels of IGF-1 in late stage (and more often fatal) ARDS, is in keeping with Ahasic's findings, but the conclusions are quite different. Andonegui concludes that high concentrations of IGF-1 in the lung tissue (rather than low concentrations in the serum) are what is critical for the development of severe ARDS.

In November 2019, using a mouse model, Li and colleagues demonstrated that IGF-1 plays an important role in H1N1 influenza-related lung injury [7]. In their experiments, mice infected with H1N1 influenza virus (PR8) and treated with the IGF-1 receptor blocker picropodophyllin (PPP) had significantly less tissue damage and greater survival than infected controls. Furthermore, infected mice treated with additional exogenous IGF-1 had increased mortality compared with infected controls. Using Western blot, the researchers found that molecules in the phosphatidylinositol-3-kinases/protein kinase B (PI3K/AKT) and mitogen-activated protein kinase (MAPK) signaling pathways rose after N1H1 infection, further increased with the addition of IGF-1, but were reduced with IGF-1R blockade.

Extrapolating from these human and animal studies, we hypothesize that IGF-1 and activation of the IGF-1R are critical for the development of severe fibroproliferative ARDS in the setting of COVID-19 infection. We would expect to find serum concentrations of IGF-1 markedly elevated above normal levels early in COVID-19-related lung injury and then falling in later-stage and more severe disease. Conversely, concentrations of IGF-1 in BAL specimens would be anticipated to rise with increasing disease severity. Increased IGF-1 mRNA expression in lung tissues as well as increased staining for IGF-1R would be expected in more severe disease. Inhibition of IGF-1/IGF-1R would likely mitigate disease severity and decrease mortality.

## Future directions

Teprotumumab is a monoclonal antibody directed against the IGF-1R which was approved by the United States Food and Drug Administration (FDA) for the treatment of Graves' orbitopathy in 2020. In the FDA trials, teprotumumab had a benign safety profile and did not appear to increase risk of infection as many of the other biologics, including the IL-6 inhibitor tocilizumab, do [6,15,16]. While it may be tempting to start treating patients with COVID-19 with teprotumumab given the human and mouse evidence for the role of IGF-1 in the development in ARDS, additional data is needed. IGF-1 levels in serum and BAL fluid must be measured in patients with COVID-19-related ARDS. Lung tissue samples from patients with COVID-19-related ARDS must be evaluated for increased IGF-1 and IGF-1R mRNA expression and examined for increased IGF-1R staining on immunohistopathology, compared with controls. Once these are ascertained, and if the data support IGF-1 involvement, a randomized, placebo-controlled phase 2A trial of teprotumumab therapy in the setting of COVID-19-related ARDS and non-COVID-19-related ARDS designed to generate initial data on short-term efficacy, safety, dosing, and administration should be performed.

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## 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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