Update on treatment of COVID-19: ongoing studies between promising and disappointing results

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SUMMARY

The COVID-19 pandemic represents the greatest global public health crisis since the pandemic influenza outbreak of 1918. We are facing a new virus, so several antiviral agents previously used to treat other coronavirus infections such as SARS and MERS are being considered as the first potential candidates to treat COVID-19. Thus, several agents have been used by the beginning of the current outbreak in China first and all over the word successively, as reported in several different guidelines and therapeutic recommendations. At the same time, a great number of clinical trials have been launched to investigate the potential efficacy therapies for COVID-19 highlighting the urgent need to get as quickly as possible high-quality evidence.

Through PubMed, we explored the relevant articles published on treatment of COVID-19 and on trials ongoing up to April 15, 2020.

Keywords: COVID-19, treatment, update.

INTRODUCTION

In December 2019, a new infection by the coronavirus, named Severe Acute Respiratory Syndrome (SARS)-CoV-2 causing severe acute respiratory syndrome, began in Wuhan, Hubei Province, China, and quickly spread around the world and was declared as a global concern (pandemic) by the World Health Organization (WHO).

Although still preliminary, current data suggest that bats are the most probable initial source of the current coronavirus disease-19 (COVID-19), previously known as "2019 novel coronavirus" (2019nCoV) outbreak, apparently spreading worldwide from a "wet market" [1].

The COVID-19 pandemic represents the greatest global public health crisis since the pandemic influenza outbreak of 1918, a bit more than a century ago.

Facing a new and unknown virus, antiviral agents previously used to treat other coronavirus infections such as SARS and Middle East Respiratory Syndrome (MERS) have been considered as the first potential candidates to treat COVID-19. Thus, several agents have been used by the beginning of the current outbreak in China first and all over the word successively, as reported in several different guidelines and therapeutic recommendations [2,3].

At the same time, a great number of clinical trials have been launched to investigate the potential efficacy therapies for COVID-19, highlighting the urgent need for an effective therapy, and to get as quickly as possible high-quality evidence.

The scope of the present review is to look for and update all the information currently available in literature concerning the main treatments of COVID-19 including small size experiences and case reports and to update the database concerning the ongoing clinical trials approved by national and International Drug Agencies.

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METHODS

We searched only on PubMed database for relevant articles published in English-language through April 14, 2020. We included only the terms of those drugs and/or therapeutic agents currently utilized without an approval indication for treatment of COVID-19. Therefore, we searched for the following keywords: "chloroquine", "hydroxychloroquine", "remdesevir", "favipiravir", "lopinavir/ritonavir", "tocilizumab", "convalescent plasma" and "immunoglobulins" and "COVID-19". We included in the search all clinical studies available on the mentioned including case reports. Furthermore, ongoing studies were searched using the same above reported keywords in the following websites: ClinicalTrials.gov and the Chinese Clinical Trial Registry.

HYDROXYCHLOROQUINE

Background

Chloroquine (CQ) and its derivate hydroxychloroquine (HCQ) belong to the class of aminoquinolines, which apart their efficacy as anti-malarial agents have relevant effects against a number of RNA viruses including Zika virus, Chikungunya-virus, SARS-CoV and MERS-CoV on the basis of *in vitro* or *in vivo* studies. Aminoquinolines activity against emerging virus has been proposed due to their capacity of targeting endosomal acidification as the major determinant of antiviral activity. This activity makes CQ/HCQ large-spectrum antiviral agents to be administered to newly recognized viral pathogens without effective alternatives in terms of targeted treatment [4].

HCQ and CQ are active also against SARS-CoV-2, as assessed by *in vitro* studies demonstrating their ability in inhibiting viral replication at multiple points during the initial phases of viral infection. Mainly, HCQ/CQ contrast SARS-CoV-2 by accumulating into lysosomes, elevating endosomal pH and by interrupting lysosome-endosome fusion, finally contrasting the release of the viral contents into intracellular space and cellular infection [5]. Moreover, SARS-CoV-2 is known to up-regulate cell surface angiotensin converting enzyme 2 (ACE2) receptor, which is an important virus receptor. HCQ/CQ inhibit such viral attachment by cell-surface protein glycosylation. Besides these well-known mechanisms of action, antiviral activity of HCQ/CQ can be explained by the binding to sialic acids of respiratory tract cells and to sialic-acid-containing gangliosides, which in turn inhibits cell/virus fusion by interacting with N-terminal domain of SARS-CoV-2 spike protein [6].

Moreover aminoquinolines influence immune system through cell signalling and regulation of pro-inflammatory cytokines, making HCQ an important immunomodulatory agent largely used for the treatment of inflammatory diseases such as rheumatoid arthritis. Such immunomodulatory effect can be relevant if we look at the inflammatory changes reported in patients with COVID-19 pneumonia [7].

Interestingly, CQ/HCQ have been demonstrated to reach high concentrations in many tissues with particular concentration into the lung where levels are 200-700 times higher than those in the plasma. All these characteristics suggest that HCQ/CQ can report the highest activity in treating early COVID-19 pneumonia or as a post-exposure prophylaxis of Health Care Workers accidently exposed to the virus [4, 9-10].

Clinical trials

On the basis of the preliminary results of a Chinese study assessing CQ efficacy in SARS-CoV-2 patients, treatment was more effective than untreated control by inhibiting the pneumonia exacerbation and finally shortening disease course with a faster viral clearance [11].

Further data derive from two small comparative studies, enrolling respectively 36 and 30 patients. The study by Gautret evaluated the efficacy of HCQ/azithromycin administration in an open label study enrolling 20 treated cases and 16 control cases and highlighted that HCQ treatment resulted in a higher proportion of negative nasal swabs at days 3 to 6 after treatment was started. The protocol proposed by this study considered HCQ 600 mg per day divided in 3 doses for ten days [12].

Another study by Chen et al. enrolling 30 patients did not demonstrate any difference in term of negative nasal swab after a 5-day period of HCQ at the dosage of 400 mg per day [13].

Other data derive from studies released prior to their peer review evaluation. On the basis of the study by Chen et al. evaluating 62 patients with mild illness caused by SARS-CoV-2 randomised to receive or not a 5-day course of HCQ (400

mg/d), an HCQ based treatment resulted in better outcome as assessed by less severe lesions at the chest CT scan performed at the end of HCQ treatment and by the absence of disease progression [14]. Instead, different conclusions can be drawn from the data reported by a study from Brazil, which highlights that high dosage of CQ (600 mg tid during a 10-day period) administered to patients with severe infection by SARS-CoV-2 result in an increase of Q-T prolongation in 25% of the cases without any benefit in terms of cure in respect to historical untreated control patients. Moreover, a study evaluating the data collected from 4 hospitals belonging to Paris area highlighted that HCQ treatment did not result in a reduction of the rate of death or intensive care admission in respect to standard supportive therapy, when cases with moderate-severe COVID-19 pneumonia were evaluated. Also, this study highlights that HCQ was associated with a high frequency (9.5%) of patients with Q-T prolongation) [16]. These articles are preprints and have not been certified by peer review. Thus, they report new medical research that have yet to be evaluated and so should *not* be used to guide clinical practice.

Ongoing trials

Since SARS-CoV-2 outbreak was identified, a number of institutional protocols have proposed CQ/HCQ administration to infected patients and, currently, 63 trials (including those on prophylaxis) have been submitted to clinicaltrials.gov, but data on these studies are not currently available and the majority of data on CQ/HCQ efficacy derives from *in vitro* or *in vivo* investigations.

Although 63 ongoing trials are currently registered on trials.gov (accessed 12/04/2020) data on efficacy are lacking. In Table 1 are reported the main features of the trials registered at the

Table 1 - Main features of the trials registered to evaluate the efficacy of chloroquine (CQ) and hydroxychloroquine (HCQ).

N.	*NTC Number*	*Intervention*	*Outcome*	*Population*	*Date approval*	*Status*	*Country*
1	NCT04342221	HCQ vs Placebo	Viral clearance at 6 days	220	March 2020	Recruiting	Germany
2	NCT04342169	HCQ vs Placebo	Viral clearance day 1-14	400	April 2020	Not yet recruiting	USA
3	NCT04341870	AZH5+HCQ10+Sarilumab vs Sarilumab	Ventilation/death	60	April 2020	Not yet recruiting	France
4	NCT04341727	HCQ Vs HCQ+AZH vs CQ vs CQ+AZH	Recovery/fever resolution	500	April 2020	Recruiting	USA
5	NCT04341493	HCQ+Nitazoxanide vs HCQ	Mechanical ventilation	86	April 2020	Recruiting	Mexico
6	NCT04341207	HCQ+AZH in cancer patients	3 months mortality	1000	April 2020	Recruiting	Germany
7	NCT04340544	HCQ vs Placebo	Symptoms resolution	2700	April 2020	Not yet recruiting	Germany
8	NCT04339816	HCQ+AZH vs HCQ+PLB vs PLB in ICU	Pts free from ventilation	240	April 2020	Not yet recruiting	Check Republique
9	NCT04338906	HCq + Camostat Mesylate vs HCQ (7 days)+PLB	Not hospitalized within 14 days	334	April 2020	Not yet recruiting	Germany
10	NCT04338698	HCQ+AZH (10) vs HCQ vs supportive	Viral load	500	April 2020	Not yet recruiting	Pakistan
11	NCT04335552	Supportive vs HCQ +/-AZH early vs delayed 5 days	Progress in WHO scale	500	April 2020	Nor yet recruiting	USA
12	NCT04334967	HCQ vs Vit C	Hospital Vs no hospital	1250	March 2020	Enrolling by invitation	USA
13	NCT04335084	HCQ + AZH + Vit. C + D	Symptoms resolution	600	April 2020	Not yet recruiting	USA

N.	NTC Number	Intervention	Outcome	Population	Date approval	Status	Country
14	NCT04334382	HCQ vs AZH for outpatients	Hospitalization	1550	April 2020	Recruiting	USA
15	NCT04333914	CQ analog vs Tocilizumab vs Nivolumab v SOC in cancer	28-day survival	273	April 2020	Recruiting	France
16	NCT04334148	HCQ vs Plb	Viral load	15000	April 2020	Recruiting	USA
17	NCT04333732	Low/Standard/No CQ	Viral load	55000	April 2020	Nor yet recruiting	Multinational
18	NCT04333654	HCQ vs Placebo	Covid outcome scale	210	April 2020	Recruiting	USA
19	NCT04332835	HCQ+AZH +/- Plasma	Viral load G and M levels	80	April 2020	Not yet recruiting	Colombia
20	NCT04332094	HCQ+HCQ+/-Tocilizumab	Mortality	276	April 2020	Recruiting	Spain
21	NCT04331600	Telemedicine+SOC +/-CQ 500	Hospitalization/death	400	April 2020	Not yet recruiting	Poland
22	NCT04330586	Ciclesonide +/- HCQ open randomised	Viral clearance 14 days	141	April 2020	Not yet recruiting	Corea
23	NCT04329923	400 to 1200 per day HCQ, vs placebo	Improvement of symptoms HCW Proph Y/N	400	April 2020	Not yet recruiting	USA
24	NCT04329832	HCQ vs AZH per 5 days	COVID outcome scale	300	March 2020	Recruiting	USA
25	NCT0432961	HCQ vs PLB to prevent severe disease	Intubation or death	2660	April 2020	Not yet recruiting	Canada
26	NCT04329572	HCQ+AZH	Change in respect to baseline of respiratory parameters	400	April 2020	Not yet recruiting	Brazil
27	NCT04323527	CQ vs SOC open	Viral clearance	440	March 2020	Recruiting	Brazil
28	NCT04322396	HCQ vs AZH vs PLB for 7 days	National Early Warning Score equal to zero	226	April 2020	Recruiting	Denmark
29	NCT04328012	Losartan vs HCQ vs Kaletra Vs PLB	NCOSS	4000	April 2020	Recruiting	USA
30	NCT04325893	HCQ Vs PLB	Death or ventilation	1300	April 2020	Recruiting	France
31	NCT04322396	CQ+AZH in early vs PLB	Hospitalization	226	April 2020	Recruiting	Denmark
32	NCT04342169	HCQ 10 days vs control	Severe infection or death	400	April 2020	Not yet recruiting	USA
33	NCT04328272	Low vs High dose CQ	Mortality	75	March 2020	Not yet recruiting	Pakistan
34	NCT04322123	HCQ + AZH vs HCQ vs Control	COVID ordinal scale	630	April 2020	Recruiting	Brazil
35	NCT04321993	HCQ vs Lopinavir vs Baricitinib vs Sarilumab	Clinical status on outcome scale	1000	April 2020	Not yet recruiting	Canada
36	NCT04321616	HCQ vs Rendesevir vs SOC	In hospital mortality	700	March 2020	Not yet recruiting	Norway
37	NCT04321278	HCQ+AZH vs HCQ random	Ordinal scale of 7 points	440	March 2020	Recruiting	Brazil
38	NCT04342169	HCQ vs SOC random	Decline in viral load	400	April 2020	Not yet recruiting	USA
39	NCT04308668	HCQ vs PLB in severe	Mortality	3000	March 2020	Recruiting	USA
40	NCT04307693	Lopinavir vs HCQ Mild	Viral load	150	March 2020	Recruiting	Korea

Note: AZH = Azitrhomycin, PLB = placebo.

clinicaltrials.com. All trials have been registered in March-April 2020 and only 19 out of 40 are recruiting. The global population that will be included in the studies (control groups included) is represented by about 95000 patients. The majority of the studies are or will be conducted in USA (12 out of 40).

Ongoing studies in China
Twenty-six more trials are registered at the Chinese clinical trials Registry. All of them have been approved in the period March-April 2020 and all of them are randomized prospective studies with patient population ranging between 30 and 360. The final enrollment for all studies would concern more than 3000 patients. The completion date and the status of recruitment is not reported [17].

REMDESIVIR

Background
Remdesivir has a similar structure to tenofovir, a nucleotide analogue of adenosine 5-monophosphate with antiviral activity against hepatitis B virus (HBV) and human immunodeficiency virus (HIV). It was developed by Gilead Science Inc. and has not been licensed or approved anywhere so far.
In 2016, it was reported that remdesivir is active *in vitro* against Ebola virus, against Marburg virus, Paramyxoviridae (such as parainfluenza type 3 virus, Nipah virus, Hendra virus, and measles and mumps viruses) and Pneumoviridae (such as respiratory syncytial virus).
In addition, remdesivir demonstrated to be effective *in vitro* against many human and zoonotic coronaviruses, including SARS-CoV and MERS-CoV [17, 20, 21]. A recent study reported the *in vitro* antiviral activity of remdesivir against the causative aetiological pathogen of Wuhan pneumonia, SARS-CoV-2 [18]. The activity of remdesivir against SARS-CoV-2 consists in inhibiting RNA-dependent RNA Polymerase competing with ATP to be incorporated into the growing chain of RNA, causing the stop of transcription after 3 more nucleotides incorporation.

Clinical studies
Remdesevir was utilized for compassionate use in January 2020 for the first patients affected by COVID-19 in Washington. The patient clinical conditions improved fast and the oropharyngeal swab test was negative for SARS-CoV-2 one day later suggesting a promising therapeutic effect of remdesivir [19].
On 10th April 2020 the first international observational clinical study reporting the experience of remdesivir for treatment of COVID-19 has been reported on *New England Journal of Medicine*. Remdesevir was given on compassionate-use basis to 61 patients hospitalized during the period from January 25, 2020, through March 7, 2020 for COVID-19 with an oxygen saturation of 94% or less, enrolled at multiple sites in USA, Japan, Canada, and Europe on the basis of a compassionate use program. Patients received a 10-day course of remdesivir, consisting of 200 mg administered intravenously on day 1, followed by 100 mg daily for the remaining 9 days of treatment. In this cohort of patients hospitalized for severe COVID-19 who were treated with compassionate-use remdesivir, clinical improvement in term of oxygen support requirement was observed in 36 of 53 patients (68%), with the greater efficacy being reported in those requiring non-invasive ventilation. Mortality rate in these patients was 13% [20].

Ongoing clinical studies
At moment two phase 3, randomized, double-blind, placebo-controlled multicentre clinical trials of remdesivir are currently ongoing in China. These trials have been submitted to ClinicalTrials.gov on 31 January 2020 and are designed to evaluate the efficacy and safety of parenteral remdesivir in hospitalized adults with mild-to-moderate COVID-19, (Title: A Phase 3 Randomized, Double-blind, Placebo-controlled Multicenter Study to evaluate the Efficacy and Safety of Remdesivir in Hospitalized Adult Patients with Mild and Moderate 2019-nCoV Respiratory Disease - NCT04252664 and severe COVID-19 (Title: Phase 3 Randomized, Double-blind, Placebo-controlled, Multicenter Study to Evaluate the Efficacy and Safety of Remdesivir in Hospitalized Adult Patients With Severe 2019-nCoVRespiratory Disease. NCT04257656 [21, 22].
The number of cases planned to be enrolled is 308 and 452, respectively. A 10-day regimen of remdesivir treatment is as follows: 200 mg loading dose on Day 1, followed by 100 mg once-daily maintenance doses for 9 days in both studies.

A phase 3 clinical trial entitled "A Phase 3 Randomized Study to Evaluate the Safety and Antiviral Activity of Remdesivir (GS-5734™) in Participants with Moderate COVID-19 Compared to Standard of Care Treatment" has been submitted as well to ClinicalTrials.gov funded by Gilead.
The number of cases planned to be enrolled is 1600 according to a randomized open label protocol.
Participants will receive continued standard of care therapy together with RDV 200 mg on Day 1 followed by RDV 100 mg on Days 2, 3, 4, and 5. The enrolment started on March 31st, 2020 and the estimated time completation is May 2020 [23].

FAVIPIRAVIR (AVIGAN)

Background
Favipiravir (FPV) is a purine nucleic acid analogue that selectively inhibits RNA-dependent RNA polymerase RNA viruses and has been approved in Japan for the treatment of influenza.
In addition to the inhibition of influenza virus, a wide range of RNA viruses, such as arena-, bunya-, lavi- and filoviruses causing hemorrhagic fever, favipiravir *in vitro* study showed inhibition of SARS-CoV-2.
During the 2014-2015 Ebola virus (EBOV) outbreak initiated in West Africa, a proof-of-concept trial with favipiravir was carried out in Guinea, and patients treated with favipiravir showed a trend towards improved survival.
Thus, faviripavir is considered a potential candidate for treatment of COVID-19 although few *in vitro* data are available and preclinical animal studies are missing [24].

Clinical studies
At moment no clinical study published in a peer review journal is available in literature.
On March 17th, Chen and coll. presented a preprint on the website MedRxiv of the study registered at the Chictr.org.cn, number ChiCTR2000030254. This article is a report of new medical research that has yet to be evaluated and so should not be used to guide clinical practice.

Table 2 - Clinical trials registered at the Chinese Clinical Trials Registry to determine the efficacy and safety of Favipiravir for treatment of patients affected by COVID-19.

Registration Number	*Title/Institution*	*Sample size*	*Date of approval*	*Estimated completation time*
ChiCTR2000030894	Favipiravir Combined With Tocilizumab in the Treatment of novel coronavirus pneumonia (COVID-19) - A Multicenter, Randomized, Controlled Trial Peking University First Hospital	150	2020/03/16	2020-06-25
ChiCTR2000030254	the Efficacy and Safety of Favipiravir for novel coronavirus–infected pneumonia: A multicenter, randomized, open, positive, parallel-controlled clinical study Zhongnan Hospital of Wuhan University	150	2020/02/26	2020-05-31
ChiCTR2000029600	Clinical study for safety and efficacy of Favipiravir in the treatment of novel coronavirus pneumonia (COVID-19) The Third People's Hospital of Shenzhen	240	2020/02/06	2020-03-20
ChiCTR2000029548	Randomized, open-label, controlled trial for evaluating of the efficacy and safety of Baloxavir Marboxil, Favipiravir, and Lopinavir-Ritonavir in the treatment of novel coronavirus pneumonia (COVID-19) patients The First Affiliated Hospital, Zhejiang University School of Medicine	90	2020/02/04	2020-04-29
ChiCTR2000029544	A randomized controlled trial for the efficacy and safety of Baloxavir Marboxil, Favipiravir tablets in novel coronavirus pneumonia (COVID-19) patients who are still positive on virus detection under the current antiviral therapy The First Hospital Affiliated to Zhejiang University's Medical School	30	2020/02/03	2020-06-03

The authors carried on a prospective, multicenter, open-label, randomized superiority trial to compare the efficacy and safety of favipiravir and arbidol to treat COVID-19 patients. 120 patients were assigned to favipiravir group and 120 to arbidol group. The clinical recovery rate of day 7 did not significantly differ between the favipiravir group (61.20% (71/116)) and the arbidol group (51.67%, 62/120) (P=0.1396, OR: 1.47). The latency to fever reduction and cough relief in favipiravir group was significantly shorter than that in arbidol group (both P<0.0001).

In conclusion among patients with confirmed COVID-19, favipiravir, compared to arbidol, did not significantly improve the clinically recovery rate by 7 days. Favipiravir significantly improved time-to-relief for fever and cough [25].

Ongoing trials in China

Six different clinical studies have been registered at the Chinese Clinical Trials Registry in April 2020. All of them are comparative prospective randomized trials comparing the efficacy and safety of favipiravir with other antivirals. The estimated time of completion of the patients' enrolment is the end of May 2020 (Table 2) [26].

Five different clinical studies are reported at the website ClinicalTrial.gov. All of them are comparative prospective randomized trials comparing the efficacy and safety of favipiravir with other antiviral or versus placebo or versus conventional therapy. The estimated time of completation of the patients' enrolment is the end of May 2020 (Table 3).

Table 3 - Clinical trials registered at the ClinicalTrial.gov to determine the efficacy and safety of Favipiravir for treatment of patients affected by COVID-19.

Title	*Type of study*	*Design*	*Number partecipants*	*Date approval*	*Date completion*	*Site*
Clinical study to evaluate the performance and safety of favipiravir in COVID-19	Multicenter, randomized, double-blind, placebo-controlled (1:1)	Favipiravir vs placebo	100	March 25, 2020	July 2020	California, United States
Various combination of protease inhibitors, oseltamivir, favipiravir, and hydroxychloroquine for treatment of COVID-19, a randomized control trial	Multicenter, prospective, open label	Oseltamivir plus Hydroxychloroquine versus Lopinavir/ Ritonavir plus Oseltamivir versus Darunavir/ Ritonavir plus Oseltamivir plus Hydroxychloroquine	320	April 15, 2020	October 2020	Thailand
Favipiravir combined with tocilizumab in the treatment of corona virus disease 2019-	Multicenter, randomized controlled		320	March 8, 2020	May 2020	China
The mechanism, clinical outcome and therapeutic intervention of corona virus disease 2019 patients whose nucleic acids changed from negative to positive	Randomized	Faripiravir vs conventional treatment	210	April 1, 2020	September 2020	China
The Results of COVID 19 Treatment: a real-life experience on patients with COVID 19	Randomized	Faripiravir vs conventional treatment	100	April 15, 2020		Egypt

LOPINAVIR/RITONAVIR

Background
Lopinavir/ritonavir is a medication for the human immunodeficiency virus (HIV) used in combination with other medications to treat adults and children over 14 days of age who are infected with HIV-1. Chu et al. found that lopinavir/ ritonavir has anti-SARS-CoV activity *in vitro* and in clinical studies [27].

Clinical trials
Cao and coll., have recently published on NEJM the results of a randomized, controlled, open-label trial involving hospitalized 199 adult patients with confirmed SARS-CoV-2 infection, with an oxygen saturation of 94%. Patients were randomly assigned in a 1:1 ratio to receive either lopinavir-ritonavir in addition to standard care, or standard care alone. Treatment with lopinavir-ritonavir was not associated with a difference from standard care in the time to clinical improvement. Mortality at 28 days was similar in both groups. The authors concluded that in hospitalized adult patients with severe COVID-19, no benefit was observed with lopinavir-ritonavir treatment beyond standard care.

Ongoing trials
One trial NCT04307693 comparing the safety and efficacy of lopinavir/ritonavir with hydroxy-chloroquine is ongoing and recruiting patients in Korea (see the paragraph hydroxy-chloroquine) [28].

TOCILIZUMAB

Background
It has been recently demonstrated that patients affected by severe COVID-19 requiring admission to ICU present with a cytokine storm with increased plasma concentrations of interleukins IL-6, IL-2, IL-7, and IL-10 and tumor necrosis factor (TNF).

Considering that the excessive and aberrant immune responses and cytokine storms surely play an important role in severe cases, it can be reasonable that neutralizing key inflammatory factors in CRS will be of great interest in the treatment of severe cases.
Considering the absence of specific drugs, a range of existing host-directed therapies could potentially be repurposed to treat COVID-19 as the treatment of cytokine storm has become an important part of rescuing severe patients.
Tocilizumab (TCZ) is a humanized antiinterleukin-6-receptor (IL-6R) monoclonal antibody that inhibits interleukin-6 (IL-6) used in several rheumatologic conditions like rheumatoid arthritis, juvenile idiopathic arthritis, Castleman's disease, giant cell arteritis and cytokine release syndrome caused by Chimeric Antigen Receptor T cell therapies.
So far, it has been experimentally administered by intravenous route in the treatment of COVID-19 in China and Italy with encouraging results. Whether TCZ can restore T cell counts in COVID-19 patients by suppressing IL-6 signaling remains uninvestigated [29].

Case reports
The first patient affected by COVID-19 and treated with TCZ is reported in March 2020 on *New England Journal of Medicine*. The authors reported the case of a 57-year-old woman with systemic sclerosis (SSc), associated with interstitial lung disease (SSc-ILD), insulin-dependent type 2 diabetes mellitus and WHO grade I obesity who developed COVID-19. Treatment with the anti-interleukin (IL) 6 receptor blocker tocilizumab, with 8 mg/kg body weight every 4 weeks intravenously, was started, leading to a good control of both arthritis and SSc-ILD, with gradual improvement of musculoskeletal and respiratory symptoms, lung function and high-resolution CT imaging. Four weeks after the last tocilizumab infusion, the patient presented cough, headache and general malaise and reported contact with a patient with COVID-19 2 weeks earlier. The nasopharyngeal swab was positive for SARS-CoV2 and was quarantined at home and monitored by daily telephone calls. The symptoms remained mild and, 10 days later, she reported to be free of symptoms. A follow-up nasopharyngeal swab for SARS-CoV2 performed on March 26 turned out negative. In this case, a patient with insulin-dependent type 2 diabetes mellitus and SSc-ILD treated with tocilizumab developed a mild form of COVID-19.
This is actually not the first patients affected by COVID-19 treated with TCZ, but the first patient who was already under treatment with TCZ for SSc-ILD when developed COVID-19 [30].

A 60-year-old man working in Wuhan, China affected by Multiple Myeloma (MM) developed chest tightness without fever and cough on 1 February 2020. The swab specimens were tested by real-time reverse transcriptase–polymerase chain reaction and resulted positive 3 days later. The patient was diagnosed with COVID-19 and was given 200-mg umifenovir (Arbidol) tablets orally, 3 times daily.
On 16 February 2020, the patient conditions worsened with shortness of breath and arterial oxygen saturation (93% at rest). On hospital admission the patient's illness was evaluated as severe and 40 mg of methylprednisolone treatment, administered IV daily, was given on days 2 to 6. On hospital day 9 (illness day 24), the patient was given one dose of 8 mg/kg tocilizumab, administered IV. On hospital day 12, his chest tightness disappeared. After tocilizumab administration, the IL-6 level decreased, and the patient was declared to be cured and was discharged from the hospital on 13 March 2020.
This case has been the first to prove that tocilizumab could be effective in the treatment of COVID-19 [31].

Clinical studies
The first retrospective observational study was published in the *Journal of Medical Virology* ahead of print on April 6th, 2020. Fifteen patients infected by COVID-19 were treated with tocilizumab from Jan 27 to Mar 5, 2020 at Tongji Hospital in Wuhan, China. The median age (min-max) of the patients was 73 (62-80) years. Two (13.3%) of them were moderately ill, six (40.0%) were seriously ill and seven (46.7%) were critically ill. Ten (66.7%) patients had one or more co-morbidities. The dose of TCZ used in patients was range from 80 mg to 600 mg per time in combination (eight patients) or not with methyl-prednisone, on twice or more. The authors concluded that single dose of TCZ failed to improve the disease activity in critically ill patients also in combination with glucocorticoid. However, repeated doses (even repeated with a lower dose) of TCZ might improve the condition of critically ill patient [32].

FDA Clinical trials
On April 3rd, 2020 FDA has approved (registration number NCT04320615 (a clinical trial entitled "A Randomized, Double-Blind, Placebo-Controlled, Multicenter Study to Evaluate the Safety and Efficacy of Tocilizumab in Patients with Severe COVID-19 Pneumonia"
Estimated primary completion date is August 31, 2021 and estimated study completion date is September 30, 2021.
Three-hundred-thirty hospitalized patients with COVID-19 pneumonia, confirmed per WHO criteria (including a positive PCR of any specimen; e.g., respiratory, blood, urine, stool, other bodily fluid) and evidenced by chest X-ray or CT scan, SPO2 </=93% or PaO2/FiO2 <300 mmHg, will receive according to a double blind randomized protocol tocilizumab iv at the dosage of 8 mg/kg, up to a maximum dose of 800 mg. (up to 1 additional dose may be given if clinical symptoms worsen or show no improvement (group 1) or 1 IV infusion of placebo matched to TCZ.
Clinical outcome is assessed using a 7-Category Ordinal Scale [Time Frame: Day 28] [33].

AIFA clinical trials
The Italian Medicines Agency (AIFA) announced on March 19 the launch of the clinical phase 2 study named TOCIVID-19 to evaluate the efficacy and safety of TCZ in the treatment of pneumonia during COVID-19.
The trial, a single-arm study including two different groups of patients treated with the same protocol, has the goals to produce good quality data from a methodological point of view and to track all the off-label treatments with tocilizumab already ongoing, to evaluate systematically their impact on mortality.
The study will include two groups of patients: the first one with 330 patients hospitalized for COVID-19 pneumonia with first signs of respiratory distress or intubated within 24 hours before; the second group (observational study) including those patients already treated and/or intubated since more than 24 hours. Tocilizumab will be given iv at the dosage of 8 mg/kg up to a maximum of 800 mg per dose; a second dose can be administered after 12 hours if respiratory function is not restored. Francesco Perrone, Head of the Clinical Trial Department, National Institute for Oncology Fondazione Pascale, Naples – Principal Investigator of TOCIVID-19 declared:
«Our study was designed by the National Health System to support the National Health System. The drug company producing tocilizumab launched on the 19th of March an international randomized trial, also involving

330 patients. We know that randomization is the gold standard for regulatory agencies: but we are experiencing an unprecedented emergency. We cannot randomize the patients, in our view it would be unethical: we have to treat all of them. At the same time, we need to collect reliable data and provide a tool for a proper follow-up of off-label treatments occurring right now all over the country. Our study is the result of a very efficient collaborative effort from many national institutions and it will also help the other countries to face the pandemic. We will use an online platform developed for drug trials in oncology. All our data will be available only for the Italian Medicines Agency. They will decide how to share them to support our doctors and patients.» [34].

Ongoing clinical trials in China

At moment two multicenter clinical trials have been registered at the Chinese Clinical Trials Registry.

The first one has been registered with the number ChiCTR2000030894 on 3rd March 2020 with the following title "Favipiravir Combined with Tocilizumab in the Treatment of novel coronavirus pneumonia (COVID-19) - A Multicenter, Randomized, Controlled Trial" sponsored by the Peking University First Hospital.

The study is designed as a parallel trial including three groups of patients:

- Group 1 (sample size 90 patients) taking Favipiravir Combined with Tocilizumab
- Group 2 (sample size 30 patients) taking only Favipiravir
- Group 3 (sample size 30 patients) taking only Tocilizumab

The aims of the study are to measure the following outcomes: viral nucleic acid test negative conversion rate and days from positive to negative, duration of fever, lung imaging improvement time, mortality rate because of corona virus disease 2019, rate of non-invasive or invasive mechanical ventilation when respiratory failure occurs, mean in-hospital time, concentration of C-Reactive Protein, lymphocyte absolute value and its percentage. The enrolment started on March 1st, 2020 and the estimated time completation is 31st May 2020 [35].

PLASMA AND IMMUNOGLOBULINS

Background

The potential therapeutic benefits of plasma transfusion of a convalescent or cured person from infectious diseases and hyperimmune immunoglobulin began far ago and this therapeutic approach has been adopted whenever specific antimicrobial agents have not been available for new developing infections disease. The evidence of efficacy of these practices are based on studies of varying size and quality describing the clinical experience in treating viral infections, including those due to SARS-CoV, Spanish influenza A (H1N1), avian influenza A(H5N1), and 2009 pandemic influenza A (H1N1). All these clinical experiences have been accurately investigated in 2015 by John Mair-Jenkins et al. by means of systematic review and meta-analysis showing a statistically significant reduction of mortality. In this context, convalescent plasma can be a potential promising option for treatment of patients affected by severe COVID-19 patients [36].

Case reports

In order to evaluate the efficacy of convalescent plasma therapy in COVID-19 patients, Ye et al enrolled six laboratory confirmed COVID-19 patients to receive the transfusion of ABO-compatible convalescent plasma. This intervention proved to be efficacious by determining the alleviation of symptoms, changes in radiologic abnormalities and laboratory tests, without onset of adverse effects observed during the treatment. Transfusion of convalescent plasma determined the resolution of ground glass opacities and consolidation at X-ray in five patients out of six and fast elimination of virus at throat swab in two patients. The authors concluded that convalescent plasma therapy is effective and specific for COVID-19 and can represent a promising state-of-art therapy during COVID-19 pandemic crisis [37].

Jin Young Ahn from Korea first described accurately two patients affected by COVID-19 treated with convalescent plasma. The first patient a 71-years-old man diagnosed with COVID-19 started the therapy about 10 days after his hospitalization following a significant worsening of his general conditions and respiratory distress till a diagnosis consistent with severe acute respiratory distress syndrome (ARDS). The convalescent plasma was obtained from a male donor who had recovered from COVID-19 for 21 days. The second patient, a 67 years old woman affected by COVID-19 with acute respiratory distress, received convalescent plasma obtained from a male donor who had recovered from COVID-19 for 18

days. Both patients presented ARDS and showed a favorable outcome after the use of convalescent plasma in addition to systemic corticosteroid [38]. Kai Duan and coll. treated ten patients affected by severe COVID-19 confirmed by real-time viral RNA test. One dose of 200 mL of convalescent plasma (CP) derived from recently recovered donors with the neutralizing antibody titers above 1:640 was transfused to the patients in addition to maximal supportive care and antiviral agents. After plasma transfusion, the level of neutralizing antibody increased rapidly up to 1:640 in five cases, while that of the other four cases maintained at a high level (1:640). The clinical symptoms were significantly improved along with increase of oxyhemoglobin saturation within 3 days. The viral load became undetectable after transfusion in seven patients. No severe adverse effects were observed. The authors concluded that convalescent plasma therapy is a well-tolerated treatment and could potentially improve the clinical outcomes through neutralizing viremia in severe COVID-19 cases. Nevertheless, the optimal dose and timing for its administration for the best outcome needs to be further investigated [39].

IMMUNOGLOBULINS

Hua Shi and coll. have recently reported the case of a patient affected by COVID-19 who developed respiratory failure and shock accompanied by persistent diarrhoea despite conventional therapeutic interventions. The patient avoided mechanical ventilation and acquired an immediate clinical and radiological improvement after treatment of intensive plasma exchange (PE) followed by intravenous immunogloblin (IVIG) [40].
In Table 4 are reported the main features of the clinical registered trials to evaluate the efficacy and safety of convalescent plasma for treatment of COVID-19. All trials have been registered between March and April 2020 and all of them are ongoing. Only seven out of 23 trials are already enrolling patients. Eight studies out of 23 will enroll patients in USA [41].

CONCLUSIONS

Up-to-date, despite the large use of antiviral and/or anti-inflammatory drugs, no proven treatment is available for the current COVID-19 pandemic.
In fact, despite the large number of papers published on this topic (often as ahead of print publications) in the last 2-3 months, only a few data are available from open observational studies, case report and case series as all medications are currently utilized based on their *in vitro* activity or previous clinical experience on other coronavirus diseases (SARS and MERS).
While preliminary studies seem to provide promising results for some of these drugs, some others are giving more disappointing information.
Due to the need of urgent responses and high-quality evidence on the efficacy and safety of therapeutic agents currently utilized by the beginning of the pandemic with different approaches, different bundles, different drug combination and different timing, several clinical trials have been approved by the Clinical Trials Agencies, including many therapeutic agents such as hydroxychloroquine,

Table 4 - Clinical trials registered at the ClinicalTrials.gov to determine the efficacy and safety of convalescent plasma for treatment of patients affected by COVID-19.

No.	*NTC Number*	*Title*	*Status*	*Partecipants*	*Date of start*	*Date of completation*	*Country*
1	NCT04333355	Safety in Convalescent Plasma Transfusion to COVID-19	Not yet recruiting	20	April 15, 2020	December 20, 2020	Mexico
2	NCT04340050	COVID-19 Convalescent Plasma	Recruiting	10	April 10, 2020	December 31, 2020	USA
3	NCT04343261	Convalescent Plasma in the Treatment of COVID 19	Not yet recruiting	15	April 10, 2020	April, 2021	USA
4	NCT04347681	Potential Efficacy of Convalescent Plasma to Treat Severe COVID-19 and Patients at High Risk of Developing Severe COVID-19	Not yet recruiting	40	April 12, 2020	April 12, 2021	USA

No.	NTC Number	Title	Status	Partecipants	Date of start	Date of completation	Country
5	NCT04345991	Efficacy of Convalescent Plasma to Treat COVID-19 Patients, a Nested Trial in the CORIMUNO-19 Cohort	Not yet recruiting	120	April 14, 2020	June 21, 2020	Saudi Arabia
6	NCT04346446	Efficacy of Convalescent Plasma Therapy in Severely Sick COVID-19 Patients	Recruiting	20	April 14, 2020	June 30, 2020	India
6	NCT04342182	Convalescent Plasma as Therapy for COVID-19 Severe SARS-CoV-2 Disease (CONCOVID Study)	Recruiting	426	April 8, 2020	July 1, 2020	Netherlands
7	NCT04345679	Anti COVID-19 Convalescent Plasma Therapy	Not yet recruiting	20	April 14, 2020	April 1, 2021	Hungary
8	NCT04343755	Convalescent Plasma as Treatment for Hospitalized Subjects With COVID-19 Infection	Recruiting	55	April 9, 2020	April, 2020	USA
9	NCT04327349	Investigating Effect of Convalescent Plasma on COVID-19 Patients Outcome: A Clinical Trial	Enrolling by invitation	30	March 28, 2020	September 30, 2020	Iran
10	NCT04332380	Convalescent Plasma for Patients with COVID-19: A Pilot Study	Not yet recruiting	1200	April 1, 2020	December 31, 2020	Colombia
11	NCT04332835	Convalescent Plasma for Patients with COVID-19: A Randomized, Open Label, Parallel, Controlled Clinical Study	Not yet recruiting	80	April 1, 2020	December 31, 2020	Colombia
12	NCT04345523	Convalescent Plasma Therapy vs. SOC for the Treatment of COVID19 in Hospitalized Patients	Recruiting	278	April 3, 2020	July, 2020	Spain
14	NCT04344535	Convalescent Plasma vs. Standard Plasma for COVID-19	Enrolling by invitation	500	April 8, 2020	August 31, 2021	USA
15	NCT04344015	COVID-19 Plasma Collection	Recruiting	2000	April 13, 2020	April 12, 2021	USA
16	NCT04292340	Anti-SARS-CoV-2 Inactivated Convalescent Plasma in the Treatment of COVID-19	Recruiting	15	February 1, 2020	December 31, 2020	China
17	NCT04334876	Rapid SARS-CoV-2 IgG Antibody Testing in High Risk Healthcare Workers	Not yet recruiting	340	April 1, 2020	January 1, 2021	USA
18	NCT04323800	Efficacy and Safety Human Coronavirus Immune Plasma (HCIP) vs. Control (SARS-CoV-2 Non-immune Plasma) Among Adults Exposed to COVID-19	Not yet recruiting	150	May 1, 2020	January, 2023	USA
19	NCT04345289	Efficacy and Safety of Novel Treatment Options for Adults With COVID-19 Pneumonia	Not yet recruiting	1500	April 20, 2020	June 15, 2021	Netherland
20	NCT04346589	Convalescent Antibodies Infusion in Critically Ill COVID 19 Patients	Not yet recruiting	10	April, 2020	June, 2020	Italy
21	NCT04348877	Plasma Rich Antibodies from Recovered Patients From COVID19	Not yet recruiting	20	April 20, 2020	December, 2020	Egypt
22	NCT04344977	COVID-19 Plasma Collection	Not yet recruiting	2800	April 15, 2020	April 1, 2025	USA
23	NCT04342195	Acquiring Convalescent Specimens for COVID-19 Antibodies	Recruiting	12	March 5, 2020	March, 2021	USA

remdesivir, lopinariv/ritonavir, favipiravir, tocilizumab, convalescent plasma and immunoglobulins, and including several thousand patients worldwide.
The majority of these trials, designed as randomized (blind or not), are ongoing and we'll hopefully get the preliminary results by the end of June 2020.

Conflict of interest
None to declare.

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