Blocking TNF signaling may save lives in COVID-19 infection

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Abstract
Global vaccination effort and better understanding of treatment strategies provided a ray of hope for improvement in COVID-19 pandemic, however, in many countries, the disease continues to collect its death toll. The major pathogenic mechanism behind severe cases associated with high mortality is the burst of pro-inflammatory cytokines TNF, IL-6, IFNγ and others, resulting in multiple organ failure. Although the exact contribution of each cytokine is not clear, we provide an evidence that the central mediator of cytokine storm and its devastating consequences may be TNF. This cytokine is known to be involved in activated blood clotting, lung damage, insulin resistance, heart failure, and other conditions. A number of currently available pharmaceutical agents such as monoclonal antibodies and soluble TNF receptors can effectively prevent TNF from binding to its receptor(s). Other drugs are known to block NFkB, the major signal transducer molecule used in TNF signaling, or to block kinases involved in downstream activation cascades. Some of these medicines have already been selected for clinical trials, but more work is needed. A simple, rapid, and inexpensive method of directly monitoring TNF levels may be a valuable tool for a timely selection of COVID-19 patients for anti-TNF therapy.

Keywords Covid-19 · Tumor Necrosis Factor (TNF) · NFkappaB · Cytokine storm · Immune therapy

Introduction
Respiratory distress and activation of blood clotting in severe COVID-19 cases result in unusually high mortality rates, particularly among people of advanced age and those that have comorbidities—cardiovascular or pulmonary disease, obesity, and diabetes. Severe disease is associated with “cytokine storm”, a delayed onset burst of pro-inflammatory cytokines in circulation. The cytokines associated with fatalities are TNF, IL-6, IL-8, IFNγ and possibly others [1]. It is difficult to identify the pivotal cytokine(s) in this process, but some facts argue in favor of TNF.

TNF is involved in pathogenesis of comorbidities linked to severe COVID-19 disease

Numerous pathologies are associated with elevated TNF levels, from autoimmune disorders to sepsis and cancer. In the respiratory system, TNF causes bronchial hyperreactivity, narrowing of the airways, damage to the respiratory epithelium, stimulation of collagen synthesis and fibrosis [2, 3]. Chronic obstructive pulmonary disease (COPD) is a known risk factor for severe COVID-19 disease [4]. Circulating TNF levels are increased in COPD [5]. The role of TNF in this disease has been suggested, and TNF inhibition was shown effective in lowering the incidence of hospitalization in one study [6] but did not improve health status and lung function in the other [7]. However, TNF blockage in COVID-19 patients with COPD may be advocated as a measure to reduce additive damage to already compromised lungs. In addition, pulmonary fibrosis is observed in a significant proportion of patients after acute COVID-19 pneumonia [8]. Although the role of TNF in this process is not established, there is evidence for TNF involvement in a closely related idiopathic pulmonary fibrosis [9]. Administration of anti-TNF drugs during the...
The ability of TNF to activate tissue factor on endothelial cells and monocytes and induce severe blood clotting during infection has been well documented [14–18]. TNF also inhibits fibrinolysis by increasing plasminogen activator inhibitor [19]. Reports on pro-coagulant activities induced by IL-6 are scarce [20, 21]. Increased blood clotting observed in COVID-19 patients is a well-documented complication requiring anti-coagulant therapy.

Both TNF and IL-6 levels are elevated with age: this chronic inflammation termed inflammaging is suggested to serve as a biomarker of frailty and mortality in elderly population [22]. Age-related loss of muscle mass and strength is particularly attributed to the action of TNF [23], and exposure of human cells to TNF in vitro can induce cell senescence [24]. Strong association of TNF with ageing may explain, to some extent, higher incidence of severe COVID-19 disease in patients of advanced age. Interestingly, mTOR inhibitor has been suggested recently for treatment of severe disease based on its ability to alleviate cytokine storm [25]. The drug is also known to improve longevity and reverse age-related immunosenescence in experimental animals, and its use in older adults may prevent age-associated complications of COVID-19 by poorly understood “rejuvenating” mechanisms [26]. On the other hand, the effects of mTOR inhibition may be reduced to a direct inhibition of TNF synthesis or signal transduction [27, 28].

Pro-inflammatory cytokines TNF, IL-6 and others are elevated in major depressive disorder, which is strongly associated with COVID-19 infection [29, 30]. TNF blockade using adalimumab in patients with rheumatoid arthritis with depression reduced serotonin transporter in the brain and improved the depression score [31]. On the other hand, a number of reports demonstrate anti-inflammatory effect of various antidepressants [30, 32]. Of interest is a retrospective multicenter study reported by a French group demonstrating that antidepressants reduce the risk of intubation and death in hospitalized patients with COVID-19 [33]. At least two clinical trials are currently underway to investigate the impact of this class of drugs on the disease outcomes (NCT04342663, NCT043777308).

Both TNF and IL-6 levels may serve as independent predictors of COVID-19 severity. However, only TNF but not IL-6 levels were higher in COVID patients with diabetes, hypertension, chronic kidney disease and chronic heart failure, thus providing a strong argument of TNF being a central factor for severe disease in these individuals [34]. In addition, in contrast to TNF, systemically administered IL-6 is fairly well tolerated [35], again suggesting that elevation of TNF rather than IL-6 is responsible for the pathology observed in complicated COVID-19 scenarios. Although some studies suggest that anti-IL-6 monoclonal antibody Tocilizumab is beneficial for the patients with severe COVID-19, other reports did not support that observation [36]. Similarly, clinical trials with Sarilumab, an IL-6 receptor blocker, did not meet primary and secondary endpoints in hospitalized COVID-19 patients [37]. Future clinical studies are believed to shed more light on particular roles of these two cytokines in the disease.

Factors that activate TNF

Various factors activate production of TNF. Signals from toll-like receptors (TLRs), T cell and B cell receptors to antigens (TCR, BCR), receptors to Fc fragments of immunoglobulins (FcRs), cytokines (IL-1, IL-2, IFNγ, GM-CSF, TNF itself), mitogens, superantigens, radiation, osmotic stress, high glucose levels, microbes and their products induce TNF [38]. TNF production in response to a “danger signal” is very rapid. Activation of innate immunity through pattern recognition receptors, such as TLRs, results in a rapid release of TNF which is followed by IL-6, and blocking TNF attenuates IL-6 levels, again, suggesting that IL-6 is a secondary cytokine in the cytokine cascade [39]. Single-stranded RNA of SARS-CoV2 should be recognized by TLR7, TLR8, and TLR3. It is of a particular interest that SARS-CoV2 has RNA genome of 30,000 bp, the largest among RNA viruses (for comparison, Influenza A virus has a genome of only 13,500 bp) [40]. One can speculate that the size of RNA may contribute to an enhanced innate immune response to the virus resulting in the cytokine storm.

Blocking TNF upstream of TNF receptors

TNF blocking agents have been used for two decades to treat various inflammatory conditions and have a good safety record. The most well studied are monoclonal anti-TNF neutralizing antibodies (mAbs) and soluble TNF Receptor (TNFR)-Fc fusion protein. Both drugs have FDA approval for treatment of several autoimmune diseases, and both drugs prevent interaction of TNF with its receptors TNFR1 and TNFR2. Anti-TNF drugs have been suggested.
for the treatment of SARS in 2004 [41], and accumulating evidence indicates that TNF blockade is beneficial for COVID-19 patients. First, a small study from Germany demonstrated a significant therapeutic effect of anti-TNF mNAb on the outcomes in severe COVID-19 cases in hospitalized patients [42]: mortality rate was 14% in anti-TNF-treated group compared to 35% in control group. Then, preliminary data of 600 cases from 40 countries have been published and indicated that anti-TNF monotherapy for rheumatic diseases was associated with a reduced risk of hospitalization of COVID-19 patients (odds ratio = 0.40) [43]. Later, a meta-analysis of more than 6000 cases revealed that TNF inhibitors administered to patients with immune-mediated inflammatory diseases alone were better protectors from severe COVID-19 associated hospitalizations and deaths than azathioprine/6-mercaptopurine or methotrexate [44]. Another study reported that TNF blockers administered to patients with rheumatoid arthritis and spondyloarthropathies significantly (by > 80%) reduced the risk of COVID-19 infection [45].

Moreover, based on the data from SECURE-IBD database a beneficial effect of anti-TNF mNAb was reported in COVID-19 patients with inflammatory bowel disease: namely, only 30 out of 198 (15%) patients with IBD receiving anti-TNF therapy required hospitalization for COVID-19, and only 3% of them died, whereas 67% IBD patients on steroid therapy were hospitalized and 25% of them died [44]. Finally, Kridin et al. recently analyzed outcomes of COVID-19 in patients with psoriasis treated with anti-TNF biologics and found that TNF blockade significantly decreased the risk of COVID-19 infection [45].

The major signal transduction pathway activated by TNF binding to its receptors involves nuclear factor kappa B (NFkB). Therefore, it is reasonable to suggest that many effects of TNF may be blocked at the level downstream of the receptors by NFkB inhibitors. In addition to mTOR inhibitor mentioned earlier, numerous known and potential drugs have been found to inhibit NFkB [46, 47]. Aspirin and sodium salicylate inhibit activation of NFkB by blocking IκB kinase [48]. Glucocorticoids suppress expression of inflammatory genes by binding glucocorticoid receptor with NFkB, and increasing expression of inhibitory protein of NFkB, IκBa. Sulfasalazine and gold compounds also inhibit NFkB activation and were suggested for treatment of rheumatoid arthritis [49].

Well known cardiac glycosides inhibit NFkB which in turn decreases production of inflammatory cytokines [50]. These drugs also demonstrate anti-viral activity to SARS-CoV-2 by inhibiting membrane Na–K ATPase, used by RNA viruses for entering the cell, and by inhibiting translation, which makes them very attractive in COVID-19 patients with cardiac insufficiency [51–53].

Nifedipine, a blocker of calcium channels used as an antihypertensive also inhibits NFkB. In an experimental rat model of vascular lung leakage induced by high altitude hypoxia, a condition that has much in common with pulmonary damage in COVID-19 patients, the drug inhibited vascular leakage, oxidative stress, and reduced inflammatory cytokine production [54].

Another class of antihypertensive drugs, ACE inhibitors, also suppress NFkB and inflammation, reduce blood pressure, and limit viral entry [55, 56]. This is particularly interesting since ACE2 is the major receptor for SARS-CoV-2 Spike glycoprotein, and several studies demonstrated that the use of ACE inhibitors was associated with a reduced risk of severe COVID-19 disease, morbidity, and mortality probably due to a direct inhibition of viral Spike protein binding to ACE2 [57, 58].

Bortezomib is a proteasome and NFkB inhibitor used for treatment of multiple myeloma [59]. It has been recently suggested that this class of drugs may also be used as a therapy for COVID-19 because it interferes with SARS-CoV-2 entry into eucaryotic cells, inhibits RNA and protein synthesis and viral replication, induces endoplasmic reticulum stress, and alleviates cytokine production [60].

A large group of kinase inhibitors initially introduced for treatment of malignancies should also be considered. Tyrosine kinase inhibitor imatinib, for instance, has been shown to down regulate several inflammatory cytokines and NFkB levels [61, 62]. A successful case report on administration of imatinib for treatment of a progressing COVID-19 pneumonia has been published recently: 3 days after administration of the drug at 400 mg once daily, the patient’s body temperature normalized, and oxygen treatment was discontinued. The patient was discharged on day 16 and remained asymptomatic with a significant improvement on chest radiograph on day 20 after discharge [63].

Janus kinases (JAKs) participate in signal transduction following cytokine binding to their receptors, including pro-inflammatory cytokines [64]. JAK inhibitors have been shown to reduce serum IL-6, IFNγ, IL-1, IL-17 and TNF levels in a way similar to TNF blockers in patients with rheumatoid arthritis and ulcerative colitis [65–67]. In vitro, they inhibit TNF-induced NFkB activation in human macrophages [68]. JAK inhibitors have also been suggested as a novel therapy for COVID-19 and have been used by several

**Blocking TNF signals downstream of TNFRs**

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groups based on their ability to reduce both viral entry and cytokine production [69]. Beneficial effects of JAK inhibitors in human disease have been reported, including reduction of TNF and other cytokine levels [70, 71]. Baricitinib in combination with antiviral Remdesivir has been issued an emergency authorization by FDA as a treatment for hospitalized patients [72–74]. Noteworthy, another JAK inhibitor added to standard therapy has been reported effective in hospitalized COVID-19 patients with pneumonia in a multicenter randomized, placebo-controlled trial: the cumulative incidence of death or respiratory failure through day 28 was 18.1% in the JAK inhibitor group and 29.0% in the placebo group (risk ratio, 0.63; 95% confidence interval [CI], 0.41–0.97; P = 0.04) [75].

Who should receive anti-TNF therapy, and when?

The most optimal biomarker for use as a criterion to start anti-TNF/anti-NFkB/anti-kinase therapy is yet to be established. Direct measurement and subsequent monitoring of circulating TNF levels using express tests, such as currently unavailable immunochromatography, seems to be the method of choice, since it can be used in an outpatient setting. However, other biomarkers such as IL-6 may be used as long as they reflect the brewing of cytokine storm. The decision to initiate anti-TNF therapy should be made in COVID-19 patients admitted to the hospital [76] and considering each patient’s presentation of symptoms and complications. Clinical trials on TNF blockade have started in Oxford and Tufts Universities, but more studies could significantly advance our understanding of which of a variety of available drugs are most likely to improve outcomes [76–78]. Although TNF/NFkB inhibitors are considered relatively safe even when administered in a long term, a safety concern should always be kept in mind considering TNF inhibitors are immunosuppressive.

Concluding remarks

- TNF is involved in pathogenesis of severe COVID-19 and may play a central role in “cytokine storm”.
- TNF or its downstream mediators may be inhibited by administration of existing drugs: direct TNF binders, NFkB blockers, and kinase inhibitors.
- Clinical trials are urgently needed to test different TNF/NFkB/kinase inhibitors for treatment or prevention of severe COVID-19 cases, and to establish indications and end-point criteria for such treatment.
- Rapid tests like lateral flow/immunochromatography for measurement of TNF or other biomarkers may be invaluable tools for timely assessment of patients and decision making in administration of TNF inhibitors.
- Although this paper may seem biased towards the benefits of anti-TNF therapy, the bias is intentional, as the review aims to draw attention of the reader to a possible role of TNF in COVID-19. The limited space did not allow us to extensively discuss other aspects of COVID-19 pathogenesis.
- In heterogeneous human population, TNF may be up-regulated to a different degree, and its detrimental effects may be different due to different sensitivity of each individual, comorbidities, and other factors. Currently, it is difficult to establish any threshold after which an individual patient will inevitably deteriorate. Probably, the only way of learning that is a clinical trial, as mentioned earlier.

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