Should arbidol be used in the treatment of COVID-19?

Authors: Katrina Loren R. Rey, MD, DPPS (krrey@up.edu.ph), Abigail F. Melicor, MD (afmelicor@yahoo.com)
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KEY FINDINGS

There is insufficient evidence to recommend arbidol for patients with COVID-19.

- Arbidol (Umifenovir) has a broad-spectrum antiviral activity that inhibits the replication of influenza viruses in vitro. It is used as prophylaxis and treatment of influenza in Russia and China [1,2].
- A proposed mechanism against SARS-CoV-2 identifies the spike glycoprotein essential for cell adherence and entry as the target of the drug [3].
- Based on two unpublished clinical trials, with low to moderate quality of evidence, there is insufficient evidence to support the use of arbidol for COVID-19 patients. One randomized controlled trial (RCT) showed no significant difference in the clinical recovery rate for arbidol compared to favipiravir for moderate to severe COVID-19 cases. However, favipiravir showed borderline significance favoring benefit in the clinical recovery rate in the subgroup of moderate COVID-19 patients. Favipiravir also showed significant time of fever reduction, shorter cough relief and prevention of new-onset dyspnea [4].
- Another RCT showed no significant differences between arbidol compared to lopinavir/ritonavir and supportive care alone in the viral clearance, disease progression, clinical status on days 7 and 14 of treatment and chest CT scan improvement [5].
- Observational studies on the effect of arbidol on viral shedding [6,8], viral clearance [7,10] and length of hospital stay [8,10,11] have conflicting results but showed significant chest CT scan improvement [7,9] and reduction in mortality in favor of arbidol [9,11]. However, these studies have low quality of evidence.
- Adverse events for arbidol reported in COVID-19 clinical trials and observational studies include mild diarrhea and nausea [4,5,7,8,10,12], elevated serum uric acid [4], elevated SGPT/ALT [4,5,6,12] and elevated bilirubin [7].
- There are ten ongoing clinical trials on arbidol and results are expected from May 2020 to February 2021.
- The National Health Commission & State Administration of Traditional Chinese Medicine mentioned the use of arbidol at a dose of 200 mg three times daily for adults for no longer than 10 days as part of the possible antiviral agents as treatment for COVID-19 [17]. No other guidelines have recommended arbidol [13-16].

RESULTS

There are two unpublished randomized controlled trials [4,5] and seven observational studies (6 retrospective cohort, 1 retrospective case series) all done in China [6-12]. There are ten ongoing clinical trials from China, Iran and Egypt. Characteristics of the included studies are presented in Appendix 1.

A multi-center, open-label, randomized controlled trial conducted by Chen *et al*. compared favipiravir and arbidol with 236 adult COVID-19 patients randomly assigned to favipiravir group (n = 116) and arbidol group (n = 120). Analysis for subgroups of moderate cases, severe cases and cases with hypertension and/or diabetes mellitus were reported. There was no significant difference in the clinical recovery rate for arbidol compared to favipiravir for moderate to severe COVID-19 cases (p = 0.1396, computed RR 0.80, 95% CI 0.60, 1.08). However, favipiravir showed borderline significance favoring benefit in the clinical recovery rate in the subgroup of moderate patients ($p = 0.0199$, RR 0.65, 95% CI 0.44, 0.94). Favipiravir also showed significant time of fever reduction, shorter cough relief ($p < 0.0001$) and prevention of new-onset dyspnea ($p < 0.0174$) [4]. Results are of low quality due to non-blinding, difference in the baseline characteristics and variation in establishment of patient diagnosis.

An exploratory RCT in a single center or the ELACOI study compared 3 treatment groups: arbidol group (n=35), lopinavir/ritonavir (LPV/r) (n=34) and supportive care alone (n=17) for mild to moderate cases COVID-19 cases. After 14 days of treatment no significant effect was reported in SARS-CoV-2 negative conversion of arbidol compared to LPV/r (RR 0.5829 95%CI: 0.1509 to 2.2513) and supportive treatment (RR 0.3643 95% CI: 0.0916 to 1.4484). Arbidol did not have significant effect on disease progression compared to LPV/r (RR 0.3643, 95% CI: 0.1054 to 1.2590) and supportive treatment (RR 0.7286, 95% CI: 0.1341 to 3.9596). Chest CT scan improvement and symptom resolution were also similar for the three groups on days 7 and 14 of treatment [5]. Evidence is of moderate quality due to small sample size, imprecise results and limited applicability to mild and moderate cases.

Observational studies on the effect of arbidol on viral shedding [6,8], viral clearance [7,10] and length of hospital stay [8,10,11] have conflicting results but showed significant chest CT scan improvement [7,9] and reduction in mortality in favor of arbidol [9,11]. In two different retrospective cohorts, there was significant chest CT scan improvement in the combination of arbidol and LPV/r compared to LPV/r monotherapy (69% vs 29%, $p<0.05$) [7] and higher average reduction in CT scan lesion size in the arbidol-treated group compared to the arbidol-untreated group (46.30% vs 36.80%) [9]. There was also a reduction in mortality in favor of arbidol-treated group compared to the arbidol-untreated group (HR 0.350, 95%CI 0.177 to 0.689) [9]. However, these studies have low quality of evidence because they were non-randomized controlled trials with limited sample size. Three studies showed selection bias favoring arbidol [6,9,11].

Adverse events for arbidol reported in COVID-19 clinical trials and observational studies include mild diarrhea and nausea [4,5,7,8,10,12], elevated serum uric acid [4], elevated SGPT/ALT [4,5,6,12] and elevated bilirubin [7]. No discontinuation of treatment was reported due to occurrence of adverse drug reactions from arbidol. Adverse reactions resolved after treatment [4,12].

There are ten ongoing clinical trials on arbidol (umifenovir) (6 in China, 3 in Iran, 1 in Egypt). The dose, duration of treatment and comparators are highly varied which includes Interferon-β 1a, Lopinavir/Ritonavir, Hydroxychloroquine, Carrimycin, honey and standard treatment. The primary outcomes were viral clearance and clinical improvement. Results from some studies are expected from May 2020 to February 2021. Characteristics of ongoing clinical trials are seen in Appendix 2.

CONCLUSION

Based on two unpublished randomized controlled trials, with low to moderate quality of evidence, there is insufficient evidence to support the use of arbidol for COVID-19 patients. However, in one RCT, compared to arbidol, favipiravir showed borderline significance favoring benefit in the clinical recovery rate in the subgroup of moderate COVID-19 patients. Favipiravir also showed significant time of fever reduction, shorter cough relief and prevention of new-onset dyspnea. The observational studies have conflicting

results on the effect of arbidol on viral shedding, viral clearance and length of hospital stay but showed significant chest CT scan improvement and reduction in mortality in favor of arbidol. However, these studies have low quality of evidence. Adverse events reported for arbidol include elevated serum uric acid level, elevated SGPT/ALT, elevated bilirubin, mild diarrhea and nausea. High-quality randomized controlled trials are still warranted to recommend its use in COVID-19.

Declaration of Conflict of Interest

No conflict of interest

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Table 1. Characteristics of included studies

No.	Title/Author	Study design	Country	Population	Intervention Group(s)	Comparison Group(s)	Outcomes	Key findings
1	Favipiravir versus Arbidol for COVID-19: A Randomized Clinical Trial Chen C, Huang J, Cheng Z, Wu J, Chen S, Zhang Y, et al.	Multi-center, open-label, randomized controlled trial	Wuhan, China	Adult patients (> 18 years old) with COVID-19 (N = 236) Exclusion: elevated ALT/AST >6x or Child Pugh C, severe patients whose expected survival time<48 hours .	Favipiravir group (n = 116) Routine treatment + famiravir tablets (1600 mg/time on the first day, twice a day; 600 mg/time from the second day to the end of the experiment, twice a day). Course of treatment 7-10 days but may be extended according to researcher's judgment.	Arbidol group (n = 120) Routine therapy + arbidol (200 mg each time, 3 times a day, from the first day to the end of the trial). Course of treatment 7-10 days but may be extended according to researcher's judgment.	Primary outcome: Clinical recovery rate at 7 days or end of treatment, which was stratified as ordinary patients with COVID-19, critical patients with COVID-19, COVID-19 patients with hypertension and/or diabetes. Secondary outcomes: fever reduction, cough relief, auxiliary oxygen therapy or noninvasive mechanical ventilation, rate of respiratory failure Safety outcome: adverse events (abnormal liver function tests, serum uric acid, psychiatric symptoms, digestive tract reactions)	There was no significant difference between the clinical recovery rate after 7 days for the two groups ($p = 0.1396$). For moderate cases, there is a statistically significant difference for Favipiravir compared to arbidol ($p = 0.0199$) with Favipiravir showing beneficial results (RR 0.65, 95% CI 0.44 to 0.94). No significant difference was seen for severe cases ($p = 0.4712$, RR 0.94, 95% CI 0.84 to 1.06). Result for patients with hypertension and/or diabetes was not statistically significant ($p = 0.7704$) and were inconclusive (RR 0.93, 95% CI 0.58 to 1.50). For moderate COVID-19 patients and those with hypertension and/or diabetes, the time of fever reduction and cough relief in the favipiravir group was significantly shorter than that in the arbidol group ($p < 0.0001$). No significant difference was observed on the need for O2 support or noninvasive mechanical ventilation between the two groups but Favipiravir was beneficial in preventing new-onset dyspnea ($p = 0.0174$, RR 0.30, 95% CI 0.10 to 0.87). For adverse events, no significant difference between the cumulative adverse events for the two groups ($p = 0.1410$) but elevated serum uric acid level was significantly higher in the FPV group ($p = 0.0014$, RR 5.52, 95% CI 1.65 to 18.44). Adverse reactions resolved upon patient's hospital discharge.
2	An exploratory randomized controlled study on the efficacy and safety of lopinavir/ritonavir or arbidol treating adult patients hospitalized with	Single-center, randomized controlled trial	China	Hospitalized, laboratory confirmed COVID-19 patients (n=86)	Arbidol 200 mg 3x daily for 7-14 days + supportive care (n=35)	Lopinavir/ritonavir 200mg/50mg 500mg 2x daily for 7-14 days + supportive care (n=34)	Primary: Time of positive-to-negative conversion of SARS-CoV-2	The mean time for positive-to-negative conversion of SARS-CoV-2 was 9.0 days in the LPV/r group, 9.1 days in the arbidol group and 9.3 days in the control group with no significant difference (p=0.981)

	mild/moderate COVID-19 (ELACOI) Yueping L, Zhiwei X, Weiyin L, Weiping C, Chunyan W, Yujuan G, et al.					Or Supportive care alone (n=17)	Secondary: Rate of positive-to-negative conversion of SARS-CoV-2 at day 7 and day 14 of treatment Rate of fever resolution (axillary temperature ≤37.3°C for more than 72 hours) Rate of cough alleviation Improvement rate of chest CT at day 7 and 14; Deterioration rate of clinical status (mild/moderate to severe/critical)	The rate of positive-to-negative conversion was 35.3% (day 7) and 85.3% (day 14) in the LPV/r group, 37.1% (day 7) and 91.4 (day 14) in the arbidol group and 41.2% (day 7) and 76.5% (day 14) in the control group. There was no significant difference in the secondary outcomes between the three groups. Adverse events with arbidol include diarrhea (8.6%) and nausea (5.9%). The LPV/r group had diarrhea (26.5%), loss of appetite (14.7%) and elevation of ALT (4.8%). No adverse events in the control group
3	Arbidol monotherapy is superior to lopinavir/ritonavir in treating COVID-19 Zhu Z, Lu Z, Xu T, Chen C, Yang G, Zha T, Lu J, Xue Y.	Retrospective cohort	China	Laboratory-confirmed COVID-19 patients (n = 50)	Lopinavir/ritonavir group (n = 34) 400 mg/100mg twice a day for 7 days Conventional therapy (O2 (2L/min for 30mins 3x a day), atomized inhalation of recombinant human interferon-α 2b injection (5 million units, twice a day)	Arbidol group (n = 16) 0.2 g three times a day Conventional therapy (O2 (2L/min for 30mins 3x a day), atomized inhalation of recombinant human interferon-α 2b injection (5 million units, twice a day)	Cycle threshold values of open reading frame 1ab (*ORF1ab*) and nucleocapsid (*N*) genes by RT- PCR assay Development of adverse drug reaction	For both *ORF1ab* and *N* genes, there was no significant differ- ence in baseline Ct values between the two groups (both P >0.05). On day seven after admission, the viral load was undetectable in half of the patients receiving arbidol and in 23.5% of the patients treated with lopinavir/ritonavir group. 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 ($p < 0.01$). Three patients in the lopinavir/ritonavir group and three patients in the arbidol group showed an elevated level (< 125 U/L) of ALT in the first week of admission ($\chi2 = 0.047$, $P = 0.99$).
4	Arbidol combined with LPV/r versus LPV/r alone against Corona Virus Disease 2019: A retrospective cohort study.	Retrospective cohort	China	Adults with laboratory-confirmed COVID-19 without Invasive ventilation (n=33)	Arbidol combined with LPV/r (n=16) Arbidol 200 mg every 8 h and lopinavir (400	LPV/r only (n=17) lopinavir (400 mg)/ritonavir (100 mg) orally every 12 h until coronavirus	Negative conversion rate of coronavirus on Day 7 and Day14	SARS-CoV-2 could not be detected for 12(75%) of 16 patients' nasopharyngeal specimens in the combination group on Day 7, compared with 6 (35%) of 17 in the monotherapy group ($p < 0.05$).

	Deng L, Li C, Zeng Q, Liu X, Li X, Zhang H, Hong Z, Xia J.				mg)/ritonavir (100 mg) orally every 12 h until coronavirus is detected negative by RT-PCR for 3 times (5-21 days)	is detected negative by RT-PCR for 3 times (5-21 days)	Pneumonia on chest CT on day7	On day 14, 15 (94%) of 16 and 9 (52.9%) of 17 SARS-CoV-2 could not be detected ($p < 0.05$). 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 ($p < 0.05$).
5	Chloroquine, arbidol (umifenovir) or lopinavir/ritonavir as the antiviral monotherapy for COVID-19 patients: a retrospective cohort study Huang H, Guan L, Yang Y, Grange JML, Tang G, Xu Y, et al.	Retrospective cohort	China	Hospitalized, laboratory confirmed COVID-19 patients between January 19-March 16 (n=27)	200 mg (Umifenovir) every 8 hours (n=11)	500mg chloroquine phosphate 12-hourly (n=10) Or 400mg/100mg lopinavir/ritonavir 12-hourly (n=6)	Primary: Viral shedding interval (RT-PCR) Secondary: Length of hospital stay Hospitalization expenses (USD) Percentage of patients positive for SARS-CoV-2 at day 10 and day 14 Adverse events	The median viral shedding interval in the arbidol group was 8.0 days (95%CI: 4.9-11.1) while the longest median interval was in the lopinavir/ritonavir group at 13.0 days (95%CI: 12.2-23.8) and the shortest median interval in the chloroquine group at 5.0 days (95%CI: 0.4-9.6). At day 10 of treatment, SARS-CoV-2 testing was negative for 8 patients (72.7%) in the arbidol group, 9 patients (90%) in the chloroquine group, and no patient in the lopinavir/ritonavir group. At day 14, all patients in arbidol and chloroquine groups were negative while only 3 patients in the lopinavir/ritonavir group were negative. Hopitalization expenses were reduced for chloroquine and arbidol groups compared to the L/R group. No significant difference in the hospital stay, hospital expenses, SARS-CoV-2 testing on day 10 and 14 of treatment for the chloroquine and arbidol group. Adverse events included nausea, vomiting, dysphoria and blurred vision for the chloroquine group (2 patients); diarrhea for arbidol group (1 patient) and L/R group (3 patients)
6	The effect of Arbidol Hydrochloride on reducing mortality of Covid-19 patients: a retrospective study of real world data from three hospitals in Wuhan Qibin L, Xuemin F, Lu T, Xianxiang C, Ungil C, Ke W, et al.	Retrospective cohort	China	Hospitalized, laboratory confirmed COVID-19 patients from Dec 13 to March 21 (n=504)	Arbidol (n=257)* Lopinavir* (n=259) Oseltamivir* (n=66) *may have been taken with other antivirals or other	Other antivirals or other treatment	Primary Mortality Secondary Change in CT scan lesion	Mortality was 7.0% for Arbidol, 12.12% for Oseltamivir, 14.29% for LPV/r. The OR after adjusting for sex, pre-existing condition, age, O2 saturation, lesion size and day of admission was 0.169 (95%CI: 0.071 to 0.398) for Arbidol, 0.212 (95%CI: 0.072 to 0.623) for Oseltamivir, and 0.363 (95%CI: 0.165 to 0.795) for LPV/r. Further adjustment of

					treatment (IVIG, glucocorticoid)			antiviral medications use revealed OR of 0.183 (95%CI: 0.075 to .446) for Arbidol and 0.220 (95%CI: 0.069 to 0.707) for Oseltamivir. After adjusting for patients' characteristics and antiviral medication use, the ratio of the lesion size after the treatment vs that before among patients taking Arbidol was 85.20% (95% CI, 74.47% to 97.48%; P=0.0203)
7	Umifenovir treatment is not associated with improved outcomes in patients with coronavirus disease 2019: A retrospective study Lian N, Xie H, Lin S, Huang J, Zhao J, Qichang L.	Retrospective cohort	China	Hospitalized, laboratory confirmed COVID-19 patients (n=81)	Umefinovir 0.2g 3x a day and supportive treatment (n=45)	Supportive treatment alone (n=36)	Primary: Rate of negative test for SARS-CoV-2 within 1 week from admission Time for positive-to-negative conversion Secondary Changes in CT scores after treatment Length of hospital stay	After 1 week, rate of negative SARS-CoV-2 was 73% for the treatment group and 78% for the control group with no significant difference. Median time to negative test from admission was longer for the umefinovir group (6 days vs 3 days, p<0.05). But median time to negative test from onset of symptoms was similar between the two groups (18 days for treatment vs 16 days for control, p>0.05). Length of hospital stay was longer in the treatment group (13 days vs 11 days, p=0.04) One patient in each group had disease progression requiring mechanical ventilation. Adverse events include diarrhea and nausea with 5 from treatment group and 3 from control group.
8	Clinical Features of 69 Cases with Coronavirus Disease 2019 in Wuhan, China. Wang Z, Yang B, Li Q, Wen L, Zhang R.	Retrospective case series	Wuhan. China	Adult patients with COVID-19 (n=67)	Arbidol-treated (n=36) 0.4 g 3x a day, median duration of 9 days *received other antiviral, antibiotic and supportive care	Arbidol-untreated (n=31) *received other antiviral, antibiotic and supportive care	Prognosis (hospitalized, discharge, death)	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.
9	Incidence of Adverse Drug Reactions in COVID-19 patients in China: an active	Retrospective chart review	China	Patients admitted for COVID-19 (n = 217)	All treatment for COVID-19		Adverse drug reactions by China Hospital	94 ADRs were identified in 82 patients. ADRs were mainly drug-induced gastrointestinal disorders (23.0%), liver

	monitoring study by Hospital Pharmacovigilance System Sun J, Deng X, Chen X, Huang J, Huang S, Li Y, Feng J, Liu J, He G.			mean age was 45.7 ± 16.6 years. 28.6% of them had underlying basic diseases (hypertension, cardiovascular disease, cerebrovascular disease, diabetes, cancer, chronic kidney disease, chronic liver disease, HIV, and COPD).	Lopinavir/ Ritonavir (n = 179) Umifenovir (n = 119) Chloroquine (n = 37)		Pharmacovigilance System (CHPS)	system disorders (13.8%), rash (4.15%) and hyperlipidemia (1.38%) ADRs were associated with lopinavir/ritonavir (60/94 or 63.8%), umifenovir (17/94 or 18.1%) and chloroquine (5/94 or 5.3%). Majority of the ADRs recorded were predominantly drug-induced gastrointestinal disorders (nausea, vomiting, diarrhea) and liver system disorders (elevated SGPT). 96.8% of ADRs occurred within 14 days of hospitalization. GI reactions occurred usually within 7 days. After treatment, all the ADRs were either cured (62.8%) or improved (37.2%). Multivariable analysis showed that length of stay (OR: 2.02, [95% CI: 1.03-3.96], *P*=0.04), number of drugs used in hospital (OR: 3.17, [95%CI: 1.60-6.27], *P*=0.001) and underlying basic diseases (OR:2.07, [95%CI: 1.02-4.23], *P* = 0.04) were independent risk factor for ADRs in the patients.

Table 2. Characteristics of clinical trials

No.	Clinical Trial ID / Title	Status	Start and estimated primary completion date	Study design	Country	Population	Intervention Group(s)	Comparison Group(s)	Outcomes
1	NCT04350684 Umifenovir in Hospitalized COVID-19 Patients (UAIIC)	Enrolling by invitation	4/15/20 – 4/24/20	randomized, double-blind, placebo-controlled, clinical trial	Tehran, Iran	Adult symptomatic COVID-19 confirmed cases by RT-PCR or Chest CT scan within 10 days of symptom-onset with SpO2 ≤ 93% And RR ≥ 22 (n=40) Exclusion: ▯ prolonged QT or PR intervals, 2nd or 3rd Degree heart block, Arrhythmias	Umifenovir + Interferon-β 1a + Lopinavir / Ritonavir + Single Dose of Hydroxychloroquine + Standards of Care	Interferon-β 1a + Lopinavir / Ritonavir + Single Dose of Hydroxychloroquine + Standards of Care	Time to clinical improvement (14 days) Secondary: ▯ Mortality ▯ SpO2 improvement ▯ Incidence of new mechanical ventilation use ▯ Duration of hospitalization

						□ Pregnant or lactating women. □ Alcohol or drug addiction in the past 5 years. □ ALT/AST levels > 5 times the upper limit of normal			□ Cumulative incidence of serious adverse events
2	NCT04252885 The Efficacy of Lopinavir Plus Ritonavir and Arbidol Against Novel Coronavirus Infection (ELACOI)	Recruiting	1/28/20 – 5/30/20	Randomized, Open-label, Controlled Study	China	Adults laboratory-confirmed with COVID-19, no serious renal or liver dysfunction (n=125) Exclusion: Severe nausea, vomiting, diarrhea and other clinical manifestations affect the oral or absorption of the drugs, serious underlying disease, pregnancy and lactation, alcohol or drug abuse	Standard treatment plus a regimen of lopinavir (200mg) and ritonavir (50mg) (oral, q12h, every time 2 tablets of each, taking for 7-14 days) (n=50) Standard treatment+arbidol (100mg) (oral, tid, 200mg each time, taking for 7-14 days) (n=50)	Standard treatment (n=25)	Rate of virus inhibition Secondary: Disease progression (temperature, RR, SpO2, chest imaging)
3	NCT04260594 Clinical Study of Arbidol Hydrochloride Tablets in the Treatment of Pneumonia Caused by Novel Coronavirus	Not yet recruiting	2/7/20 – 7/1/20	Randomized, Open label, Multicenter Study	China	Symptomatic adults confirmed with COVID-19 by RT-PCR (n=380) Exclusion: COVID-19 severe patients or critical condition, hematologic, liver, renal dysfunction, abnormal blood coagulation, neurologic disorder, heart disease, pregnant and immunocompromised	Arbidol tablets 2 tablets/time, 3 times/day for 14-20 days Basic treatment	Basic treatment	Virus negative conversion rate in 7 days Secondary: □ Virus negative conversion rate (14-20 days) □ Antipyretic rate □ Symptom relief □ SpO2 improvement □ Disease progression □ Mortality □ severe adverse reactions □ Change curve of peripheral blood lymphocyte count
4	NCT04286503 The Clinical Study of Carrimycin on Treatment Patients With COVID-19	Not yet recruiting	2/23/20 – 2/28/21	Multicenter, Randomized, Open-controlled Study	China	Adults diagnosed with COVID-19 pneumonia with SOFA score 1 – 13 points (n=520) Exclusion: Other viral pneumonia. Immunocompromised, taken antibiotics in past week, cannot take oral medications, severe underlying disease,	Carrimycin Basic treatment	Lopinavir/ritonavir tablets or Arbidol or chloroquine phosphate Basic treatment	Resolution of fever Pulmonary inflammation resolution time Negative conversion SARS-CoV-2 in throat swabs

						pregnancy and lactation, AST/ALT > 5x upper limit of normal (ULN), ECMO, critical patients with < 48 hrs life expectancy			
5	NCT04273763 Evaluating the Efficacy and Safety of Bromhexine Hydrochloride Tablets Combined With Standard Treatment/ Standard Treatment in Patients With Suspected and Mild Novel Coronavirus Pneumonia (COVID-19)	Active, not recruiting	2/16/20 – 6/1/20	Random, open label, sequential design	China	Adults with COVID-19 either laboratory (RT-PCR) with clinical symptoms or clinically diagnosed as suspected cases (n=18) Exclusion: ALT ≥ 5x ULN, total bilirubin ≥ 3x ULN or Crea ≥ 1.5x ULN, serious severe liver disease, severe COVID-19 pneumonia, history of severe GI diseases, lactose intolerance, pregnant or lactating women	Bromhexine Hydrochloride Tablets Arbidol Hydrochloride Granules Recombinant Human Interferon α2b Spray	Arbidol Hydrochloride Granules Recombinant Human Interferon α2b Spray	Clinical recovery within 14 days Rate of aggravation within 14 days Secondary: ▯ Clinical remission rate ▯ Dynamic changes of oxygenation index ▯ Time to cure ▯ Rate to cure ▯ Time to defervescence ▯ Time to cough remission ▯ Time to dyspnea remission ▯ Days of supplemental oxygenation ▯ Patients requiring supplemental O2 ▯ Patients on mechanical ventilation ▯ Time of negative COVID-19 nucleic acid results ▯ Rate of negative COVID-19 nucleic acid results ▯ Rate of ICU admission ▯ 28-day mortality
6	NCT04323345 Efficacy of Natural Honey Treatment in Patients With Novel Coronavirus	Recruiting	4/15/20 – 12/15/20	Randomized, Controlled, Single Masked, Investigator Initiated, Multi-center Trial	Cairo, Egypt	COVID-19 patients (5-75 years old) wither clinically or RT-PCR confirmed Exclusion: Children below 5 years old, severely ill patients with either terminal disease, cannot tolerate oral honey or NGT feeding	Natural honey in a dose of 1gm/kg/day divided into 2 to 3 doses for 14 days Standard care	Standard care: Supportive measures and lopinavir/ritonavir tablets or Arbidol or chloroquine phosphate or Hydroxychloroquine or oseltamivir with or without azithromycin	Rate of recovery from positive to negative swabs Resolution of fever Resolution of lung inflammation by CT or Xray Secondary:

									Mortality Days to negative swab result
7	IRCT20180725040596N2 Effect of Arbidol in treatment of COVID-19	Recruiting	4/29/20 – 9/22/20	Two arm parallel group, phase 3 trial, randomization using random blocks	Iran	Adults diagnosed with COVID-19 by chest CT-scan or RT-PCR test (n=100) Exclusion: Pregnancy and lactation, Respiratory failure, renal or liver failure, Anemia or thrombocytopenia, Coagulation disorders, immunodeficiency, comgenital heart disease, arrhythmia	oral Hydroxychloroquine with Arbidol orally at a dose of 50 mg 4 times daily for 5 to 10 days	standard treatment regimen including Kaletra (Lopinavir-Ritonavir) and Hydroxychloroquine	Antipyretic rate; Improvement of complete blood count ESR and CRP tests; Virus negative conversion rate; Improvement of blood oxygen saturation and no adjuvant oxygen therapy; Improvement of chest X-Ray
8	IRCT20200322046833N1 Evaluation of the efficacy and safety of Umifenovir in the treatment of hospitalized patients with covid-19: A randomized clinical trial	Recruitment complete	3/28/20 – 4/20/20	Randomized, double-blind, clinical trial	Iran	Symptomatic adults with probable and definitive diagnosis of covid-19 (virology or imaging) Exclusion: Hypersensitivity to drugs, pregnancy and lactation	Hydroxychlorquine 400 mg every 12 hours in the first day then 200 mg every 12 hours Atazanavir/Ritonavir 300/100 mg once daily Umifenovir 100 mg 2 capsules every 6 hours.	Hydroxychloroquine 400 mg every 12 hours for the first day then 200 mg every 12 hours Atazanavir / ritonavir 300/100 mg 2 placebo capsules (hand made) every 6 hours.	Clinical improvement
9	ChiCTR2000029993 A pilot study for Integrated Chinese and Western Medicine in the treatment of non-critical novel coronavirus pneumonia (COVID-19)	Recruiting	2/18/20	multicenter, randomized, open-label, parallel controlled trial	China	Adult with fever and with clinical diagnosis of COVID-19 (n=40) Exclusion: Critical cases with respiratory failure in need of mechanical ventilation, shock, organ failure in need of ICU, other respiratory infection, pregnant and lactating, immunodeficiency, liver dysfunction	Arbidol Hydrochloride Tablets, Liushen Capsule, standard therapy (n=20)	Standard therapy (n=20)	Symptom relief, time to conversion to negative COVID-19 RNA, time and rate of normalization of inflammatory biomarkers, time to recovery, frequency of antipyretic use, severe case occurrence, secondary infection, mortality, adverse effects
10	ChiCTR2000029621 Clinical study of arbidol hydrochloride tablets in the treatment of novel coronavirus pneumonia (COVID-19)	Recruiting	2/7/20	Multicenter, randomized, open-label, controlled trial	China	Mildly symptomatic adults with COVID-19 confirmed by nucleic acid positive by RT-PCR Exclusion:	Arbidol tablets + basic treatment (n=190)	basic treatment (n=190)	Virus negative conversion rate in the first week, symptom relief, fever resolution, SpO2 improvement, disease progression, mortality, Change

						Critical disease condition, renal or liver dysfunction, abnormal blood coagulation, pregnant and lactating, immunodeficiency, neurologic and developmental problems, heart disease			curve of peripheral blood lymphocyte count adverse reactions