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Comment & Opinion

The severe COVID-19: A sepsis induced by viral infection? And its immunomodulatory therapy

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ABSTRACT

COVID-19 is known for its magical infectivity, fast transmission and high death toll based on the large number of infected people. From the perspective of the clinical manifestation, autopsy examination and pathophysiology, the essence of COVID-19 should be viewed as a sepsis induced by viral infection, and has the essential characteristics as sepsis induced by other pathogens. Therefore, in addition to etiological and supportive treatment, immunomodulatory therapy is also appropriate to severe COVID-19. Although there is still a lack of consensus on immunotherapy for sepsis so far, relatively rich experiences have been accumulated in the past decades, which will help us in the treatment of severe COVID-19. This article will elaborate immunotherapy of sepsis, though it may not be consistent.

In late 2019, COVID-19 ravaged Wuhan, China, and then spreads rapidly to the whole world. This outbreak has led to hundreds of thousands people being killed to date, huge economic losses and public panic. What's the COVID-19 pathophysiological essence of COVID-19? How to treat it more effectively? This is a great challenge to global medical and public healthcare systems. COVID-19 is known for its magical infectivity and the speed of transmission, but its essence is worth to be explored that will more effectively guide the treatment. This paper will expound from several aspects.

Clinical manifestation and autopsy discovery

Major clinical symptoms of COVID-19 are fever, fatigue, cough, and breathing difficulties.[1,2] Some critical patients need mechanical ventilation or extra-corporeal membrane oxygenation. If severe enough, shock and multiple organs failure will occur, which require other corresponding supportive treatment. Hematological examinations presented hypoxemia, elevated cytokines and C-reactive protein (CRP), abnormal liver and myocardial enzymes, decreased lymphocytes, declined platelets and increased D-dimmer. Imaging shows that there is a significant inflammatory infiltration and part consolidation of the lungs. Pathogens tested positive for 2019-nCoV, and accompanied with or without evidences of bacterial infection. Elderly patients are at high risk of critical illness and death. At present, the data of autopsy were mainly from a small number of elderly patients who died. Owing to lack of formal literatures published, the limited information mainly obtained from some conferences and information reports on the internet. The lungs bear the most severe damage, i.e. serious inflammatory cells infiltration, a large amount of exudation, hyaline membrane, part fibrosis, even bleeding and necrosis. Heart, liver, kidney and other organs also have different degrees of inflammatory response and damage. Spleen and lymphatic tissue reveal serious atrophy. There may be disseminated intravascular coagulopathy (DIC), etc. The above symptoms are similar to sepsis caused by bacterial infections. It is reasonable to speculate that the essence of severe COVID-19 is a sepsis induced by viral infection, which has the all hallmarks of sepsis including specific pathogen (2019-nCoV), severe systemic inflammatory response (so-called inflammatory storm), deep immunosuppression (lymphocyte depletion and lymphatic tissue atrophy) and multiple organs failure, even persistent inflammation, immunosuppression, and catabolism syndrome (PICS) in some patients.

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What's the sepsis?

Sepsis is defined as infection causes the maladjusted response of body and the deadly organ failure, which is a common syndrome in critical patients and the most serious threat to the prognosis in that patients.[3] The pathogens can be bacteria, fungi, viruses or other microbes. As early as the 19th century, Osler, the father of modern medicine, had pointed out that disease was an undesirable reaction of body to the pathogenic agents. Although over one hundred years passed, it is still a great help for us to understand many diseases, especially the pathogenesis of sepsis.

The human immune system has the ability to protect the body from foreign substances invasion. When the body detects an invasion of foreign antigens, it mobilizes the immune system and other cells such as endothelial cells, epithelial cell, fibroblast, mastocyte, etc. through the pathogen associated molecular pattern/damage associated molecular pattern pathway to release and activate a variety of pro-inflammatory substances, including pro-inflammatory cytokines, cytotoxic proteases, oxygen radicals, antibodies, activated complement and clotting factors, etc. creating a so-called "cytokine storm".[4,5] The occurrence of inflammatory storm in severe COVID-19 has been a wide argument in clinicians.[6,7] In fact, inflammatory storms are not unique to COVID-19, but also in other respiratory viral infections, such as influenza, SARS, avian influenza, swine flu and MERS, etc.[8–11] COVID-19 is just a new member following them.

Though inflammatory response can certainly help to kill and clear pathogens, it also may damage normal tissue and cells. Excessive inflammatory reactions will lead to a series of significant pathological changes, such as coagulation activation and DIC, mitochondria damage, cellular apoptosis, immunosuppression, increase of vasopermeability and hypermetabolism, etc. To alleviate the excessive inflammatory response, immune system weakens the ability of antigen present cell, increases Treg cell, accelerates lymphocytic apoptosis, induces immune checkpoints, and releases large amounts of myeloid-derived suppressor cells, and so on,[12–14] thus immune suppression is formed. The biological significance of immune suppression is to enhance the tolerance to inflammation and pathogens loading of the body.

Inflammatory response and immune suppression occur almost simultaneously, but their actions are contradictory as two sides of a coin. Both moderate inflammatory response and immune suppression are the body's adaptive protection mechanism, which are beneficial. Along with the elimination of pathogens, the body will eventually restore to a normal state. However, if the inflammatory response or/and immune suppression are excessive and uncontrolled, this protective compensation is transformed into a destructive and decompensated status, sepsis then develops. With sepsis, some patients die from early over-inflammation reactions, many of whom go into a chronic course with persistent low intensity inflammation, deep immunosuppression and metabolic failure, known as PICS or chronic critical illness.[15–17] In that, patients are repeatedly attacked by unexpected variety of infections, resulting in a very high mortality following extended observation time, which is similar to a "boiling a frog in warm water" state.

The mortality rates of severe COVID-19 and other critical diseases are higher in the elderly group than in other age groups.[18–20] Why? In addition having more underlying chronic diseases, the elderly are also at high risk for sepsis. Angus et al.[21] speculated an overall incidence of sepsis was 3/1000, but 26.2/1000 in the elderly (>85) years old, and the mean age of severe sepsis was 63.8 years old. Martin et al.[22] published data from 500 hospitals in the US, showing that patients over 65 years old accounted for about 12% of the total hospitalized population, but accounted for 65% of sepsis (relative risk = 13.1). Why are the older patients more likely to get into sepsis? Immunosenescence is an important factor that causes internal stability imbalance and a higher baseline level of inflammation named as "inflamm-ageing".[23–25] As a result, the aging patients are far less resistant to inflammatory attacks, more difficult for treatment, and have a higher risk of death than younger patients.

The characteristics of sepsis in severe COVID-19

Although severe COVID-19 is speculated to be a sepsis induced by SARS-CoV-2, it does have some characteristics different from the sepsis induced by bacteria that we are familiar with.

In bacterial infection, a violent inflammatory response is often triggered quickly by bacteria. However, early invasion of 2019-nCoV does not cause an obvious inflammatory response because of its concealment of antigenicity, until it is replicated in a large number within cells, and then released. It creates an incubation period different from common bacterial infections, and has a relatively chronic course. However, if the virus is explosively released, it must appear the violent inflammatory which may explain a phenomenon posed by some clinicians: a few patients seemingly stable may suddenly deteriorate and die within a very short period of time.

It also has been observed that there was a low level of pro-inflammatory cytokines in a few cases. Can inflammatory response be ruled out in them? Perhaps it is resulted from deep suppression of immune cells, since a large number of pro-inflammatory cytokines are derived from these cells. It should be emphasized that the inflammatory response is never driven alone by pro-inflammatory cytokines, but also by many stressful or damaging products,[26–28] such as heat shock proteins, high mobility group proteins, activated thrombin, cellular contents, mitochondria, etc. They are released by different cells under attack by pathogenic agents, then initiate and promote the inflammatory responses. Those substances are not yet routinely tested clinically as indexes of inflammatory response currently. Strong evidence of a systemic inflammation in severe COVID-19 is the mysterious decline in lymphocytes and the severe atrophy of lymphatic organs. According to the current understanding, the inflammation response is the one of the most important mechanism of lymphocytes apoptosis through the membrane and mitochondrial pathways.[29,30] In short, low levels of pro-inflammatory cytokines alone are not enough to rule out the existence of inflammatory responses.

Lungs bear with the most serious damage among all organs as found in autopsy, whether it means the 2019-nCoV is more specific to the lung or not. This is not necessarily, which may be more related to the histological and anatomical characteristics and the vulnerability of the lung. Macrophages are densely located in the lung, accounting for more than 95% of the leukocytes. Inflammation can result in the massive death of macrophages by means of cell pyroptosis, necroptosis and necrosis, which not only decreases defense ability of the lung, but also ignite more heavy inflammatory response, therefore more severe damage in lung than others.[7,31] Moreover, the alveolar cavity is separated from the blood only by a thin layer of endothelial-epithelial septum, of which the destruction allows a large amounts of plasma and cells into the mesenchyme, even flooding the alveoli. In fact, the development of acute lung injury (ALI)/respiratory distress syndrome (ARDS) is always the earliest and the most common signs in all kinds of critical patients, not just in COVID-19.

Based on the above understanding, it is important to suppress the excessive inflammatory response and repair the deep immunosuppression in treatment of sepsis and severe COVID-19 patients, which is so-called "immunomodulatory therapy" or "immunotherapy". And due to a lack of effective antiviral drugs at present, it could be regarded as "sub-etiological treatment".

Immunomodulatory therapy

The researches of immunomodulatory therapy in sepsis have been going on for decades, and countless anti-inflammatory and immune-enhanced drugs have been tried, but the vast majority have become passers-by, so far no one obtained solid support by enough evidences and to be unanimously accepted by clinicians.[32,33] In the surviving sepsis campaign guidelines, immunotherapy is really in a blank state,[34] including its latest version of the anti-COVID-19 guideline.[35] In China, there is also no specific item of immunomodulatory therapy in the COVID-19 diagnosis and treatment protocol (trial version 7) released by the National Health Commission (NHC). However, some drugs with immunomodulatory potential are recommended, including Xuebijing (a Chinese medicine), corticosteroid (methylprednison), tocilizumab, chloroquine. Nevertheless, more therapeutic regimens add thymosin a1 (Ta1) and ulinastatin for critical patients which are released by NHC, several national critical care medicine societies and local societies.

No matter what drugs are adopted for immunotherapy, a basic principle should be emphasized that anti-inflammatory therapy should do as little damage to immune function as possible and immune enhancement therapy should avoid inflammatory rebound as much as possible. Based on the principle, there are actually only a few drugs to be chosen. The goal of immunotherapy should be to curb the excessive but retain moderate inflammatory; repair of the deep immunosuppression should allow retaining moderate. It is actually the normal compensatory response in the case without complete infection control. This paper will focus on analyzing the use of corticosteroids, ulinastatin (UTI) and Ta1 for severe COVID-19 treatment.

Corticosteroids

Corticosteroids are the traditional and the most classic anti-inflammatory drugs, which can inhibit the release of pro-inflammatory substances, stabilize the cell membrane, and improve the permeability. However, corticosteroids are also the powerful immunosuppressive agents, the most important and common drugs used for immunosuppressive treatment in organ transplantation, autoimmune and allergic diseases. This dual attributes make corticosteroids a double-edged sword in treatment of sepsis.

The treatment of sepsis with large doses of corticosteroids has been clearly denied more than 30 years ago. A study reported by Bone et al.[36] showed that no significant benefits were found in the prevention of shock, reversal of shock and decrease of mortality by the treatment with high-dose methylprednisolone (30 mg/kg, 4 times a day). The mortality at 14 days in the subgroup of patients with renal impairment (>2 mg/dl) was significantly increased (59% *vs*. 29%, $p < 0.01$), and all death cases were significantly relative to secondary infection. In 1990s, a meta-analysis of the treatment of sepsis with corticosteroids showed a trend toward the increased mortality (*relative risk (RR)* = 1.13, 95% *CI*: 0.99–1.29) and gastrointestinal bleeding (*RR* = 1.17, 95% *CI*: 0.79–1.73).[37] The authors concluded "Current evidence provides no support for the use of corticosteroids in patients with sepsis or septic shock, and suggests that their use may be harmful". But many clinicians are still reluctant to give up the treatment and try to challenge the above conclusion with low dose of the corticosteroids. The results were still controversial and not encouraging. Some studies did obtain positive results that the low-dose corticosteroids were helpful in reversing hypotension and shortening the duration of administration of vasopressors in septic shock, but mainly in cases with relative adrenal insufficiency.[38,39] It did not mean that the use of corticosteroids as an conventional anti-inflammatory strategy for the treatment of sepsis or septic shock was advisable. Corticosteroids were recommended for use only in cases where septic shock cannot be corrected by adequate fluid resuscitation and vasopressors. Once the hypotension was corrected, corticosteroid was required to discontinue.[33] A meta-analysis published in 2018 also concluded that though the duration of shock, mechanical ventilation and intensive care unit (ICU) stay are reduced, the short- and longer-term mortality are unaffected and adverse events increased regarding septic shock treated with low dose corticosteroids.[40] More impressive, a survey of more than 1.5 million out-of-hospital users of prednisone showed that even in short-term (5–7 days) and with low-dose (17.5–20 mg/d) of oral prednisone, the incidence rate of fractures, venous thrombosis and sepsis were still very high.[41] The sepsis had the highest incidence rate of 5.3 (95% *CI*: 3.80–7.41) within 30 days of drug initiation.

Notably, corticosteroids had been widely used in previous outbreaks as anti-inflammatory agents, but controlled trials were lacked for prognosis. In the treatment of SARS, it was found that although corticosteroids temporarily alleviated the inflammatory response, the duration of virus clearance was significantly prolonged.[42,43] An analytical study concluded that "Despite an extensive literature reporting on SARS treatments, it was not possible to determine whether treatments benefited patients during the SARS outbreak. Some may be even harmful".[44] A harsh fact is that corticosteroids can accelerate lymphocyte apoptosis. If critical patients had severe lymphocytic depletion and lymphatic organ atrophy, corticosteroids may further aggravate their immune function, then deteriorate their later course and prognosis. In the current treatment of COVID-19, corticosteroids are also criticized by some clinicians,[45] while still are advocated by others.[46,47] Indeed, we may have to focus it as "lifesaving therapy" in emergency situations. If corticosteroids are maintained as an anti-inflammatory strategy for several days, the risk of exacerbating immunosuppression will be significantly increased. If we have other safer choices, corticosteroids are not the only choice. This is the reason why UTI was proposed here.

UTI

UTI, an active trypsin inhibitor in urine, was first discovered by Bauer from urine in 1909, then successfully purified by Sumi and developed by Mochida Co. (Japan). The medicine was named Miraclid (miracle + drug) to market in 1985. Currently, Techpool Co. (China) is the largest manufacturer in the world with the capable of producing UTI on a large scale.

Trypsin inhibitor is actually serine protease inhibitors, whose inactive precursors is activated by serine proteases, in turn, inhibits those enzymes containing serine proteases, thus creates a negative feedback regulation of anti-inflammatory. The strongest known activator is elastase, as well as other cytotoxic proteases released by immune cells, all of which have pro-inflammatory properties. In addition to inhibiting serine protease, trypsin inhibitor can also stabilize cell membranes, inhibit calcium influx and NF-κ B activation, and antagonize oxygen free radicals. Several clotting factors are also serine proteases, which are also inhibited by trypsin inhibitor, and can prevent coagulatory activation and DIC induced by systemic inflammatory response and sepsis.[48–50] UTI is the prototype of active trypsin inhibitors in urine, and has the same biological activity as trypsin inhibitor as a natural anti-inflammatory and anticoagulant barriers in the body. Previous studies have observed that many inflammatory diseases are accompanied by elevated levels of UTI,[51] which is the reflection of the activation of anti-inflammatory mechanism in body. However, the occurrence of diseases indicates that the self-compensation no longer provides adequate protection for body, and giving exogenous UTI is appropriate and necessary.

Currently, the on-label of UTI only lists acute pancreatitis and circulatory failure. In fact, it is used far beyond our imagination. According to an analytic reported in 2013, there were more than 3000 literatures of experimental and clinical studies with UTI, covering dozens of diseases, and involving genetics/metabolism, inflammation/immunity, coagulation, tumor, and so on.[52] Up to 2014, during 15 years since UTI became available in China, there have been more than 2.5 million cases using this drug, whose efficacy and safety have been fully demonstrated. A double-blind study of UTI safety was conducted in 51 healthy subjects.[53] Subjects were 3×10^5 u -80×10^5 u one-off injection within 2 h. There are 10 subjects in 11 cases of adverse events, characterized by mild dizziness, pain at the injection site and leukocyte count down, but it does not occur in the highest dose group (8×10^5 u). All the adverse events can automatically disappear, not found to have serious adverse reactions. This study suggested that UTI has sufficient safety properties to be well tolerated by humans. With the consideration of that UTI is constantly consumed in the inflammatory response, it can be inferred that the sepsis patients may have a greater tolerance to UTI than healthy individuals. Currently, UTI has been recommended for anti-inflammatory therapy for a variety of diseases by consensus of ten academic societies in China, which reflects the practitioner's trust to it. To date, no serious adverse reactions, including immune suppression, were reported, even at very large doses.[54]

For treatment of sepsis, there have been a large number of literatures with almost consistent positive evaluation. In 2018, a causal mediation analysis showed that it had a significantly lower mortality rate at 28-day in UTI group than that in control group (31% *vs*. 55%; $p < 0.001$), in that 35% of cases were directly associated with reduced inflammatory response e.g. CRP, and also did not rule out a role in protecting glycocalyx, endothelial cells, and inhibiting cells apoptosis.[55] A meta-analysis in 2019 showed that UTI significantly decreased the all-cause mortality ($OR = 0.48$, 95% *CI*: 0.35–0.66, $p < 0.00001$), APACHE II score, the incidence of multiple organ dysfunction syndrome.[56] Another meta-analysis of treatment with UTI for ALI and ARDS also demonstrated[57] its efficacy in improving lung oxygenation (mean standard deviation = 1.85, 95% *CI*:1.42–2.29, $p < 0.00001$) and significantly reducing mortality in ICU ($RR = 0.48$, 95% *CI*: 0.38–0.59), which was reasonable as an evidence to be recommended in severe COVID-19 treatment. It should also be noteworthy that some German and Japanese authors recently proposed that camostat or nafamostat respectively has the action of against 2019-nCoV invasion cells.[58,59] The mechanism was interpreted that 2019-nCoV invading cells requires S protein to bind to membrane ACE2, also to be activated and cleaved by a serine protease named transmembrane protease serines (TMPRSS2) on the membrane to achieve membrane fusion, which is a key step for invasion. Camostat and nafamostat can prevent S protein from activation and cleavage through inhibiting TMPRSS2, thereby to prevent membrane fusion. With camostatin, two clinical studies of "Camoco-19" (NCT04321096) and "CLOCC" (NCT04338906) to treat severe COVID-19 are under way. Both camostat and nafamostat are synthetic serine protease inhibitors, but UTI is a nature serine protease inhibitor which almost has the same pharmacological action and indications as camostat or nafamostat. Therefore, it is possible that UTI also has the similar effect of antiviral invasion like camostat and nafamostat. However, an experiment study conducted by Yamamoto et al.[60] excluded this speculation with a MERS virus model. It is necessary to further clarity the cause of UTI's failure and to seek solutions.

Not only in China, UTI also appears as an anti-inflammatory drug in the WHO R&D Blue book[61] and in the Indian Experts Consensus[62] in this outbreak. More significantly, Stanford University will conduct a multicenter, double-blind, controlled clinical study of UTI for COVID-19 treatment in June 2020 (NCT04393311),[63] which is the first clinical study to use UTI in the US.

Ta1

Ta1, from thymic hormone fragment 5 (F5), is a 28-amino acid peptide that is the central of thymic hormone function and was first described by Goldstein. After the success of synthetic Ta1 in 1970s, Italian SciClone Co. and Patheon pharmaceutical factory launched the medicine named Zadaxin, which entered China market in 1990s. Currently, there are two other Ta1 products made in China, named Maipuxin and Heri respectively.

Ta1 can promote the proliferation, differentiation and maturation of T cell; induce the transformation of stem cells (CD34) to mature CD4 and CD8; up-regulate T lymphocyte receptor expression to activate dendritic cell (DC); improve the ability of DC to engulf bacteria and release cytokines; increase the antigen presenting cells MHCII expression; enhance the expression of IL-2 receptor in T cells; and antagonize corticosteroid-induced lymphocyte apoptosis etc,[64,65] so it is a strong immune booster and at least 100 times powerful than F5.[64] A study of Ta1 antagonizing the pro-apoptotic effect induced by corticosteroid showed that in a dexamethasone pretreated model, the anti-apoptotic efficacy of Ta1 lasted for about 12 h. The range of dose should be limited, which is not the bigger the dose was, the better the effective was.[66] The time-dependent and dose-dependent features of Ta1 have certain references for guiding the use of Ta1 clinically.

In 2013, Wu et al.[67] reported a multicentric randomized controlled trial using Ta1 with 1.6 mg, twice per day for 7 days for the treatment of sepsis, which showed a trend of reducing mortality (26% *vs*. 35%, $p = 0.062$) at 28-day and a significant decrease of mortality in hospital (28.7% *vs*. 39.4%, $p = 0.032$). A meta-analysis in 2017 on the treatment of sepsis with Ta1 showed that the 28-day mortality was reduced about 30% ($RR = 0.69$, 95% *CI*: 0.60–0.80, $p < 0.0001$), and CD3+, CD4+, CD4+/CD8+ were significantly increased, and the levels of TNFa, IL-1 beta and IL-6 were significantly decreased, suggesting that Ta1 does not only cause no inflammatory rebound, but also may inhibit the release of proinflammatory cytokines.[68] No clear explanation for that, it maybe that Ta1 ensured the pathogens were more effectively cleared by means of improving the immune function, therefore weakened the inflammatory response. Moreover, Ta1 may be involved in a negative immunomodulatory effects. Indeed, we have learnt that Ta1 has biphasic regulation effects through acting on DC.[69] In traditional DC and plasmacytoid DC (pDC), Ta1 plays a positive immunomodulatory role by activating MyD88. In pDC, it can exert negative immune regulation by activating indoleamine 2, 3-dioxygenase (IDO) to induce Treg to realize immune tolerance, depending on the status of the body.[70] These characteristics make Ta1 as the safest and most effective immunomodulator for the treatment of a variety of immune disorders, including autoimmune diseases. The use of Ta1 has obvious advantages for treatment of complex immune disorders, such as sepsis which both inflammation and immunosuppression always coexist.

UTI combination with Ta1

Based on the understanding that sepsis is a biphasic event of inflammatory response and immunosuppression, a combinative treatment with anti-inflammatory and immunoenhancement may be more reasonable and complement each other. This idea was supported by an experimental study in a rat cecal ligation and perforation model,[71] in which the 96-h mortality in the control group was 66.7%, in the UTI group alone 50.0%; in the Ta1 group alone 44.4%; and in the combination group 30.6%. In 2003, the first

multi-center randomized controlled trial (RCT) of UTI combination with Ta1 for treatment of sepsis in China was conducted.[72] The results showed this regimen reduced absolute mortality at 28- and 90-day respectively 13.18% (from 38.32% down to 25.14%, $p = 0.0088$) and 14.96% (from 52.10% down to 37.14%, $p = 0.0054$). A meta-analysis of treatment of sepsis with Ta1 and UTI showed a $RR = 0.67$ of the treatment group compared with the control group (95% *CI*: 0.57–0.80, $p < 0.00001$).[73] Another meta-analysis of different authors also showed a similar results like the above ($RR = 0.68$, 95% *CI*: 0.57–0.81, $p < 0.00001$).[74]

Summary

As a new disease, severe COVID-19 tends to overwhelm our efforts in the treatment. In spite of many new therapies being proposed, they are hard to be used if without adequate evaluation because of the uncertainty and higher risks. In contrast, it may be more worthwhile to use those therapies accumulated in normal times from other similar diseases, such as sepsis, ARDS, multiple organ system etc., depended on our understanding to severe COVID-19. Based on the clinical and autopsy data, it should consider that the essence of severe COVID-19 is a sepsis induced by viral infection. Thus it is reasonable to adopt the treatment strategy similar to sepsis, such as immunomodulatory treatment, in which UTI and Ta1 should be the safest and most effective drugs according to the accumulated data. To date, there is no evidence showing that UTI is an anti-inflammatory agent can results in immunosuppression, and Ta1 as an immunopotentiator can causes inflammatory rebound, which is the great advantage over other treatments in sepsis and severe COVID-19. The problems are that up to date, relevant studies with UTI and Ta1 were mainly carried out in China and there were some defects in the sample size and protocol design, which leave a gap with the first level of evidences. However, the near-universal praises are not by chances. It can be a better choice than other controversial treatments in the treatment of severe COVID-19. The specific usage of UTI and Ta1 is still uncertain. Considering the influence of age, basic state, disease severity, pharmacokinetics, additional treatments and other factors, it may be more reasonable to guide the treatment according to the patient's response and the dynamic trend of the diseases, which is so-called individuality.

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Declaration of Competing Interest

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