



# A Brief Overview to TNF- $\alpha$ Inhibitors Therapy on Covid-19: Functions Inside Cell Cascades

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## Abstract

Viral Covid-19 has spreaded all over the World only in a few months and caused much deaths. Covid-19 is belong to coronavirus family (called also SARS-CoV-2). Virus entry into cell occurs by unification with membrane receptors by releasing viral capsids or by endocytosis. TNF inhibitors aim to block receptors that bind to intracellular pathways as soluble form or by membrane bounding. Some TNF- $\alpha$  inhibitors have been used on severe Covid-19 patients nowadays.

**Keywords:** Receptor; Cell; Covid-19; Inhibitors

## Introduction

SARS-CoV-2, also named Covid-19, was emerged firstly in Wuhan, China at the end of November, 2019 and began to spread as a pandemic viral-infected illness all over the World. Originally, it is a type of coronaviruses. Coronaviruses are belong to Coronaviridae family and positive single stranded RNA viruses encircled with an envelope [1]. Generally they are divided into 4 groups as alpha ( $\alpha$ ), beta ( $\beta$ ), gamma and delta ( $\delta$ ) coronaviruses [2]. SARS-CoV (severe acute respiratory syndrome coronavirus) is a type of the Alphacoronavirus genus [3] and emerged firstly in late 2002 in China as a characteristic pneumonia [4]. As reported previously, SARS viruses are mostly fatal therefore, highlighting of the pathological disorders of SARS is very important [4]. Apoptotic and MAPKs (Mitogen Activated Protein Kinases) activations play significant role in SARS-CoV viral infections [4,5-7]. Several in vitro and in vivo studies showed that MAPK signal cascade may inhibit viral infections (SARS-CoV-infections) by involving in apoptosis or regulating extracellular cytokine activation [4]. Virus penetration inside cell takes place by fusion with membrane by releasing viral mirids or by endocytosis [8,9]. Recent studies showed that during transmission of human SARS-CoV viruses, Covid-19 (SARS-CoV-2) also uses the same receptor for angiotension converting enzyme (ACE2) [10]. This mini review targets to emphasize the importance

of relationship between TNF (Tumor Necrosis Factors) inhibitors and intracellular signal transduction mechanism on Covid-19.

## Tnf Inhibitors

Tumor Necrosis Factors (TNF) are generally known as proteins that are responsible from killing malign cells; among them especially TNF- $\alpha$  and TNF- $\beta$  are cytokines and have same receptors. They play important role on autoimmune diseases. Biological effects of TNF against disease depend on speed of stimuli in response [11]. Responses contain fever, shock, tissue and organ (especially lung in coronaviruses) injury, tumor necrosis, anorexia, induction of other cytokines and immunoregulatory molecules, cell proliferation, differentiation, and apoptosis [11,12]. Also, TNFs are so important in initiation and enhancing inflammation on Covid-19 patients [6]. According to the latest studies, pathological disorders of lung of Covid-19 patients showed capillary fluids are outflowed and immune-inflammatory lymphocytes, neutrophils, and macrophages are enlisted [13]. FDA approved some important TNF-inhibitors for treatment of inflammatory diseases about 20 years ago [14]. Therefore, clinical researchers are tend to search on novel TNF inhibitor molecules [14,15]. Some TNF inhibitor molecules was shown in Table 1 and a few of them are used thesedays for the treatment of Covid-19.

**Table 1:** Table of signal target, action mechanism and administration of some TNF-inhibitor drugs.

TNF-Inhibitors	Cellular Signaling	Action Mechanism	AdminisTration	Ref.
Infliximab	chimeric (mouse-human) antibody 2 (cA2)-apoptosis in TNF-expressed cells via caspases, and neutralizate soluble TNF- $\alpha$	holds to TNF- $\alpha$	infusion	Mauser and Hyams [21], Arnaldez, O'Day [17]]
Adalimumab	human monoclonal antibody- apoptosis in TNF-expressed cells via caspases	holds to TNF- $\alpha$	subcutaneous injection	Lügering, Schmidt [21], Mitoma, Horiuchi [13], Arnaldez, O'Day [17]]
Tocilizumab	inhibits IL-6-mediated signaling	holds to TNF- $\alpha$ and IL (Interleukin)-6 receptors	intravenously (IV) or subcutaneously	Gerriets, Bansal [24], Arnaldez, O'Day [17], Feldmann, Maini [14], Rahmati and Moosavi [15]]
Etanercept	TNF-R2 (Tumor Necrosis Factor 2) fused to human IgG1 Fc-it can be potentially antiseptic for Covid-19 patients	holds both to TNF- $\alpha$ and TNF- $\beta$	subcutaneous injection	Gerriets, Bansal [24], Arnaldez, O'Day [17], Feldmann, Maini [14]]
Golimumab	human monoclonal antibody- apoptosis in TNF-expressed cells via caspases	holds to TNF- $\alpha$	intravenously (IV) or subcutaneously	Gerriets, Bansal [24], Arnaldez, O'Day [17], Feldmann, Maini [14]]
Sarilumab	inhibits IL-6-mediated signaling	binds to IL-6 receptors	subcutaneous injection	Gerriets, Bansal [24], Arnaldez, O'Day [17], Feldmann, Maini [14], Rahmati and Moosavi [15]]
Ruxolitinib	JAK1 and JAK2	JAK/STAT inhibitor, and binds to IFN $\gamma$ (Interferon)	oral administration	Gerriets, Bansal [24], Ali, Salhotra [3], Arnaldez, O'Day [17], Feldmann, Maini [14], Rahmati and Moosavi [15]]

Among cytokines, IL-6 is the key receptor in severe Covid-19 patients. Coronavirus spike proteins contribute to increase of IL-6 production in immune and epithelial cells [2,16]. Tocilizumab and sarilumab block the activation of IL-6 receptor and under clinical phase studies. Turkey, China (21 severe trial), a case from France and Iran treat ICU (Intensive Care Unit) Covid-19 patients with tocilizumab and showed successful performance [17]. Fever and respiratory disorders began to improve in patients after a few days [12,15,18,19]. According to updated output number Covid-19 patients (on 22<sup>th</sup> May 2020) in Turkey, mortality rate has diminished vigorously (to 27) and also ICU and entubated patients are decreasing day by day. These data showed that treatment strategy was discovered successful in Turkey.

TNF- $\alpha$  can be in soluble or membrane bound form. Cell signaling of TNF- $\alpha$  in Covid-19 is complex and react with several tumor necrosis factor receptors [17]. Multiple signal cascades activate JAK (Janus kinase) and STAT (Signal transducer and activation of transcription). On account of this pathway activation PI3K activation initiates and destroyed cells begin to proliferate, survive, differentiate and pro-inflammatory transcription takes place. Ruxolitinib is a type of IL-6 receptor blocking molecule and inhibits JAK/STAT signaling pathway by binding to IFN $\gamma$  [17]. It can be also potential molecule like other IL-6 inhibitor molecules for treatment of critical Covid-19 patients and also may be used as combinetherapy with other antiviral compounds [20-24].

## Conclusion

Covid-19 has become a serious pandemi for months, there is no direct therapy for patients so clinical researchers need urgent treatment plan. Latest studies showed that TNF- $\alpha$  inhibitors could be potential candidate for spesific therapy, because mortality rate showed that cancer, diabetes and immunological disorders patients are tend to have more respiratory problems than the other. Some pathological problems cause sepsis into cell pathway. Therefore novel TNF- $\alpha$  inhibitors especially targetting apoptotic pathways (for elimination of destroyed cells) and IL-6 receptors (for blocking interleukins) could be potential candidate for the treatment of Covid-19. Highlighting the pathway mechanism behind virus penetration into cell is crucial in order to select correct drug for therapy.

## Conflicts

There is no conflicts.

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