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TNFα inhibitor may be effective for severe COVID-19: learning from toxic epidermal necrolysis

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***Abstract*:** Increased inflammatory cytokines [such as tumor necrosis factor alpha (TNFα) and interleukin-6 (IL-6)] are observed in COVID-19 patients, especially in the severe group. The phenomenon of a cytokine storm may be the central inducer of apoptosis of alveolar epithelial cells, which leads to rapid progression in severe group patients. Given the similarities of clinical features and pathogenesis between toxic epidermal necrolysis (TEN) and COVID-19, we hypothesize that the application of etanercept, an inhibitor of TNFα, could attenuate disease progression in severe group COVID-19 patients by suppressing systemic auto-inflammatory responses.

The reviews of this paper are available via the supplemental material section.

Keywords: COVID-19, toxic epidermal necrolysis, TNFα inhibitor, etanercept

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Introduction

Since 8 December 2019, an ongoing outbreak of a novel coronavirus disease (COVID-19, previously called 2019-nCov) was reported in Wuhan, China.[1,2] The infection spread rapidly across China, and in fact, to date, 76 other countries have also reported cases. In addition, the World Health Organization determined on 30 January 2020 that the spreading outbreak constitutes a Public Health Emergency of International Concern (PHEIC). By the 6 April 2020, 1,174,866 confirmed cases had been documented worldwide.[3] In general, COVID-19 is an acute resolved disease, but it can also be deadly, with a 2% case fatality rate. Although most patients exhibit mild symptoms, like fever, fatigue and dry cough, around 15–20% patients quickly became severe cases that had respiratory difficulty and failure.[4] The severe group and the more severe group show a higher mortality rate, caused mostly by multiple organ function damage,[5] so effective therapies for improving the survival of critical patients are necessary for current treatment.

Toxic epidermal necrolysis (TEN) is a life-threatening systemic disease caused by immune system hypersensitive reactions. The classification of TEN is $>30\%$ sheet-like epidermal detachment of body surface involvement, and drug hypersensitivity is responsible for 85–90% of cases of TEN.[6] Although TEN is a mucous cutaneous failure, multiple organs, such as trachea, bronchi, lungs, etc., are also involved. Tumor necrosis factor alpha (TNFα) is tightly involved in the pathogenesis of TEN, and recent studies have shown that Etanercept, an inhibitor of TNFα, could successfully decrease the mortality of TEN.[7]

In this short review, we provide a brief comparison of the clinical features, pathology, and pathogenesis between severe COVID-19 and TEN. Thus, we extrapolate that targeting TNFα might provide a potential treatment for early/middle stages of severe cases of COVID-19.

Etiology and clinical features

COVID-19 is caused by a beta coronavirus belonging to the same family as SARS coronavirus (SARS-CoV) and MERS coronavirus (MERS-CoV) but independent from them. This novel coronavirus is thought to be the causative agent of the emerging pneumonia in Wuhan, China. The COVID-19 infection is a clustering onset and

transmissive disease. Most patients infected had fever, cough, myalgia, or fatigue.[5] For the diagnosed severe group, rapidly progressing comorbidities, such as acute respiratory distress syndrome (ARDS), septic shock, metabolic acidosis, and dysfunction of coagulation, were found.[8] From experimental analysis, leucopenia (white blood cell count less than 4×10^9/l) and lymphopenia (lymphocyte count $< 1.0 \times 10^9$/l) are the most common phenomena, which are almost consistent with results in TEN. Some inflammatory markers in serum, like C-reactive protein and D dimer, are also consistently elevated in both diseases.[9] Further comparison between intensive care unit (ICU) and non-ICU patients showed that the concentrations of TNFα; interleukins-2, -7, and-10 (IL-2, IL-7, IL-10); granulocyte-colony stimulating factor (GCSF), interferon gamma-induced protein 10 (IP10), monocyte chemoattractant protein-1 and 1A (MCP1, MIP1A) in plasma were increased in ICU patients (always in severe group). These cytokines are probably leading to an activated T-helper-1 (Th1) and activated T-helper-2 cell response.[5]

Drug hypersensitivity is responsible for most cases of TEN, but a perspective article pointed out that virus-induced and autoimmune forms of epidermal necrolysis, not related to drugs, should also be focused on.[10] Fever is often the first symptom, and sore throat, cough, red eyes, and tender and pink skin are other early symptoms.[11] Although typical manifestation of TEN is epidermal necrolysis failure, some parts of its early stage are similar to COVID-19. Besides, pulmonary dysfunction also was reported in patients with TEN, which also could lead to ARDS, shock, and electrolyte disturbances. The mortality rate of TEN ranges from 20% to 30%, whereas in COVID-19-related very severe cases it is 49%.[12] Overall, severe group SARS-CoV-2 and TEN are both systemic diseases with similarities in clinical features.

Pathology and pathogenesis

The available pathology of COVID-19 was obtained from autopsy or biopsy. Recent articles have reported pathologic results of mild and severe groups of COVID-19 pneumonia. One article reported two cases who were in pulmonary malignancy surgery and were later found to be infected with COVID-19, which could provide some clues in histological analysis of the early stage of infection. The presence of focal hyperplasia of pneumocytes and interstitial thickening indicates an ongoing recovering process. This historical analysis also showed acute lung injury symptoms, such as edema and inflammatory cells infiltration, indicating an earlier stage of the disease.[13]

Another pathological study revealed evident hyaline membrane appearance and pulmonary edema formation, which suggested ARDS. Bilateral diffuse alveolar damage with massive exudation was also detected by histological examination. Interstitial thickening with inflammatory cells infiltration of monocytes were found in hematoxylin and eosin (HE) staining. Plus, flow cytometry analysis of peripheral blood cells implied that over-activated T cells, illustrated by an increase of Th17 and the high cytotoxicity of $CD8^+$ T cells, may partly explain the severe immune injury in this patient. In the light of the pathology of this severe case, timely and proper corticosteroids and ventilator support are recommended to slow down progression of disease complications.[14] According to the "Guidelines for the Diagnosis and Treatment of COVID-19 (Trial Version 7)" announced by the National Health Commission of the People's Republic of China, histological examination revealed obvious alveolar damage and mononuclear inflammatory infiltration, which may be the result of alveolar epithelial cell necrosis. Besides, type II alveolar epithelial cells proliferated significantly, and some cells were shed. Viral inclusions can be identified in type II alveolar epithelial cells and macrophages. There was vascular congestion and pulmonary edema with mononuclear and lymphocyte infiltration and intravascular hyaline thrombus in alveolar septal. Lung tissue hemorrhage and necrosis with hemorrhagic infarction were also seen.[15]

For virus interaction in pulmonary epithelial cells, COVID-19 represented a more transmissive trend due to the fact that COVID-19-S protein supports stronger interaction with human angiotensin-converting enzyme 2 (ACE2) molecules than SARS-CoV.[16] Because ACE2 molecules are located in extensive organs and tissues, multiple systems might be involved in the infection.

Similarly, the immunopathogenesis of TEN is associated mainly with $CD8^+$ cytotoxic T cell activation in the epidermis, along with other

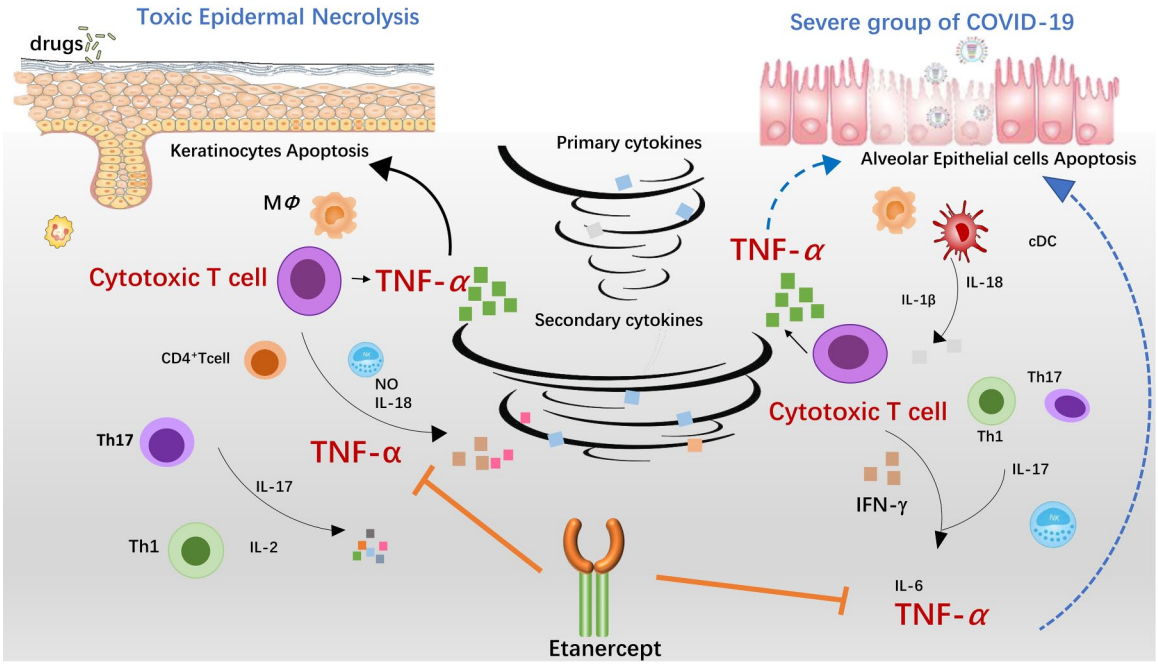

Figure 1. Cytokine storm after coronavirus/drugs stimulation, inhibited by etanercept.
After internalization into alveolar epithelial cells/keratinocytes, virus/drugs could be detected by innate immune sensors and trigger downstream immune responses, including tremendous cytokine production, called the "cytokine storm". The process of cytokine storm could mediate the apoptosis of epithelial cells in lung and skin.
cDC, myeloid dentritic cell; IL, interleukin; IFN, interferon; NO, nitric oxide; TNF-α, tumor necrosis factor alpha.

immune cells. $CD8^+$ T cells in TEN are theorized to be a central inducer in keratinocytes apoptosis,[17,18] which can be compared with $CD8^+$T cells, accounting for the inflammatory reaction in pulmonary epithelial cells. $CD4^+$T cells in the epidermis and dermis also play a role as a stimulator for various immune cells, contributing to TNFα and interleukin 8 (IL-8). Keratinocytes were activated by interferon-gamma (IFN-γ) and TNFα were shown to undergo self-apoptosis. The historical results of COVID-19 severe patients suggested diffuse alveolar damage. Therefore, we have an assumption that the apoptosis of pulmonary epithelial cells might be due to cytokines secreted by immune cells.

Over-activated T cells secrete numerous types of cytokines, which is known as a hyper-cytokinemia or a "cytokine-storm". These effects can drive and perpetuate the pathogenesis of TEN. The immunopathological mechanism of the severe group of SARS-CoV-2, especially younger patients, was also assumed to involve virus-induced cytopathic effects. The perspective theory is that acute lung injury and rapid progression in patients, especially elder patients, were dominated by an inflammatory cytokines storm (Figure 1). How to inhibit the inflammatory cytokine storm in both COVID-19 and TEN deserves more suggestive measures and experiments.

Treatments

According to the pathogenesis of TEN, and the finding of $CD8^+$Tcell-mediated cytotoxicity and cytokine expression (especially TNFα), inhibitors of TNFα were applied to treat TEN. Previous studies reported that etanercept may halt the progression of skin detachment, mediating re-epithelialization.[19] A randomized controlled trial confirmed that etanercept improved clinical outcomes in patients with TEN by decreasing predicted mortality and skin healing time compared with corticosteroid groups (conventional treatment). According to immunologic research, granulysin and TNFα expression levels decreased significantly with increased Treg population in the etanercept group compared with the corticosteroid group.[20] The pathology of severe group COVID-19 pneumonia revealed that immune cells, especially $CD8^+$T cells and Th17, were connected with the pathogenesis of the disease. A study of 1099 patients with laboratory-confirmed Covid-19 showed that a majority of patients

(58.0%) received intravenous antibiotic therapy, and 35.8% received antiviral therapy (Oseltamivir). Besides, oxygen therapy was administered in 41.3%, which was applied more in severe COVID-19 pneumonia patients.[21] Although previous routine treatments of COVID-19 pneumonia were antibiotic and antiviral drugs and oxygen therapy, the efficacy of antiviral treatments is controversial and the abuse of antibiotic drugs should be avoided.

For the severe and more severe groups, measures like mechanical ventilation, glucocorticoids, and intravenous immunoglobulin were chosen to delay the progression of this disease.[9] However, some experts do not support corticosteroid treatment for COVID-19 lung injury due to delayed clearance of viral RNA in SARS and MERS.[22]

We proposed use of etanercept temporarily in treating the severe group of COVID-19 due to the similarity to TEN in clinical symptoms and pathogenesis. The suggested usage of etanercept is 50–100 mg intracutaneously per week, with emphasis on side effects like tuberculosis infection or delayed viral clearance.

Outlook

The comprehensive lessons from TEN provide valuable insights on how to fight the COVID-19 epidemic, despite the similarities and differences between the two diseases (Table 1). Treatments that restrain over-activated inflammatory responses may ideally reduce the progression of virus-mediated immune-pathogenesis. Although, up to now, use of etanercept in COVID-19 pneumonia

Table 1. Differences and similarities between severe group of COVID-19 and TEN.

		Severe group of COVID-19	TEN
Etiology		A novel coronavirus	Drugs with/without infection
Target organ		Lung	Skin, mucous
		Both arise from epithelial tissues	
Clinical manifestations	Specific symptoms	Fever (rarely not)	Fever (rarely not)
		Hypoxemia / shortness of breath	>30% of the body surface area confluent purpuric macules with blisters and erosions
		ARDS	Epidermal sloughing with exudation
	Nonspecific symptoms	Septic shock	Secondary infection, septic shock
		Metabolic acidosis	Metabolic acidosis
		Dysfunction of coagulation	Dysfunction of coagulation
		Lactate dehydrogenase, liver enzymes (AST, ALT), muscle enzymes increased	Lactate dehydrogenase, liver enzymes (AST, ALT), muscle enzymes increased
Laboratory findings			
Leucocytes		– /↓	– / ↓
Lymphocytes		↓	↓
C-reactive protein		↑	↑
Procalcitonin		–	–
Troponin		↑	↓
D-dimer		↑	↑

(Continued)

Table 1. (Continued)

	Severe group of COVID-19	TEN
Pathological results	Alveolar damage with cellular fibrin exudate and hyaline membrane formation	A massive epidermal necrosis separated from dermis
	Interstitial mononuclear inflammatory infiltrates, dominated by lymphocytes and macrophages	Dermal inflammatory infiltrate, lymphocytic infiltration in dermal / epidermal junction
	Viral inclusions can be identified in type II alveolar epithelial cells and macrophages	
	Vascular congestion and pulmonary edema with mononuclear and lymphocyte infiltration	
Pathogenesis	Over-activation of T cells, featured by increase of Th17 and high cytotoxicity of $CD8^+$ T cells,	Activation of cytotoxic $CD8^+$ T cells and NK cells
	Th1/Th2 responses?	Genetic linkage with HLA- and non-HLA-genes
	Alveolar epithelial cells apoptosis?	Keratinocytes apoptosis
Common ground	Both are caused by apoptosis and necrosis of epithelial tissues, cytokines storm (including TNFα) involved	
Therapy		
Anti-virus therapy	No effective medicine	—
Intravenous immunoglobulin	Nonspecific treatment	Nonspecific treatment
Corticosteroids	Nonspecific treatment	Nonspecific treatment
Supportive care	Nonspecific treatment	Nonspecific treatment
Etanercept	Not applied in treatment	Target TNFα, very effective
Advantages of etanercept	No clinical evidence, suggest etanercept could improve symptoms in early stage of COVID-19 patients	Halt the progression of skin detachment, mediate the re-epithelialization
Side effect	Delayed clearance of novel coronavirus, recommend temporary application	Tuberculosis infection, chronic hepatitis B virus activation does not have side effect in temporary application
Suggestion	For early and middle stage of severe group of COVID-19 patients, 50–100 mg intracutaneous per week, two times in all. Or choose another TNF monoclonal antibody	

Increased (↑) means over the upper limit of the normal range and decreased (↓) means below the lower limit of the normal range, (–) means in the normal range.
ALT, alanine transaminase; AST, aspartate transaminase; NK, natural killer; TEN, toxic epidermal necrolysis; TNF-α, tumor necrosis factor alpha.

lacks sufficient evidence, we believe it is imperative to report our assumption of a better attempt at treating severe group COVID-19 related disease. Compared with SARS and MERS, there are currently no specific drugs that can clear virus completely. Therefore, further experiments and efforts should be taken to identify therapeutic targets of etanercept by conducting a prospective, open-label, randomized comparison study of etanercept *versus* supportive care.

Author contribution(s)

Xue-Yan Chen: Conceptualization; Formal analysis; Resources; Writing-original draft.

Bing-Xi Yan: Conceptualization; Resources; Writing-original draft.

Xiao-Yong Man: Conceptualization; Funding acquisition; Writing-review & editing.

Conflict of interest statement

The authors declare that there is no conflict of interest.

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Supplemental material

The reviews of this paper are available via the supplemental material section.

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