Annals of R.S.C.B., ISSN:1583-6258, Vol. 25, Issue 4, 2021, Pages. 2920 – 2936
Received 05 March 2021; Accepted 01 April 2021.

A Review on Common Treatments for COVID-19 and Use of Tocilizumab (ACTEMRA) in Reducing Effects of the Disease

Mohammadreza Bozorgmanesh[1], Yeganeh Yousefifar[2], Mohammad Jamalian[3], Behnam Mahmoodiyeh[4], Alireza Kamali[5*]

[1]Department of Orthopedics, Arak University of Medical Sciences, Arak, Iran.
[2]Infectious Research Center, Arak University of Medical Sciences, Arak and Tehran University of Medical Sciences, Tehran, Iran.
[3]Department of Forensic Medicine and Poisoning, Arak University of Medical Sciences, Arak, Iran.
[4]Department of Anesthesiology and Critical Care, Arak University of Medical Sciences, Arak, Iran.
[5*]Department of Anesthesiology and Critical Care, Arak University of Medical Sciences, Arak, Iran.
E-mail: alikamaliir@yahoo.com

ABSTRACT

Because of the increasing cases of COVID-19 and the lack of effective drugs for novel coronavirus pneumonia, there is an urgent need to find efficient targeted drugs. Based on the analysis of the disease spectrum in China, in addition to quarantine, a great number of patients require treatment immediately. In the absent of successful randomized controlled trials (RCTs), old anti-viral drugs and methods were used to treat patients that have been marketed for other purposes, such as anti-malarial drugs, biotherapy, interferon, and safety adjustment and as well as old Chinese medicine.

Studies on the effects of plasma on improved patients are promising. Several pharmaceutical companies have also begun testing for the vaccine all around the world.

Tocilizumab, the most effective way to inhibit CRS during cell therapy studies on chimeric antigen receptor T cells, and Karrizumab, as an inhibitor of immune system in NCP treatment, are highly important in treating the disease.

Under the brand name of Actemra, Tocilizumab was received approval from the US Food and Drug Administration on January 8, 2010. Tocilizumab Injection was used to treat adults with giant cells arthritis (GCA) and inflammation of the blood vessels (vasculitis). The use of this drug in the treatment of COVID-19 provides a significant remedial response because it is an anti-interleukin-6 receptor and recombinant humanized monoclonal antibody.

KEYWORDS

COVID-19, Novel Coronavirus Pneumonia, Tocilizumab.

Introduction

The coronavirus pneumonia caused by the new coronavirus (2019-nCoV), recently named by the World Health Organization as COVI-19, appeared in December 2019 in Wuhan, Hubei Province, China. During the Chinese Spring Festival in January 2020, COVID-19 was spread to other cities of China. There are a variety of coronaviruses with the ability to cause mild respiratory illness in human beings. On the contrary, SARS-CoV and MERS-CoV, in which hosts were bat and animal-human transmission was confirmed, could cause severe respiratory illnesses(1, 2).

According to the World Health Organization, the number of newly confirmed cases of novel Coronavirus continues to increase around the world (3-10). Like SARS-CoV (11) and MERS-CoV, (12) 2019-nCoV is fatal. As of February 3, 2020, 362 out of 17391 confirmed 2019-nCoV was killed (10).

Based on the analysis of whole genome sequence, 2019-nCoV is more identical to bat-like CoVs such as SARS (MG772933) than SARS-CoV (13). However, 2019-nCoV is more than 85% identical to SARS-CoV (14). Significantly, in the high affinity of RBD in Spike protein, multiple studies showed that 2019-nCoV employs the same SARS-CoV receptor, angiotensin-converting enzyme-2 (ACE-2) (15-17). However, it has been shown that dipeptidyl peptidase-4 (DPP-4), the primary receptor of MERS-CoV, isn't a 2019-nCoV receptor (16).

Age and gender are two important factors affecting case fatality rate (CFR) of SARS and COVID-19. Older patients have been shown to have higher CFRs compared to younger patients with COVID-19 and SARS (18, 19). Similar to SARS, it appears to has higher CFRs than women in COVID-19, (13, 14). At the same time, a study on SARS in Hong Kong showed that there was a direct association between the increased age and decreased gender-depended

Annals of R.S.C.B., ISSN:1583-6258, Vol. 25, Issue 4, 2021, Pages. 2920 – 2936
Received 05 March 2021; Accepted 01 April 2021.

difference in CFP, argued that the same might be true of COVID-19(14).

Comparing the Main Pathological Features between SARS and COVID-19

The most important features of the main pathology between COVID-19 and SARS can be summarized as follows.

The acute respiratory distress syndrome (ARDS) induced by COVID-19 has been well established in the literature and will not be addressed in the present article. Patients with COVID-19 show high rates of renal impairment, which is an indication of kidney dysfunction (20). This is also the case with SARS patients (21-25). The expression level of ACE2, which is a receptor of both SARS-CoV and 2019-nCoV, is relatively high in kidney, testis, and gastrointestinal tract (Figure 1). Because SARS cause serious damage to testis (20), one can reasonably argue that 2019-nCoV may also cause testicular damage in males. However, further clinical evidence is required to substantiate this hypothesis.

A leading factor in the disease development is cytokine release syndrome (CRS). Patients with COVID-19 showed higher values of IL-10 and IL-6 with increasing disease severity (21). Elevated levels of IL-6 and IL-10 cytokines have also been reported in CRS patients (22, 23). A monoclonal antibody with the ability to target the IL-6 receptor is Tocilizumab, which was already registered during a clinical trial in Anhui Provincial Hospital under registration number of ChiCTR2000029765 in the Chinese Clinical Trials.

SARS patients indicate high levels of lymphocyte depletion, atrophy of the white pulp and Necrosis of the spleen (21-25). Moreover, a decrease in the amount of immune cells including macrophages, natural killer cells (NKCs), CD4+T, dendritic cells (DCs), and CD8+T have been noticed in SARS patients. Similarly, patients with COVID-19 also show a significant decrease in the number of CD8+T and CD4+T cells, however, further investigation is needed to confirm spleen impairment among these patients. In addition, the important role of CD4+T (but not CD8+T) cells in the control of SARS-CoV has been reported in some studies. It may be possible to consider various approaches for rescuing T cells in CRS control procedure.

Introducing Tocilizumab

Tocilizumab is a humanized antihuman IL-6 receptor antibody (human IgG1 subclass) with a significant therapeutic response. Its light and heavy chain consists of 214 and 448 amino acids. The four polypeptide chains inside and between the molecules are linked by disulphide bonds. The United States Food and Drug Administration (FDA) approved Tocilizumab on January 8, 2010. The injection of Tocilizumab for adults with inflammation of the blood vessels (vasculitis) and giant cells arthritis (GCA) was approved by the FDA in May 2017. The results of a double blind, placebo-controlled clinical trial showed that patients receiving Tocilizumab showed continual improvement from week 12 to 52, including normalization of inflammatory tests, symptoms of giant cells arthritis, and reduced consumption of corticosteroids.

1. The Mechanism of Action

Tocilizumab is an antagonist of interleukin 6 (IL-6). Produced by inflammatory stimuli, extracellular IL-6 mediates various immune reactions. Through inhibiting IL-6 receptors, Tocilizumab can decrease cytokine and produce an acute phase response.

2. Pharmacodynamics

The content of C-reactive protein (CRP) was decreased in the first days of the second week. Administration of both doses changed chemical and drug parameters including increased haemoglobin, decreased rheumatoid factor, serum amyloid A, and erythrocyte sedimentation rate). However, a dose of 8 mg per kg of body-weight was found to produce the highest improvement.

3. Pharmacokinetics

- Absorption: Maximum plasma concentration: 1 hour.

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- Distribution: Distribution volume: 4.6 liters.
- Elimination: elimination half-life: during 11 days at 4 mg/kg and 13 days at 8 mg/kg.

4. Application in Cytokine Release Syndrome

It has been used for the treatment of chimeric antigen receptor (CSR) under the influence of T lymphocytes, resulting from a severe and life-threatening cytokine release syndrome (CRS) in adults and children over 2 years of age. Subcutaneous injection has not been approved for cytokine release syndrome. At 8 mg/kg intravenous injection, a maximum of 3 additional doses of Tocilizumab may be prescribed if CRS clinical signs do not improve after the first dose (It should not exceed 800 mg per dose). The interval between successive doses should be no more than 8 hours and It can be prescribed as a single medication or with corticosteroids (26-32).

5. Contraindications

Hypersensitivity to the drug and its compounds, active infection.

6. Side Effects

Blood pressure, headache, injection site reactions, gastritis, hyperlipidemia, pruritus, oral ulcer, upper respiratory tract infection, rash, increased alkaloid phosphatase, skin reactions associated with injection, oral rash, upper abdominal pain, and dosage-related reactions including a decrease in the number of neutrophils to less than 1000 cells/mm^3.and a decrease in platelets to less than 100,000 cells/mm^3.

7. Drug Interactions

Atorvastatin, alprazolam, amlodipine, methotrexate, hydroxychloroquine, golimumab, hemophilus influenzae type B vaccine, abatasapt doraavirin, alfaspt, basiliximb, kanakinumab, baricitinib, adenovirus type 4 and 7, and live and oral amlodipine: Tocilizumab may lower blood levels and the effects of amlodipine. Dose adjustment may be required.

Atorvastatin: Tocilizumab may lower blood levels and the effects of atorvastatin. Thus, if the patient is taking both drugs, atorvastatin may need to be adjusted when Tocilizumab is discontinued.

Hydroxychloroquine: Using hydroxychloroquine with Tocilizumab may increase the risk of nerve damage, which is a potential side effect of both drugs. Your doctor may prescribe hydroxychloroquine replacement drugs that do not interfere with Tocilizumab.

Methotrexate: Methotrexate may cause liver problems, and its use with other drugs such as Tocilizumab can affect the liver.

Alprazolam: Tocilizumab may lower blood levels and the effects of alprazolam. Thus, if the patient is taking both drugs, alprazolam may need to be adjusted when Tocilizumab is discontinued.

8. Warnings

• Regarding Side Effects

Increased liver enzymes: Tocilizumab is associated with increased liver transaminases. The amount of transaminases should be monitored. Treatment should be discontinued in patients with ALT or AST 5 times more than normal. Patients receiving similar drugs with liver toxicity effects (e.g. methotrexate) are at risk for increased transaminases; these increases are usually reversible and do not indicate clinical liver damage.

Gastrointestinal perforation: Use with caution in patients with an increased risk of gastrointestinal perforation. Abdominal complications should be monitored and evaluated immediately if new symptoms occur.

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Blood effects: Decreased white blood cell count (neutropenia) and platelet count (thrombocytopenia) may occur. The patient may need treatment intervention, dose adjustment, medication interval, and discontinuation of the drug. Neutrophils and platelets should be monitored. Treatment should not be started in patients with giant cell arthritis, juvenile idiopathic arthritis, rheumatoid arthritis or juvenile systemic rheumatoid arthritis with platelet count <100,000 cells/mm^3; Treatment should be discontinued in people with platelet count <50000 mm^3.

High blood lipids: Treatment is associated with high cholesterol, triglycerides, LDL, and HDL; the patient should be monitored for 4-8 weeks after onset, and then almost every 6 months. High blood lipids should be managed according to current guidelines.

Hypersensitivity: Hypersensitivity reactions may occur; drug-induced mortality has been reported by intravenous injection. Medication should be discontinued immediately and permanently in patients who are allergic to Tocilizumab.

Infection: Patients receiving Tocilizumab have been reported to have severe and potentially fatal infections (including active tuberculosis, invasive fungi, bacteria, viruses, proteases, and other opportunistic infections). Infection may lead to hospitalization or death. Many serious infections have occurred during concomitant immunosuppressive therapy. Patients are expected to be aware of the signs and symptoms of infection during and after the treatment. If a serious infection occurs during the treatment, Tocilizumab should not be used until the infection is controlled. Before treatment, the most common serious infections include pneumonia, urinary tract infections, cellulite, herpes, gastroenteritis, sepsis, and bacterial arthritis.

• Regarding Diseases

Myelin deficiency diseases of central nervous system: Use with caution in patients with or with a history of myelin deficiency diseases of the central nervous system. Rare cases of these diseases have been reported. Patients should be monitored for signs of myelin-related illness.

Hepatic impairment: It is not recommended in patients with active liver disease or impaired liver function. ALT and AST should be controlled. If ALT or AST is 1.5 times more than normal, medication should not be started.

• Special People

Elderly: Infection is more common in elderly patients than in younger patients. Use with caution in the elderly.

9. Recommended Tips

Severe and sometimes fatal infections may occur during treatment with Tocilizumab. Patients should stop taking this medicine and inform the physician if they have any symptoms. Symptoms of infection include fever, chills, body aches, flu symptoms, cough, sweating, shortness of breath, diarrhea, weight loss, skin sores, painful urination, and tiredness. The patient should inform the physician if they have ever had tuberculosis, has someone in his or her family with tuberculosis, or has recently travelled to high-risk areas for tuberculosis. It is unknown whether the drug harms a fetus. Patients should inform their physician if they are pregnant or going to become pregnant. The secretion of Tocilizumab in breast milk is unknown. Patients should not breastfeed when using Tocilizumab.

10. Use during Pregnancy

Take it if your doctor tells you to. Adverse reactions have been observed in some animal reproduction studies. As the pregnancy progresses, monoclonal antibodies are increasingly transmitted throughout the placenta, with the greatest amount occurring during the third trimester. The immune response of infants exposed to Tocilizumab may be affected. The risks and benefits of injecting live vaccines for infants exposed to Tosilizomab during pregnancy should be considered.

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11. Use during Breastfeeding

The secretion of Tocilizumab in breast milk is unknown. However, maternal immunoglobulin is secreted in breast milk. The decision to continue or discontinue breastfeeding during treatment, the risk for the baby, the benefits of breastfeeding, and the benefits of treatment for the mother should be considered.

Common Treatments for Coronaviruses

COVID-19 has no specific antiviral treatment. Clinical management is mainly based on symptomatic treatment and providing intensive care for critical cases. The focus of public health institutions including the World Health Organization have been mainly on inhibiting transmission, screening of travellers, and taking control measures. Although immediate funding has been provided for vaccine development, no supportive measures have yet been taken to develop treatment for patients with 2019-nCoV to reduce mortality. Development of new therapeutic interventions for COVID-19 infection is an urgent need that requires immediate funding and scientific investment.

The immune system of the host body become ineffective in respond to all three coronaviruses, causing severe lung injury and death (33). Similar to other two viral infections, i.e. MERS-CoV and SARS-CoV, the new coronavirus induce acute respiratory distress syndrome (ARDS) in patients. In most cases of infection-related death, there is a cytokine storm that is characterised by higher levels of plasma in interleukins 2, 7 and 10, tumour necrosis factor-α (TNF-α), macrophage inflammatory-1 alpha protein, monocyte chemoattractant protein-1, interferon gamma-induced protein 10, and granulocyte colony-stimulating factor (G-CSF). These unusual and immoderate immune reactions lead to acute fibrosis and injury of lung in patients who survived, causing functional dysfunction and decreased quality of life in these patients (36, 37). Today, the need to focus on host-directed therapy is increasingly emphasized (38).

The development and evaluation of specific drugs for the treatment of 2019-nCoV takes several years. At the same time, the efficacy of several host-directed therapies in treatment of 2019-nCoV infection is documented. Several dietary and biological supplements and various marketed drugs have been developed with supreme safety features such as sartan, fibrate, glitazone, atorvastatin and metformin, all of which have the potential to increase immune responses, reduce immunopathology, and prohibit the ARDS (39-41). There are various metal-containing formulations, including zinc, having antiviral characteristics and are safe and inexpensive (42). These formulations can be administered both as monotherapy or as adjunctive therapies with ritonavir-levinovir, rhizovir, ribavirin, cyclosporine, interferon beta-1b, antiviral peptides, and monoclonal antibodies, all of which are used in to treat 2019-nCoV infection (41). As a monoclonal antibody, Tocilizumab targets interleukin 6 and provides excellent safety characteristics. Single-clone and multi-clone antibodies can be used for post-exposure prevention.

The studies on cell therapy for ARDS treatment can be generalized to treating critically infected patients with COVID-19. Cell therapy (43) has been indicated to decrease non-purulent inflammation by using allogeneic mesenchymal stromal cells and affect tissue regeneration. It seems that 2019-nCoV infection is first associated with enhanced responses to Th2 (33), which may be an indication of a physiological response to inhibition of obvious inflammatory reactions, a clinical phenomenon that lets to identify the optimal time for interferon intervention in patients indicated with sepsis, and led to higher longevity (44). Interleukin 17 block may be beneficial for severely infected patients and those with increased plasma concentrations of interleukin 17.

It has been shown that short-term isolation and proliferation of anti-virus T cells is a life-giving method after autologous stem cell transplant in patients infected by cytomegalovirus. The development of cellular drugs (anti-2019-nCoV specific T-cells) as adjunct treatment for severely infected patients by 2019-nCoV is very promising.

At the peak of the MERS-CoV and SARS-CoV pandemics, several trials were initiated to evaluate various therapeutic interventions, but were later missed because of preventable delays and reduced cases. This left numerous questions unanswered about the coronavirus pathogenesis. It is really disappointing that registered trials on the treatment of MERS-CoV are yet incomplete. Given the continues spread and evolution of the 2019-nCoV continues and increasing numbers deaths, it is crucial to advance new therapeutic approaches to reduce the number of deaths from this infection.

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Since the outbreak of COVID-19 in January 2020, several clinical trials aimed to find a treatment for this infection have been conducted in China. Although study registration took place from 30 January to 12 February 2020 (less than 2 weeks), subtle variations from the development of the epidemic are obvious in the classification of the registered studies as a way that the number of trials on the severely infected patients had gently increased in the latter period, and attentions has been paid toward physical and psychological rehabilitation of the patients. Considering epidemic situation in China, together with the current registered trials on 2019-nCoV, we performed an introductory evaluation of the therapy prospects and drug availability for 2019-nCoV in the short term.
According to the available analysis on the reduction of mortality in 2019-nCoV, group therapies should always be considered by therapists as an option in the management of COVID-19 patients (38).

Classification of Drugs Used for COVID-19

Experimental drugs like antiviral and antimalarial drugs, biotherapy (serum, vaccine therapy, etc. obtained from living organisms), interferon, cell therapy, and immune regulation are used in treatment of infected patients with COVID-19. Moreover, there are a large body of studies on the effect of glucocorticoids and plasma as well as traditional Chinese medicine on the treatment of patients with the novel coronavirus (Figure 1; Table 1). Traditional Chinese medicine has received much attention among other treatments, showing that Western medicine is not yet effective in antiviral treatment. Almost all of the drugs were old, mostly marketed for other symptoms, and some of the drugs in the second phase of clinical trials were used for other virus infections.

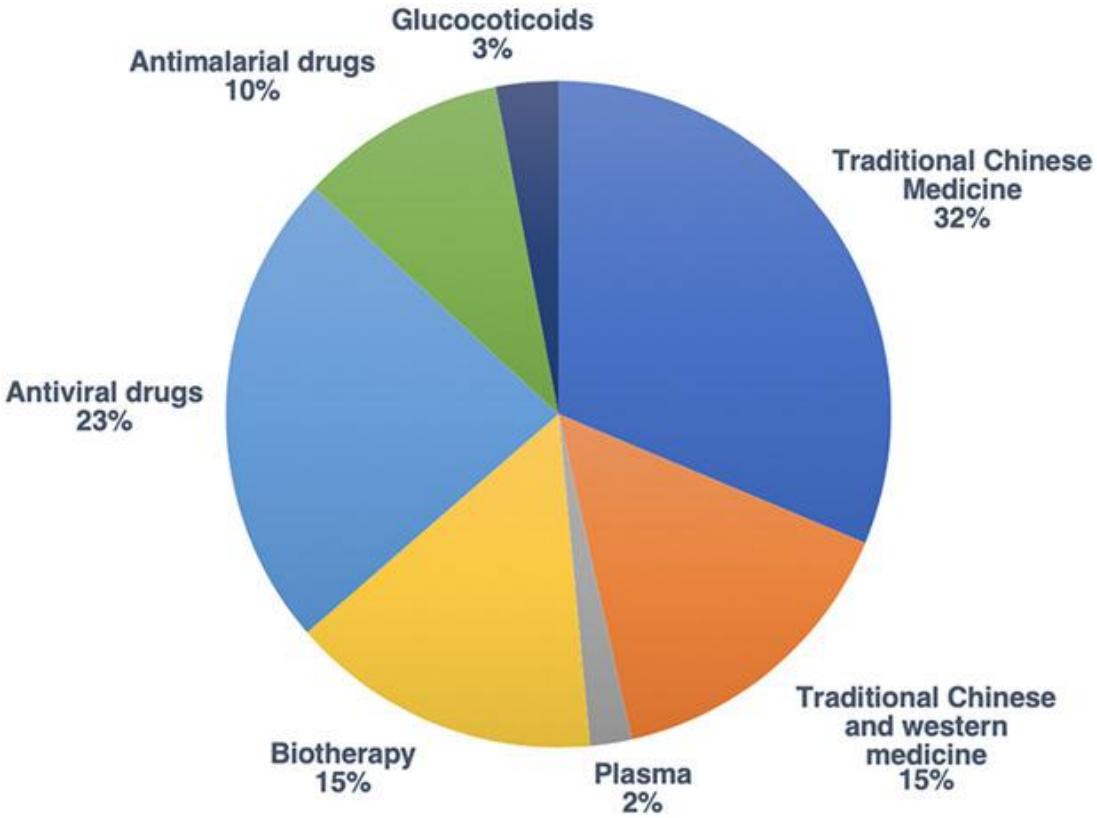

Figure 1. Experimental drugs used for the treatment of 2019–nCoV

Several future multi-center controlled studies have been performed on traditional Chinese medicine, including Guangwan and Lianhua qingwen. Meanwhile, the studies have contributed greatly to the combination of traditional Chinese and Western medicines. Given that these drugs may lead to cytokine release syndrome (CRS), patients in traditional Chinese medicine studies currently receive Western drugs, which are regarded as their basic treatment.

Antiviral drugs including Arbidol, Mir Desir, Lopinavir/Ritonavir, ASC09, and traditional biological agents like

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thymosin alpha-1 and interferon alpha are yet of most attention. So far, three studies have been performed on glucocorticoids, two of which were on hospitalized patients with severe pneumonia. Moreover, anti-malarial drugs hydroxychloroquine and chloroquine have been extensively studied (45-47). The results of these studies have been promising.

Two major drugs for NCP have been reported in clinical trials. Increasing evidence shows that the underlying mechanism of acute pneumonia may be rooted in CRS caused by a viral infection. These findings have prompted Tocilizumab, which has been the most efficient way to prevent CRS during cell therapy studies of antimicrobial chimeric T-receptors, to focus on academic issues. The first multicentre RCT for the safety and efficacy of Tocilizumab in NCP treatment was established on February 14, 2020.
At the same time, a trial was conducted in Wuhan Jinyintan Hospital to test the inhibitory potential of a new medicine in treating patients with severe NCP and lymphopenia. This immune system inhibitor was the first drug used in the NCPs. The results of these two studies will be very interesting.

Promising studies are underway to determine the effects of plasma on improved patients. In addition, development of effective vaccines can significantly reduce virus damage (48), and several pharmaceutical companies have begun research into the RNA vaccine of 2019-nCoV receptor worldwide, and it is hoped that these vaccines will enter the clinical phase in April 2020 (49).

Compared to the SARS, there are generally more choices for 2019-nCoV treatment, involving antiviral drugs like Ritonavir, Arbidol, and ASC09. Although the inhibitory effect of chloroquine against SARS virus has been reported in previous studies, the results are only in cellular levels and not entered the clinical phase. In addition, the Tocilizumab and Karrizumab may give patients more opportunity to be treated.

Drug Availability after Clinical Trial

Since most experiments last for a period of about 1 year (Table 1), the results of these trials are likely to have little contribution to the current epidemic and will be more helpful for future treatment and prevention. On the other hand, increased number of patients, in general, and critically ill patients in particular, has made the availability of effective experimental drugs an emergency in the short term. A review of the retrieved data reveals that a number of potentially effective drugs such as remdesivir, ritonavir, lopinavir, ASC09, glucocorticoids and chloroquine might be completed during a 4 months period, and over 20 trials would be accomplished during the next 6 months. The China-Japan Friendship Hospital carried out remdesivir RCT for mild to moderate NCP that is expected to be completed up to May 2020 (Table 1).

The completion of these trials according to the designed schedule can significantly affect the prognosis and control of 2019-nCoV. In a hospital affiliated to Zhejiang University School of Medicine, two multicentre open-label Randomized Controlled Trial (RCT) were conducted to assess and compare the efficacy and safety of lopinavir/ritonavir vs. ASC09/ritonavir and favipiravir vs. baloxavir marboxil vs. lopinavir-ritonavir in treatment of patients with NCP (Table 1).

Besides, many researchers have conducted short-period trials to evaluate the efficiency of traditional Chinese medicine, which might have the potential to be employed as an efficient and safe option for clinical treatment.

Moreover, the preliminary efficacy of some drugs such as remdesivir, farpiravir and chloroquine phosphate has been indicated in several clinical studies, which can be encouraging for patients and medical staff in the critical phase of the epidemic.

Studies on Severe Acute Respiratory Syndrome

So far, we have seen that there are no effective drugs to treat novel infection. With the increase in the number of diagnosed cases, Chinese government conducted over than 100 clinical trials on novel pandemic, including glucocorticoids, antimalarial and antiviral drugs, vaccines, plasma therapy, and Western drugs. Interestingly, half of these studies were devoted to Chinese medicine. Most of these trials are started by researchers and takes 1-11 months

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to complete. Early endpoints included improvement in symptoms and negative nucleic acid, though no optimal endpoint was identified. Although it takes a long time to complete the final results of the study, temporary research data may contribute the current immediate demand for drug treatment. Compared to the SARS period in 2003, Iran has a greater ability to perform clinical trials on new drugs for this new pandemic.

After the global outbreak of Severe Acute Respiratory Syndrome Coronavirus (SARS-CoV), a public effort was initiated to find effective interventions, including the development of human monoclonal antibodies (hmAbs). The use of hmAbs may be free from drawbacks in the animal or chimeric antibodies. A variety of techniques have been employed to produce neutralizing hmAbs that are specific to SARS-CoV, such as cloning of light chain variable regions from naïve and convalescent patients, immortalization of convalescent B cells, and immunization of transgenic mice. Whatever technique is used, most of hmAbs react to the spike protein receptor binding domain (S-RBD) and possibly prevent receptor binding. However, some hmAbs have been identified with the ability to bind to epitopes through the S2 domain or the located N terminal of the RBD, thus neutralizing the virus with or without inhibiting receptor binding. The therapeutic mechanism of hmAbs may be further explained via the recognition of possible combinations of hmAbs with the ability to neutralize various viruses. These results show that hmAbs can bind to epitopes through its cocktails that have various mechanisms of action. This unique characteristic of hmAbs can be used clinically against SARS-CoV infection and potentially against any other viral infections (50).

Immunotherapy-related Adverse Effects

Immunization of transgenic mice and human infection with SARS-CoV leads to generation of non-neutral epithelium (51, 52). As seen in FIPV, SARS-CoV is associated with increased potential of being infected by ADE (53, 54). Vaccination by modified Ankara vaccine, which is based on expression of S protein in the SARS-CoV, led to an increase in hepatitis in controls (55). Moreover, the results of previous studies on various hmAbs showed that hmAbs increased the infection by pseudo-typed virus that expresses cyanide protein in vitro. Notably that vaccination by an encoding cDNA of the ectopic portion of the SARS-CoV S protein terminated the increase in the infection by pseudo-typed virus (56, 57). It should be noted that XenoMouseW and HuMAbMouseW were secured with the ectopic range of S protein (58, 59). Only hmAbs produced by XenoMouseW are IgG2 isotypes (58). IgG2 isotype provides some advantages such as low affinity of FcR for macrophages and other phagocytes, and not activating the supplementary classical pathway. Therefore, ADE facilitation is less likely (57).

Cross-reactivity of antibodies against SARS is another concern. Serum samples obtained from patients with SARS infection involved antibodies that interacted with the epitope on epithelial lung cells, leading to cellular toxicity in vitro (59, 60). The main reactions took place with 2 epitopes described in S2 and there were no other epitopes in the S protein (59). The presence of multiple Ab neutralizers could make it possible for those who do not identify their autoreactive epitopes.

The Theoretical Framework and Literature Review

mAbsh is rapidly becoming a popular treatment option. Since 2009, another 7 billion m^3 have been marketed, of which 6 billion m^3 have been produced by the use of hmAbs technology (Table 1). Adalimumab was the first full-fledged hmAbs that was used to target TnF-a therapy to manage various autoimmune complications. After a few years, a hmAb panitumAb was produced from transgenic mice and approved to be used in treating colon cancer with epidermal growth factor receptors.

Most hmAbs have been approved for cancer patients or those with various autoimmune disorders (61). Presently, a hmAb is developed and confirmed to be used in patients with infections (Table 1). A human antiviral drug (palivizumAb) has been developed that can successfully prevent infections by respiratory syncytial virus (RSV), which are regarded as a major reason of illness and death among infants. PalivizumAb was produced by placing V-regions of mAb in mice within the framework of human IgG. With hmAbs, reduced efficiency, quick clearance and adverse reactions observed by the compound can be significantly avoided (62, 63). When used as a passive treatment, neutralizer antibodies are more likely to slow the virus proliferation and provide sufficient time for immune response (64). The importance of antibodies in response-providing to SARS-CoV is well established (65, 66). Higher antibody volumes and neutralization against S protein were obtained in the body of improved patients (65).

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The results of a retrospective study on 40 patients with SARS-CoV indicated that administration of serum was protected against infection, without any side effects, indicating that passive treatment could be considered as an effective and safe therapy (67). Neutralized in vitro cases can be generalized to in vivo cases, causing a reduction in the viral title (65, 68). All the hmAbs studied here are capable of providing inactive immunotherapy and immediate protection for those exposed to SARS-CoV due to in vitro exposure or re-emergence.

After the outbreak of SARS-CoV, several groups of hmAbs with therapeutic capability were rapidly produced using various techniques that may be also useful in producing other types of hmAbs for treating viruses or CoVs with the ability to transfer between animals and human. Accordingly, performing detailed studies on hmAbs specific to SARS-CoV S protein can help in better understanding of SARS-CoV's mechanism of action and hmAbs potential both as molecular biology techniques and as immunotherapeutic agents.

Zhang et al. used the expression "2019-nCoV" to search in clinicaltrials.gov and "novel coronavirus" in the Chinese Clinical Trial Register. The result of their search was 107 clinical trials by Chinese researchers by February 14, 2020, of which 17 studies were registered in clinicaltrial.gov and the others 90 in the Chinese Clinical Trial Register. The main issue of these trials was clinical therapy followed by a small pathogenesis research. Moreover, 87 studies were about drug interventions. About 20 studies were carried out in Wuhan where the highest severity of infection was observed (Figure 1), most of which were planned for a duration of 1-11 months, and 5 studies for 6 months.

Zhang et al. used the expressions "China" and "novel coronavirus" to search published studies on PubMed website by February 14, 2020. After excluding the unrelated results like comments and news, a total of 81 trials on 2019-nCoV were extracted. These studies were mainly focused on clinical characteristics of 2019-nCoV and description of its epidemiology, and only a few studies were devoted to treatment and diagnosis (imaging, nucleic acid detection) of 2019-nCoV. There were 7 trials on Radiology, in which computed tomography analyses were performed for about 80 patients in order to identify the imaging features of NCP (69) and 2 studies about nucleic acid detection in patients with 2019-nCoV (70). It is worth mentioning that although there were institutions for nucleic acid detection and some of them had government approval, the data to confirm the consistency and sensitivity was still absent. The first clinical evidence of cancerous patients exposed to 2019-nCoV was published by the New England Journal, concluding that patients with cancer may be more vulnerable to the infection because of several factors including malignant tumour, surgery, chemoradiotherapy, etc. (71). However, there was no randomized controlled trial (RCT) in terms of treatment, which is a reflection of limitation in current treatment. Generally, the needs for finding efficient drugs still is a necessity.

17 years ago, when acute respiratory syndrome (SARS) was in its severe period in China, there was relatively weak capacity and awareness to perform clinical trial on drugs. Our attempt to extract the registered trials over the period from the first SARS-CoV-infected case in November 2002 to the end of the epidemic in July 2003 failed. Thus, the literatures only provide incomplete statistics for SARS-CoV. Totally 54 drug studies were obtained, most of which were retrospective analyses and there were only a few prospective studies (72). The drugs selected for study were the same as that of 2019-nCoV, the main of which were lopinavir, ribavirin, glucocorticoids, and interferon. Although studies on vaccines were also included, the follow-up data were not reported.

During the 2019-nCoV period, the ability and awareness of conducting clinical trials in China has significantly improved compared to the SARS period. At the same time, conducting clinical trials with higher quality and evidence level made it possible to access detailed data on clinical diagnosis and treatment of COVID-19.

Variations in Optimal Results

The extracted studies have reported different results regarding survival rate, diagnosis of negative nucleic acid, and improvement in clinical symptoms, so that it is not possible to identify which one is the most appropriate. Antiviral therapy contains two main concerns. The first concern is prognosis of treatment, that is to reduce the rate of critical illness in patients with mild to moderate disease and to reduce the rate of mortality or improve the lung function in patients with severe or critical disease. These have more that can be assessed in the near future. The second concern is to reduce the time period required for the virus to become negative, thus increasing the speed of recovery and

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Received 05 March 2021; Accepted 01 April 2021.

preventing the transmission of the virus. Resolving clinical symptoms is an important factor in reducing the number of severe cases and death from the illness. Moreover, identifying virus nucleic acid plays an important role in reducing virus transmission. Nevertheless, several cases have been reported the recurrence of the disease in patients who were detected with negative virus nucleic acid after treatment. This suggests that further research is needed on the frequency and time intervals after negative detection. Improvement of clinical symptoms combined with increase the frequency of detection or prolongation of the interval let the disease progression to be estimated more accurately and better determination of whether the patient's body is still infectious.

Besides, competition against this pervasive disease in a public health emergency requires considering the previous efficient outcomes as an alternative endpoint to hasten the process of clinical trials. For instance, two studies were performed on rheumatoid arthritis (NCT04257656, NCT04252664), in which time to clinical improvement (TTCI) and time to clinical recovery (TTCR) were used as the primary endpoint instead of detecting the nucleic acid of the virus or the survival state of severely ill patients. The former was based on the time required for recovery from clinical status, and the latter was based on breathing rate, oxygen saturation, body temperature, and the recovery from clinical symptoms. Due to the fact that current mortality rate of NCP is relatively low at around 2%, the chosen endpoints were mainly relied on suggestions provided for influenza drug, for which the primary endpoint in most studies is something other than mortality. As an alternative endpoint, TTCI and TTCR require samples with smaller sizes compared to other dichotomous endpoints (e.g. the rate of disease control). The opinions and decisions by the clinical medicine should be followed when choosing the endpoints.

Analysis of the current disease status in China showed that, despite taking effective quarantine measures across the country, there are still a large number of critically ill patients who are in urgent need for treatment. According to Chinese scientists, the prognosis of the disease and the improvement of clinical symptoms are two main indicators in evaluating the efficacy of drugs in the short and long term. And when temporary research data supports it, these drugs should be used soon.

The rate of severe cases of the current illness is estimated around 15 percent. The presence of long-term complications after recovery like impaired lung function or other organ dysfunction is still unclear and needs further attention by researchers.

It's also worrying to have so many clinical trials at this rate. Because of the need, the theoretical foundations of some experiments need to be articulated in more details, and the designs may lack enough logic. The possibility that these drugs may put patients at risk is a matter of caution in this study.

Conclusion

Due to the fact that there is currently no definitive treatment for COVID-19, clinical management is generally based on symptomatic treatment; therefore, a variety of previously developed antiviral drugs for other purposes are in use. The development and evaluation of specific drugs for the treatment of 2019-nCoV will take several years. So far, several independent clinical trials have been conducted worldwide to evaluate the efficacy and safety of Tocilizumab for the treatment of COVID-19 pneumonia.

FDA has already approved the efficiency of Tocilizumab in treating patients with CRS, an acute and life-threatening syndrome. The FDA has confirmed the use of phase III, randomized, double-blind, placebo-controlled clinical experiments in evaluating the efficacy and safety of intravenous tocilizumab (Actemra) combined with standard of care for hospitalized adult patients with severe COVID-19 (73). This clinical trial (named COVACTA) was performed in cooperation with Biomedical Advanced Research and Development Authority (BARDA) to assess and compare the efficacy of tocilizumab+standard of care vs. placebo+standard of care. This will be the first US FDA-approved drug to treat Covid-19 if phase 3 testing is done slowly.

As a monoclonal antibody that targets IL-6 receptors, Tocilizumab is currently being tested at clinical trials at a hospital in Anhui Province, China; it has a good safety characteristics. Antibodies have proven to be important in response to SARS COVID; therefore, they might be effective in treating COVID-19. However, given the side effects of tocilizumab, the possibility of superimposed TB and fungal infections, the diagnosis and medication should be

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done with caution.

In one study, 114 patients with rheumatoid arthritis were treated with tocilizumab.

During TCZ treatment, 127 side effects were reported in 63 patients. Thirteen side effects were also serious in 9 patients. The most common side effect was serious infection (11 cases).

The most common type of serious infection was bacterial pneumonia (6 cases with acute respiratory failure). Other side effects included cellulite, hyponatremia, and urinary tract infection. In addition, the most common non-serious side effect was nasopharyngitis.
Four and 19 cases were observed with a history of old pulmonary tuberculosis and latent tuberculosis, respectively. Also, 12 patients with tuberculosis have completed months of isoniazid chemoprophylaxis. Six patients were not received Isoniazid prophylaxis because of the normal chest radiography; none of them had active TB infection.
None of the patients with hepatitis B showed HBV again. In 3 patients, malignancy was observed. One patient diagnosed with ovarian cancer just after receiving a single dose of TCZ. Moreover, each of intracranial and basal cell carcinoma were observed in one patient.

Twelve patients discontinued TCZ because of the side effects (74).

One study investigated 4,199 patients with rheumatoid arthritis in control group and 4,009 patients in the treatment group with 4 and 8 mg/kg tocilizumab.

The rate of new contamination in the control group was 3.5%, while this rate was 4.9% in tocilizumab 8mg/kg group and 3.3% in tocilizumab 4 mg/kg group. In both groups of control or tocilizumab-treated, serious infection had a direct relationship with age, BMI, a history of using TNF inhibitors, diabetes, and a history of chronic lung disease (restrictive or obstructive).

Within study population, the rate of serious infections was 4.7%, including pneumonia, gastroenteritis, and urinary tract infections as the most common diseases. The continued TCZ treatment relatively stabilized the rate of serious infections.

In the present study, 22 opportunistic infections (14 serious cases) were reported in 20 patients. The opportunistic infections included tuberculosis (8 cases), candidiasis (including systemic, esophageal, and gastrointestinal tract; 6 cases), fungal infections (3 cases), cryptogenic pneumonia (1 case), and other mycobacterial infections (mycobacterium avium and non-specific; each 1 case). All these infections were observed in patients treated with tocilizumab 8 mg/kg. Patients in the control group showed no sign of opportunistic infections.

Eight cases of tuberculosis infection have been reported in se7ven patients in the tocilizumab group. In one patient, tuberculosis and have been reported. None of the patients with the relevant medical history reported a history of tuberculosis or exposure to tuberculosis. Pulmonary tuberculosis, tuberculous pleurisy and unknown tuberculosis were reported in 4, 3 and 1 patient, respectively (75).

According to the results of the present study, in patients with COVID-19, tocilizumab should be used with caution, following standard and approved trials.

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Classification	Register number[a]	Study desire	Enrollment	Drug of interest	Combinations	Disease condition	Study time	Primary endpoint
Antiviral drugs	ChiCTR2000029308	RCT	160	LPV/r	Standard treatment	NCP	2020-01-10 to 2021-01-10	Clinical improvement
	ChiCTR2000029539	RCT	328	LPV/r	Standard treatment	Mild NCP	2020-02-03 to 2021-02-02	Adverse outcome
	ChiCTR2000029496	RCT	200	LPV/r	Novaferon	NCP	2020-01-29 to 2021-01-29	RNA negativity
	ChiCTR2000029539	RCT	328	LPV/r	Standard treatment	NCP	2020-02-03 to 2021-02-02	Adverse outcome
	NCT04252664	RCT	308	Remdesivir	...	Mild/moderate NCP	2020-02-05 to 2020-04-27	TTCR
	NCT04257656	RCT	452	Remdesivir	...	Severe NCP	2020-02-06 to 2020-05-01	TTCI
	ChiCTR2000029600	Non-RCT	120	Favipiravir	Interferon-alpha	NCP	2020-01-30 to 2020-04-29	RNA-negative, rate of liver or kidney damage
	ChiCTR2000029621	RCT	380	Arbidol	Basic treatment	NCP	2020-01-01 to 2020-12-31	RNA negativity
	ChiCTR2000029603	RCT	160	ASC09F	...	NCP	2020-02-06 to 2020-05-31	Adverse outcome
	ChiCTR2000029580	RCT	70	Ruxolitinib	MSC	Severe NCP	2020-01-31 to 2020-12-31	Safety
	ChiCTR2000029541	RCT	100	Darunavir/cobicista	Thymosin α1	NCP	2020-02-01 to 2020-12-01	RNA negativity
	ChiCTR2000029759	RCT	60	ASC09F, arbidol	...	Mild/normal NCP	2020-02-15 to 2020-05-01	Clinical improvement
	NCT04261270	RCT	60	ASC09F, ritonavir	Oseltamivir	NCP	2020-02-01 to 2020-07-01	Adverse outcome
	ChiCTR2000029548	RCT	30	Favipiravir, baloxavir marboxil	...	NCP	2020-02-04 to 2020-06-03	RNA negativity, clinical improvement
	ChiCTR2000029387	RCT	36	LPV/r + ribavirin	Interferon alpha-1b	Mild/moderate NCP	2020-01-25 to 2021-01-25	RNA negativity
	ChiCTR2000029468	Non-RCT	120	LPV/r + FTC/TAF	LPV/r	NCP	2020-02-01 to 2020-06-30	Survival rate
	ChiCTR2000029573	RCT	600	LPV/r + arbidol	Novaferon	NCP	2020-02-05 to 2020-06-30	RNA negativity
Antimalarial drugs	ChiCTR2000029542	Non-RCT	20	Chloroquine	Standard treatment	NCP	2020-02-03 to 2020-07-30	RNA negativity, mortality
	ChiCTR2000029826	RCT	45	Chloroquine	...	Serious/critically ill NCP	2020-02-17 to 2020-03-17	Mortality rate
	ChiCTR2000029741	RCT	112	Chloroquine	LPV/r	Mild/normal NCP	2020-02-12 to 2020-12-31	Length of stay and severe, oxygen index, mortality
	ChiCTR2000029762	RCT	60	Hydroxychloroquine	...	Severe NCP	2020-02-12 to unknown	RNA negativity
	ChiCTR2000029559	RCT	300	Hydroxychloroquine	...	NCP	2020-01-31 to 2020-02-29	RNA negativity, T-cell recovery time
	ChiCTR2000029803	RCT	320	Hydroxychloroquine	Arbidol	NCP	2020-02-15 to 2022-02-15	...
	ChiCTR2000029760	RCT	240	Hydroxychloroquine	LPV/r	Mild/moderate NCP	2020-02-12 to 2020-08-11	Time to clinical recovery
	ChiCTR2000029740	RCT	200	Hydroxychloroquine	Standard treatment	NCP	2020-02-11 to 2020-02-29	Oxygen index, max respiratory rate, lung CT
	ChiCTR2000029761	RCT	240	Hydroxychloroquine	Standard treatment	Normal NCP	2020-02-13 to 2020-04-30	RNA negativity
Glucocorticoids	ChiCTR2000029386	RCT	40	Glucocorticoid	LPV/r + interferon-α	Severe NCP	2020-01-29 to 2021-01-29	Mortality, clinical improvement
	ChiCTR2000029656	RCT	100	Low-dose glucocorticoid	Standard treatment	NCP	2020-02-14 to 2020-04-14	ECG, CT, complications, vital signs
	NCT0424459	RCT	80	Glucocorticoid	Standard treatment	Severe NCP	2020-01-26 to 2020-12-25	Lung injury score
Other therapies	ChiCTR2000029806	RCT	120	Camrelizumab, thymosin, conventional treatment	...	Severe NCP with lymphocytopenia	2020-01-01 to 2021-01-31	Lung injury score
	ChiCTR2000029765	RCT	188	Tocilizumab	...	Severe NCP	2020-02-10 to 2020-05-10	Cure rate
	ChiCTR2000029757	RCT	300	Convalescent plasma	Standard treatment	Severe NCP	2020-02-14 to 2021-02-05	Clinical improvement
	NCT04269525	Single arm	10	DMSC	...	Severe NCP	2020-02-06 to 2020-09-30	Oxygen index
	NCT04261426	RCT	80	Immunoglobulin	Standard treatment	Severe NCP	2020-02-10 to 2020-06-30	Clinical improvement

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Received 05 March 2021; Accepted 01 April 2021.

Classification	Register number[a]	Study desire	Enrollment	Drug of interest	Combinations	Disease condition	Study time	Primary endpoint
TCM	ChiCTR2000029381	Prospective	400	Xuebijing	...	NCP	2020-01-01 to 2020-12-31	Pneumonia severity index
	ChiCTR2000029432	Single arm	72	Tanreqing	...	NCP	2020-02-01 to 2020-04-30	Temperature
	ChiCTR2000029605	RCT	400	Shuanghuanglian	...	NCP	2020-02-05 to 2021-02-05	Disease recovery
	ChiCTR2000029418	RCT	42	TCM	Western medicine	Severe NCP	2020-02-03 to 2020-08-31	Critically ill rate
	ChiCTR2000029400	Non-RCT	20	TCM	LPV/r	NCP	2020-01-29 to 2020-12-31	Remission

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Received 05 March 2021; Accepted 01 April 2021.

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