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EDITORIAL

Treatments in the COVID-19 pandemic: an update on clinical trials

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1. Introduction

The coronavirus disease-19 (COVID-19), caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), has spread rapidly and widely around the world, with more than 4,900,000 confirmed cases and more than 320,000 deaths reported as of 20 May 2020. The most common clinical symptoms are fever, cough, fatigue, and dyspnea, and a few patients have some other symptoms such as headache, hemoptysis, and diarrhea [1–4]. Previous experience in the treatment of coronavirus, such as SARS-COV and MERS-COV, has provided clinicians with a reference point for dealing with the novel coronavirus. Although there is still no specific drug, the increasing number of COVID-19 related reports around the world provide relevant insights for clinical treatment. This paper will summarize and discuss the current therapeutic drugs treating COVID-19 based on these reports of clinical trials.

2. The antiviral agents of COVID-19

COVID-19 belongs to the same genus of CoV as SARS-COV and MERS-COV, both of which are beta-cov. Whole genome sequencing showed that COVID-19 shared 79.5% of sequence identity with SARS-CoV [5]. In combination with the treatment experience of SARS-COV and MERS-COV, several potential drugs have been proposed for treatment of SARS-CoV-2, including arbidol, chloroquine, and human immunodeficiency virus-1 (HIV-1) protease inhibitors (lopinavir/ritonavir), new nucleoside analogues (remdesivir, GS-5734) and convalescent plasma. As for clinical broad-spectrum antiviral drugs, neuraminidase inhibitors (oseltamivir, peramivir, zanamivir, etc.) are not recommended for clinical use, since the coronavirus does not produce neuraminidase. In addition, nucleoside analogues are not recommended neither due to their little efficacy in vitro experiments or existing clinical studies. However, nucleoside analogues can be used in combination with interferon for antiviral treatment [6,7].

2.1. Arbidol

Arbidol (umifenovir) is a broad-spectrum antiviral compound approved in several countries for prophylaxis and treatment of influenza. It has been shown to inhibit SARS-CoV-2 in vitro [8]. In vivo, several retrospective studies have discussed the antiviral effects and safety of arbidol in patients with COVID-19. A study comprising 69 patientsfound that arbidol could improve the rate of discharge and without deaths occurred [9]. Another study showed that the participant group that was given arbidol had a shorter duration of positive RNA test compared to those in the lopinavir/ritonavir group, and no side effects were observed [10]. In addition, when compared tolopinavir/ritonavir only, combination group of arbidol and lopinavir/ritonavir was treatment significantly elevated negative conversion rate of coronavirus' test in 7-day and 14-day, and improved the chest CT scans in 7-day [11]. However, a retrospective study found that for non-ICU COVID-19 patients, arbidol might not accelerate SARS-CoV-2 clearance nor improve prognosis, compared to the control group [12]. These reports are all retrospective studies with a small sample size, and the conclusions are controversial. The efficacy and safety of arbidol needs to be further verified through randomized controlled clinical trials. Additionally, the current clinical dosage of arbidol (200 mg, 3 times/day) may not be the ideal dosage to inhibit SARS-CoV-2 infection [8,13]; whether a higher dosage of arbidol is required for COVID-19 patients needs to be studied.

2.2. Chloroquine

Chloroquine has been widely used for prophylactic and curative treatment of malaria, and its anti-coronavirus properties was firstly reported in 2006 [14]. Several studies confirmed the efficacy of hydroxychloroquine and chloroquine on COVID-19 in in-vitro and preliminary in-vivo clinical trials [15,16]. Further, hydroxychloroquine was found to be more potent than chloroquine in inhibiting SARS-CoV-2 in-vitro [17]. Based on existing reports of clinical trials of hydroxychloroquine and chloroquine, a recent systematic review and meta-analysis found that compared to control/conventional treatment, hydroxychloroquine seems to be promising in terms of less number of cases with radiological progression, less time to body temperature normalization, and lower total cough days. However, no difference was observed in terms of virological cure (OR 2.37, 0.13–44.53), death or clinical worsening of disease (OR 1.37, 1.37–21.97), and safety (OR 2.19, 0.59–8.18) [18]. Some studies reported that chloroquine combined with azithromycin has a synergistic effect on the treatment of

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COVID-19 [19,20]; but the findings are limited by the fact that most of the data was from the same research group and the sample size was small. Another study did not find any strong antiviral activity or clinical benefit in hospitalized patients with severe COVID-19 when treated with a combination of hydroxychloroquine and azithromycin [21]. Thus, the benefit of combined chloroquine and Azithromycin treatment remain to be explored. Further, chloroquine has a wide range of adverse effects on cardiac function and conduction, including the risk of arrhythmia at high doses or even therapeutic doses, which may lead to prolonged QT interval or increased risk of Torsade DE Pointes (TdP) [22]. Cardio vascular complications are common in COVID-19 patients and are associated with poor prognosis [23,24]; the use of chloroquine may further negatively affect prognosis of such patients. Similarly, azithromycin might prolong the QT interval [25]. In clinical practice, doctors should pay enough attention to the patient's cardiac status before and during medication so as prevent time loss. To sum up, although hydroxychloroquine and chloroquine are cheap and promising drugs against SARS-CoV-2, they may also cause serious side effects and more clinical data is required to prove their efficacy and safety [26].

2.3. Lopinavir/ritonavir

Lopinavir/ritonavir (LPV/r) has been shown to inhibit virus replication in-vitro, in animal experiments, and to improve clinical outcomes in patients with SARS-COV or MERS-COV, making it a potential therapeutic option for SARS-CoV-2 [27]. Efficacy of lopinavir/ritonavir in the clinical treatment of COVID-19 has been discussed in many cases (Table 1). A newly reported retrospective single-center study of 94 patients found that the treatment regimen of interferon alfa (INF-α) + lopinavir/ritonavir and INF-α+ lopinavir/ritonavir + ribavirin may be beneficial for the treatment of COVID-19. In patients receiving this treatment, the clearance time of COVID-19 mRNA was positively correlated with the length of stay at the hospital. The clearance rate of COVID-19 mRNA was found to be significantly correlated with the decrease of serum creatine kinase (CK) and lactate dehydrogenase (LDH) levels. A decrease in serum LDH or CK may indicate a good response to COVID-19 therapy [28]. Another study comprising 10 patients also confirmed the positive effect of lopinavir on COVID-19, suggesting that eosinophil count was a predictor of disease progression [29]. Changes in these biochemical factors provide new indicators for clinical observation during treatment. Further, a study reported that the combination treatment of LPV-r and routine adjuvant medicine against pneumonia could produce much better efficacy on patients with COVID-19 infection compared to treatment with adjuvant medicine alone [30]. The limitation of the above mentioned three reports is that the number of cases is limited and more clinical data is needed for verification. However, several studies did not find any clinical benefits of lopinavir/ritonavir, suggesting that lopinavir/ritonavir had no significant effect on mortality and virus clearance in patients [4,27,31–34]. A randomized, controlled, open-label trial involving 199 patients reported that treatment with lopinavir/ritonavir did not affect time to clinical improvement as compared to the standard-care group (hazard ratio for clinical improvement, 1.31; 95% confidence interval [CI], 0.95 to 1.80). Mortality at 28 days and the percentage of patients with detectable viral RNA at various time points were similar in the lopinavir/ritonavir group and the standard-care group. Adverse gastrointestinal effects were more common in the lopinavir/ritonavir group, but the standard-care group experienced more serious gastrointestinal problems [34]. An observational cohort study from China found that arbidol and LPV/r did not promote the transformation of swab virus nucleic acid into negative nor did it improve symptoms in COVID-19 patients. Further, there was no significant increase in the incidence of adverse reactions after the combination of LPV-r or arbidol, such as gastrointestinal symptoms, which deter improvement of the disease [35]. The efficacy of lopinavir/ritonavir in the treatment of COVID-19 remains to be verified by further studies. Meanwhile, note that if there are adverse effects to lopinavir/ritonavir, such as diarrhea, nausea, stomatitis, fever, anemia, leukopenia, and hyperbilirubinemia, the use of the drug should be suspended or discontinued, as may be appropriate [36].

2.4. Remdesivir

Remdesivir appeared to be greatly effective in treating the cases of SARS-CoV and MERS-CoV. The inhibition of SARS-COV-2 by remdesivir has been verified in-vitro and in animal experiments, and it is superior to the effects of lopinavir/ritonavir combined with interferon-therapy [15,41]. For patients withCOVID-19, a study reports that 36 of 53 patients (68%) with severe COVID-19 who received remdesivir saw clinical improvement [42]. Acase of COVID-19 infection successfully cured by remdesivir was also reported in the US, and the patient showed significant improvement in clinical symptoms within 24 hours after treatment [43]. However, a randomized, double-blind, placebo-controlled multicenter study containing 237 patients found that compared to placebo, intravenous remdesivir did not significantly improve time to clinical improvement, mortality, or time to clearance of virus in patients with serious COVID-19. However, in patients treated within 10 days of symptom onset, remdesivir was nota significant factor, but was associated with a five-day reduction in the median time for clinical improvement [44]. The benefits of remdesivir for the treatment of COVID-19 are still uncertain, and larger sample sizes are needed to deepen our understanding of the treatment of COVID-19 with remdesivir.

2.5. Convalescent plasma

As a classic form of adaptive immunotherapy, convalescent plasma has been used for the prevention and treatment of many infectious diseases. Convalescent plasma is considered adirect and effective treatment option for COVID-19 due to the lack of a vaccine [45]. The plasma of patients recovering from COVID-19 may contain antibodies against the virus that causes the disease, which are effective against infection. The US Food and Drug Administration (FDA) has approved the use of convalescent plasma for the treatment of critically ill patients with COVID-19, and it also highlighted the need for clinical trials to prove the effectiveness and safety of convalescent plasma therapy [46]. Three reports documented 21 patients with COVID-19 after convalescent plasma therapy; all reported that convalescent plasma seemed to save lives, and no serious adverse reactions have been found in COVID-19 patients

Table 1. The clinical therapeutic effects of antiviral drugs on COVID-19.

Type of intervention	Therapeutic intervention	Treatment effects	n	Study type	Research time	Refs
Arbidol	36 (53.7%) patients received treatment of arbidol (dose of 0.4 g for three times a day, the median duration of arbidol was 9 days)	12 (33%) of 36 patients had been discharged in the arbidol-treated group, whereas 6 (19%) of 31 patients had been discharged in the arbidol-untreated group. All deaths occurred in the arbidol-untreated group.	69	Retrospective cohort study	From January 16 to 29 January 2020.	[9]
	Oral arbidol and LPV-r in the combination group and oral LPV-r only in the monotherapy group for 5–21 days	The SARS-CoV-2 could not be detected for 12(75%) of 16 patients' nasopharyngeal specimens in the combination group after seven days, compared with 6 (35%) of 17 in the monotherapy group ($p < 0 \cdot 05$). After 14 days 15(94%) of 16 and 9 ($52 \cdot 9\%$) of 17, respectively, SARS-CoV-2 could not be detected ($p < 0 \cdot 05$). The chest CT scans were improving for 11(69%) of 16 patients in the combination group after seven days, compared with 5(29%) of 17 in the monotherapy group ($p < 0 \cdot 05$).	33	Retrospective cohort study	From 17 January 2020, to 13 February 2020	[11]
	Lopinavir/ritonavir group(n = 34) received 400 mg/100 mg of lopinavir/ritonavir twice a day for a week, the arbidol group (n = 16) was given 0.2 g arbidol, three times a day	On day 14 after the admission, no viral load was detected in arbidol group, but the viral load was found in 15(44.1%) patients treated with lopinavir/ritonavir. Patients in the arbidol group had a shorter duration of positive RNA test compared to those in the lopinavir/ritonavir group ($P < 0.01$). No apparent side effects were found in both groups.	50	Retrospective cohort study	From January 23 to 29 February 2020.	[10]
	Patients in umifenovir group(n = 45) received umifenovir at 0.2 gram three times a day, and thecontrol group (n = 36) receivedsymptomatictreatment only	33/45 (73.3%) patients in umifenovir group were tested negative in SARS-CoV-2 within 7 days after admission, the number was 28/36 (77.8%) in control group ($p = 0.19$). The median time from onset of symptoms to SARS-CoV-2 turning negative were 18 days (interquartile range [IQR] 12–21) in umifenovir group and 16 days (IQR, 11–21) in control group ($p = 0.42$). Patients in umifenovir group had longer hospital stay than patients in control group (13 days [IQR, 9–17] vs 11 days [IQR, 9–14], $p = 0.04$).	81	Retrospective study	From 2 February 2020 to 20 March 2020	[12]
hydroxychloroquine and chloroquine	Oral hydroxychloroquine sulfate 200 mg, three times per day during ten days	At day6 post-inclusion, 70% of hydroxychloroquine-treated patients were virologicaly cured comparing with 12.5% in the control group ($p = 0.001$). Hydroxychloroquine is efficient in clearing viral nasopharyngeal carriage of SARS-CoV-2 in COVID-19 patients in only three to six days, in most patients.	20	open-label non-randomized clinical trial	From early March to 16 March 2020	[19]
	A combination of 200 mg of oral hydroxychloroquine sulfate, three times per day for ten days combined with azithromycin (500 mg on D1 followed by 250 mg per day for the next four days).	All patients improved clinically except one 86 year-old patient who died, and one 74 year-old patient still in intensive care. A rapid fall of nasopharyngeal viral load was noted, with 83% negative at Day7, and 93% at Day8. Virus cultures from patient respiratory samples were negative in 97.5% of patients at Day5. Patients were able to be rapidly discharged from IDU with a mean length of stay of five days.	80	uncontrolled non-comparative observational study	From 3 to 21 March 2020	[20]
	600 mg hydroxychloroquine for 10 days + azithromycin 500 mg x1, then 250 mg	One patient died, two were transferred to the ICU, and one had medications stopped secondary to QTc prolongation. 8/10 had positive nasopharyngeal swabs at days 5–6 (80%, 95% CI: 49–94).	11	Prospective open-label study	Before 30 March 2020	[21]

(*Continued*)

Table 1. (Continued).

Type of intervention	Therapeutic intervention	Treatment effects	n	Study type	Research time	Refs
Lopinavir/ritonavir	The test group (n = 42) was treated with LPV-r(400/100 mg for adults, twice a day or 800/200 mg once a day with food) combined with adjuvant medicine(interferon aerosol inhalation and arbidol), while those in the control group (n = 5) were just treated with adjuvant medicine.	Lowering the body temperature (test group: 4.8 ± 1.94 days vs. control group: 7.3 ± 1.53 days, p = 0.0364). Restoring normal physiological mechanisms (test group: the abnormal proportion of white blood cells, lymphocytes, C-reactive protein and ALT/AST could be reduced to some extent). The number of days for nCoV-RNA turning negative after treatment (test group: 7.8 ± 3.09 days vs. control group: 12.0 ± 0.82 days, p = 0.0219).No evident toxic and side effects.	47	Retrospective study	From January 22 and January 29,2020	[30]
	Lopinavir/ritonavir was started from the hospital day 8 (day 10 of illness); 2 tablets (lopinavir 200 mg/ritonavir 50 mg) were given per oral bid	When lopinavir/ritonavir was used, we found reduced viral loads and improved clinical symptoms during the treatment.	1	Observational	Confirmed to have COVID-19 on January 26	[37]
	Lopinavir/ritonavir (Kaletra, lopinavir 400 mg/ritonavir 100 mg, q12 h, po), arbidol (0.2 g, tid, po), and ShufengJiedu Capsule (a traditional Chinese medicine,2.08 g, tid, po). The duration of antiviral treatment was 6–15 days	Three patients showed significant improvement in pneumonia associated symptoms, two of whom were confirmed to be COVID 19 negative and discharged, and one of whom was negative for the virus at the first test.	4	Retrospective study	From January 21 to January 24	[38]
	Five individuals requiring supplemental oxygen were treated with lopinavir/ritonavir (400 mg/100 mg twice daily orally for up to 14 days)	Evidence of clinical benefit was equivocal. Decline in viral load as indicated by the cycle threshold value from nasopharyngeal swabs appeared similar between those treated and not treated with lopinavir/ritonavir(for 7 days or longer). Four of the 5 patients treated with lopinavir/ritonavir developed nausea, vomiting, and/or diarrhea, and 3 developed abnormal liver function test results.	18	Descriptive case	From January 23 to 3 February 2020	[32]
	Lopinavir/ritonavir (400 mg and 100 mg, respectively) twice a day for 14 days	No benefit was observed with lopinavir/ritonavir treatment beyond standard care. The lopinavir/ritonavir group vs. the standard-care group: time to clinical improvement (hazard ratio for clinical improvement, 1.31; 95% confidence interval [CI], 0.95 to 1.80), mortality at 28 days (19.2% vs. 25.0%; difference, −5.8 percentage points; 95% CI, −17.3 to 5.7), the percentages of patients with detectable viral RNA at various time points (similar), a median time to clinical improvement in a modified intention-to-treat analysis (shorter by 1 day, hazard ratio, 1.39; 95% CI, 1.00 to 1.91). Gastrointestinal adverse events were more common in the lopinavir/ritonavir group, but serious adverse events were more common in the standard-care group.	199	Randomized, controlled, open-label trial	From 18 January 2020, through 3 February 2020	[34]
	Lopinavir+Ritonavir	The mortality of elderly patients with COVID-19 (5.56%) is higher than that of young and middle-aged patients (5.26%). The proportion of elderly patients with PSI grade IV and V (22.22) is significantly higher than that of young and middle-aged patients (5.26, P < 0.05)	56	Retrospective study	From 15 January 2020 to 18 February 2020	[31]
IFN-α + Lopinavir/ritonavir	IFN-α + lopinavir/ritonavir or IFN-α + lopinavir/ritonavir + ribavirin.	COVID-19 mRNA conversion time was correlated with the hospital stay length in both IFN-α + lopinavir/ritonavir and IFN-α + lopinavir/ritonavir+ ribavirin treatment group. These two therapeutic regimens might be beneficial for treatment of COVID-19 infected patients.	94	Retrospective, single-center study	From Jan 5 to 13 February 2020	[28]
	Interferon alfa by aerosolization twice a day and 14 (39%) received lopinavir/ritonavir syrup twice a day	All patients have been cured. Mean time in hospital was 14 (SD 3) days.	36 (pediatric patients)	Observational cohort study	From Jan 17 to 1 March 2020	[39]
	Lopinavir,400 mg, every twelve hours and interferon α2b atomization inhalation, 5 million U twice daily or Single drug of LPV(in patient 7 only)	Lopinavir has a positive effect on COVID-19 patients. The result of SARS-CoV-2-RNA of patient 6 remained positive for four days after that of other six discharged cases who with continuous using of LPV turned to negative. Most patients had hypokalemia and digestive adverse effect in four days after the beginning of treatment.	10	Retrospective observational single-center study	From 22 January 2020 and 11 February 2020	[29]

(*Continued*)

Table 1. (Continued).

Type of intervention	Therapeutic intervention	Treatment effects	n	Study type	Research time	Refs
Remdesivir	Intravenous remdesivir (a novel nucleotide analogue prodrug in development) was initiated on the evening of day 7	The patient with severe pneumonia showed significant improvement in clinical symptoms within 24 hours after treatment.	1	Case report	Confirmed to have COVID-19 on January 20	[43]
	A 10-day course of remdesivir (200 mg administered intravenously on day 1, followed by 100 mg daily for the remaining 9 days of treatment)	Clinical improvement was observed in 36 of 53 patients (68%) after treatment.	53	Observational study	From January 25,2020 to 30 March 2020	[42]
	Patients received either intravenous remdesivir (200 mg on day 1 followed by 100 mg on days 2–10 in single daily infusions, n = 158) or the same volume of placebo infusions for a total of 10 days (n = 79)	Remdesivir use was not associated with a difference in time to clinical improvement (hazard ratio 1 · 23 [95% CI 0 · 87–1 · 75]). Patients receiving remdesivir had a numerically faster time to clinical improvement than those receiving placebo among patients with symptom duration of 10 days or less (hazard ratio 1 · 52 [0 · 95–2 · 43]). Adverse events were reported in 102 (66%) of 155 remdesivir recipients versus 50 (64%) of 78 placebo recipients. Remdesivir was stopped early because of adverse events in 18 (12%) patients versus four (5%) patients who stopped placebo early.	237	randomized, double-blind, placebo-controlled, multicenter trial	From 6 February 2020 to 12 March 2020	[44]
Convalescent plasma	Each received 2 consecutive transfusions of 200 to 250 mL of ABO-compatible convalescent plasma (400 mL of convalescent plasma in total, the patients received antiviral agents continuously until the SARS-CoV-2 viral loads became negative)	As assessed by Ct, viral load declined within days of treatment with convalescent plasma, and the clinical conditions of these patients improved, as indicated by body temperature reduction, improved Pao2/Fio2, and chest imaging. Four patients who had been receiving mechanical ventilation and ECMO no longer required respiratory support by 9 days after plasma transfusion.	5	Observational study	From 20 January 2020, to 25 March 2020	[40]
	One dose of 200 mL of inactivated convalescent plasma with neutralization activity of >1:640 was transfused into the patients within 4 h following the WHO blood transfusion protocol	One dose (200 mL) of convalescent plasma was well tolerated and could significantly increase or maintain the neutralizing antibodies at a high level, leading to disappearance of viremia in 7 d. Clinical symptoms and paraclinical criteria rapidly improved within 3 d.	10	Prospective study	From 23 January 2020, to 19 February 2020	[48]
Oseltamivir	38 (93%) patients received antiviral therapy (oseltamivir, orally 75 mg twice daily)	As of 22 January 2020, 28 (68%) of 41 patients have been discharged and six (15%) patients have died. The efficacy of oseltamivir was not evaluated.	41	Observational study	From 31 December 2019 to 2 January 2020	[33]

using convalescent plasma [47–49]. All of them have the limitation of small sample size and no control, so larger sample size randomized controlled trials are needed to strictly prove their effectiveness. In addition to studies on the efficacy and safety of convalescent plasma, the optimal dose, and the optimal time point of treatment also need to be considered [48,50].

3. Tocilizumab

Tocilizumab is commonly used adjuvant therapies for COVID-19 (Table 2). The use of tocilizumab is based on the observation of excess pro-inflammatory cytokine production mediated cytokine storms in critically ill patients infected with COVID-19 [3,33]. Anti-interleukin-6 (IL-6) may play a key role in cytokine storms [51,52]. In a retrospective multi-center study of 150 patients in Wuhan city, IL-6 levels in patients were found to be a clinical predictor of COVID-19 mortality [53]. IL-6 is a potential therapeutic target for COVID-19 patients to prevent or relieve cytokine storms. As the first IL-6 blocking antibody to be marketed by targeting IL-6 receptors, tocilizumab appears to be an effective therapeutic option.

Tocilizumab has been approved in China to treat patients with severe complications from COVID-19 that show elevated IL-6 plasmalevels, but no reliable evidence has been published regarding the safety or efficacy of tocilizumab in the treatment of COVID-19 patients. Retrospective studies have found that most patients with severe COVID-19 have improved clinical symptoms and good prognosis after treatment with

Table 2. The clinical therapeutic effects of tocilizumab on COVID-19.

Type of intervention	Therapeutic intervention	Treatment effects	n	Study type	Research time	Refs
Tocilizumab	The dose of tocilizumab ranges from 80 to 600 mg per time. Eight (53.3%) patients received Tocilizumab in combination with methylprednisolone. Five (33.3%) patients received tocilizumab administration twice or more	In most patients, the value of CRP at the first time it was detected after TCZ therapy was significantly decreased compared with before TCZ therapy, which dropped from 126.9 (10.7-257.9) to 11.2 (0.02-113.7) mg/L ($P < .01$). After starting TCZ therapy, serum IL-6 level in 10 (66.7%) patients tended to spike shortly in first and then decreased. The four critically ill patients who received only single dose of TCZ therapy showed no improvement.	15	Retrospective observational single-center study	From January 27 to 5 March 2020	[54]
	Patients were treated with tocilizumab (the first dose was 4–8 mg/kg body weight, and the recommended dose was 400 mg through an I.V. drip up to a maximum of 800 mg). In case of fever within 12 h, an additional dose was given (same as before), and the cumulative dose could not be more than two times + standard care	Clinical data showed that the symptoms, hypoxygenmia, and CT opacity changes were improved immediately after the treatment with tocilizumab in most of the patients. All patients have been discharged including critical ones. The mean hospitalization time was 15.1 ± 5.8 d after the treatment with tocilizumab. All patients have been discharged including critical ones. Among them, 13 (61.9%) patients were discharged within 2 wk after tocilizumab, and 6 were discharged within 3 wk.	21	Retrospective study	From February 5 to 14 February 2020	[55]
	The 'tocilizumab group' (n = 20) received standard treatment and tocilizumab. The standard treatment group (n = 25) received standard treatment butwithout tocilizumab	Our combined primary endpoint (death and/or ICU admission) was higher in the ST group than in the TCZ group (72% vs 25%, P = 0.002) .Patients in the ST group more often required invasive mechanical ventilation than patients in the TCZ group (32% vs 0%, P = 0.006).No statistical difference was observed between the two groups in terms of mortality, unlike ICU admissions; however, death clearly tended to be more frequent in the ST group than in the TCZ group (48% vs 25%, P = 0.066).	45	Retrospective study	From March 1 to 18 March 2020 (the standard treatment group), From April 1 to 13 April 2020 (the tocilizumab group)	[56]
	Tocilizumab was administered at a dosage of 8 mg/kg by two consecutive intravenous infusions 12 h apart (a third infusion was optional based on clinical response)	Overall, at 10 days, the respiratory condition was improved or stabilized in 77 (77%) patients, of whom 61 showed a significant clearing of diffuse bilateral opacities on chest x-ray and 15 were discharged from the hospital. Respiratory condition worsened in 23 (23%) patients, of whom 20 (20%) died.	100	Prospective single-center study	From March 9 to 20 March 2020	[57]

tocilizumab [51,54,55]. Compared with standard treatment alone, administering tocilizumab can reduce the rate of hospitalization and/or mortality in the intensive care unit ofCOVID-19 patients [56]. However, the sample size of these studies is small, and there may be bias. A recent prospective study in a single center with 100 patients from Italy found that patients with severe COVID-19 pneumonia with hyper inflammatory syndrome and acute respiratory failure responded to tocilizumab rapidly and continually, and with significant clinical improvements [57]. However, it is important to note that tocilizumab may cause serious adverse reactions, such as intestinal perforation, candida infection, and lipid metabolism disorder [58–60].

4. Conclusions and expert opinion

There is no specific drug to treat COVID-19 up to date. Due to the lack of clinical data, the discussion on the efficacy and safety of drugs for the treatment of COVID-19 remain controversial and limited. More centralized, randomized, controlled, double-blind clinical trials are needed to establish effectiveness and safety of drugs for treating COVID-19.

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