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”, “remdesivir”, “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).

<table>
<thead>
<tr>
<th>N.</th>
<th>NTC Number</th>
<th>Intervention</th>
<th>Outcome</th>
<th>Population</th>
<th>Date approval</th>
<th>Status</th>
<th>Country</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>NCT04342221</td>
<td>HCQ vs Placebo</td>
<td>Viral clearance at 6 days</td>
<td>220</td>
<td>March 2020</td>
<td>Recruiting</td>
<td>Germany</td>
</tr>
<tr>
<td>2</td>
<td>NCT04342169</td>
<td>HCQ vs Placebo</td>
<td>Viral clearance day 1-14</td>
<td>400</td>
<td>April 2020</td>
<td>Not yet recruiting</td>
<td>USA</td>
</tr>
<tr>
<td>3</td>
<td>NCT04341870</td>
<td>AZH5+HCQ10+Sarilumab vs Sarilumab</td>
<td>Ventilation/death</td>
<td>60</td>
<td>April 2020</td>
<td>Not yet recruiting</td>
<td>France</td>
</tr>
<tr>
<td>4</td>
<td>NCT04341727</td>
<td>HCQ Vs HCQ+AZH vs CQ vs CQ+AZH</td>
<td>Recovery/fever resolution</td>
<td>500</td>
<td>April 2020</td>
<td>Recruiting</td>
<td>USA</td>
</tr>
<tr>
<td>5</td>
<td>NCT04341493</td>
<td>HCQ+Nitazoxanide vs HCQ</td>
<td>Mechanical ventilation</td>
<td>86</td>
<td>April 2020</td>
<td>Recruiting</td>
<td>Mexico</td>
</tr>
<tr>
<td>6</td>
<td>NCT04341207</td>
<td>HCQ+AZH in cancer patients</td>
<td>3 months mortality</td>
<td>1000</td>
<td>April 2020</td>
<td>Recruiting</td>
<td>Germany</td>
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<tr>
<td>7</td>
<td>NCT04340544</td>
<td>HCQ vs Placebo</td>
<td>Symptoms resolution</td>
<td>2700</td>
<td>April 2020</td>
<td>Not yet recruiting</td>
<td>Germany</td>
</tr>
<tr>
<td>8</td>
<td>NCT04339816</td>
<td>HCQ+AZH vs HCQ+PLB vs PLB in ICU</td>
<td>Pts free from ventilation</td>
<td>240</td>
<td>April 2020</td>
<td>Not yet recruiting</td>
<td>Check Republique</td>
</tr>
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<td>9</td>
<td>NCT04338906</td>
<td>HCQ + Camostat Mesylate vs HCQ (7 days)+PLB</td>
<td>Not hospitalized within 14 days</td>
<td>334</td>
<td>April 2020</td>
<td>Not yet recruiting</td>
<td>Germany</td>
</tr>
<tr>
<td>10</td>
<td>NCT04338698</td>
<td>HCQ+AZH (10) vs HCQ vs supportive</td>
<td>Viral load</td>
<td>500</td>
<td>April 2020</td>
<td>Not yet recruiting</td>
<td>Pakistan</td>
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<tr>
<td>11</td>
<td>NCT04335552</td>
<td>Supportive vs HCQ +/-AZH early vs delayed 5 days</td>
<td>Progress in WHO scale</td>
<td>500</td>
<td>April 2020</td>
<td>Not yet recruiting</td>
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<td>12</td>
<td>NCT04334967</td>
<td>HCQ vs Vit C</td>
<td>Hospital Vs no hospital</td>
<td>1250</td>
<td>March 2020</td>
<td>Enrolling by invitation</td>
<td>USA</td>
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<tr>
<td>13</td>
<td>NCT04335084</td>
<td>HCQ + AZH + Vit. C + D</td>
<td>Symptoms resolution</td>
<td>600</td>
<td>April 2020</td>
<td>Not yet recruiting</td>
<td>USA</td>
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## Update on treatment of COVID-19

<table>
<thead>
<tr>
<th>N.</th>
<th>NCT Number</th>
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<th>Date approval</th>
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<th>Country</th>
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<td>15</td>
<td>NCT04333914</td>
<td>CQ analog vs Tocilizumab vs Nivolumab vs SOC in cancer</td>
<td>28-day survival</td>
<td>273</td>
<td>April 2020</td>
<td>Recruiting</td>
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<td>16</td>
<td>NCT04334148</td>
<td>HCQ vs Plb</td>
<td>Viral load</td>
<td>15000</td>
<td>April 2020</td>
<td>Recruiting</td>
<td>USA</td>
</tr>
<tr>
<td>17</td>
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<td>Low/Standard/No CQ</td>
<td>Viral load</td>
<td>55000</td>
<td>April 2020</td>
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<td>Multinational</td>
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<tr>
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<td>HCQ vs Placebo</td>
<td>Covid outcome scale</td>
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<td>19</td>
<td>NCT04332835</td>
<td>HCQ+AZH +/- Plasma</td>
<td>Viral load G and M levels</td>
<td>80</td>
<td>April 2020</td>
<td>Not yet recruiting</td>
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<tr>
<td>20</td>
<td>NCT04332094</td>
<td>HCQ+HCQ+/-Tocilizumab</td>
<td>Mortality</td>
<td>276</td>
<td>April 2020</td>
<td>Recruiting</td>
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<td>21</td>
<td>NCT04331600</td>
<td>Telemedicine+SOC +/-CQ 500</td>
<td>Hospitalization/death</td>
<td>400</td>
<td>April 2020</td>
<td>Not yet recruiting</td>
<td>Poland</td>
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<tr>
<td>22</td>
<td>NCT04330586</td>
<td>Ciclesonide +/- HCQ open randomised</td>
<td>Viral clearance 14 days</td>
<td>141</td>
<td>April 2020</td>
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<td>Corea</td>
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<td>23</td>
<td>NCT04329923</td>
<td>400 to 1200 per day HCQ vs placebo</td>
<td>Improvement of symptoms</td>
<td>400</td>
<td>April 2020</td>
<td>Not yet recruiting</td>
<td>USA</td>
</tr>
<tr>
<td>24</td>
<td>NCT04329832</td>
<td>HCQ vs AZH per 5 days</td>
<td>COVID outcome scale</td>
<td>300</td>
<td>March 2020</td>
<td>Recruiting</td>
<td>USA</td>
</tr>
<tr>
<td>25</td>
<td>NCT0432961</td>
<td>HCQ vs PLB to prevent severe disease</td>
<td>Intubation or death</td>
<td>2660</td>
<td>April 2020</td>
<td>Not yet recruiting</td>
<td>Canada</td>
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<tr>
<td>26</td>
<td>NCT04329572</td>
<td>HCQ+AZH</td>
<td>Change in respect to baseline</td>
<td>400</td>
<td>April 2020</td>
<td>Not yet recruiting</td>
<td>Brazil</td>
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<tr>
<td>27</td>
<td>NCT04323527</td>
<td>CQ vs SOC open</td>
<td>Viral clearance</td>
<td>440</td>
<td>March 2020</td>
<td>Recruiting</td>
<td>Brazil</td>
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<tr>
<td>28</td>
<td>NCT04322396</td>
<td>HCQ vs AZH vs PLB for 7 days</td>
<td>National Early Warning Score equal to zero</td>
<td>226</td>
<td>April 2020</td>
<td>Recruiting</td>
<td>Denmark</td>
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<td>29</td>
<td>NCT04328012</td>
<td>Losartan vs HCQ vs Kaletra Vs PLB</td>
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<td>April 2020</td>
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<tr>
<td>30</td>
<td>NCT04325893</td>
<td>HCQ Vs PLB</td>
<td>Death or ventilation</td>
<td>1300</td>
<td>April 2020</td>
<td>Recruiting</td>
<td>France</td>
</tr>
<tr>
<td>31</td>
<td>NCT04322396</td>
<td>CQ+AZH in early vs PLB</td>
<td>Hospitalization</td>
<td>226</td>
<td>April 2020</td>
<td>Recruiting</td>
<td>Denmark</td>
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<tr>
<td>32</td>
<td>NCT04342169</td>
<td>HCQ 10 days vs control</td>
<td>Severe infection or death</td>
<td>400</td>
<td>April 2020</td>
<td>Not yet recruiting</td>
<td>USA</td>
</tr>
<tr>
<td>33</td>
<td>NCT04328272</td>
<td>Low vs High dose CQ</td>
<td>Mortality</td>
<td>75</td>
<td>March 2020</td>
<td>Not yet recruiting</td>
<td>Pakistan</td>
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<tr>
<td>34</td>
<td>NCT04322123</td>
<td>HCQ + AZH vs HCQ vs Control</td>
<td>COVID ordinal scale</td>
<td>630</td>
<td>April 2020</td>
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<td>Brazil</td>
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<td>35</td>
<td>NCT04321993</td>
<td>HCQ vs Lopinavir vs Baricitinib vs Sarilumab</td>
<td>Clinical status on outcome scale</td>
<td>1000</td>
<td>April 2020</td>
<td>Not yet recruiting</td>
<td>Canada</td>
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<tr>
<td>36</td>
<td>NCT04321616</td>
<td>HCQ vs Rendesevir vs SOC</td>
<td>In hospital mortality</td>
<td>700</td>
<td>March 2020</td>
<td>Not yet recruiting</td>
<td>Norway</td>
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<tr>
<td>37</td>
<td>NCT04321278</td>
<td>HCQ+AZH vs HCQ random</td>
<td>Ordinal scale of 7 points</td>
<td>440</td>
<td>March 2020</td>
<td>Recruiting</td>
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<tr>
<td>38</td>
<td>NCT04342169</td>
<td>HCQ vs SOC random</td>
<td>Decline in viral load</td>
<td>400</td>
<td>April 2020</td>
<td>Not yet recruiting</td>
<td>USA</td>
</tr>
<tr>
<td>39</td>
<td>NCT04308668</td>
<td>HCQ vs PLB in severe</td>
<td>Mortality</td>
<td>3000</td>
<td>March 2020</td>
<td>Recruiting</td>
<td>USA</td>
</tr>
<tr>
<td>40</td>
<td>NCT04307693</td>
<td>Lopinavir vs HCQ Mild</td>
<td>Viral load</td>
<td>150</td>
<td>March 2020</td>
<td>Recruiting</td>
<td>Korea</td>
</tr>
</tbody>
</table>

Note: AZH = Azithromycin, 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].

**REMDESVIR**

**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**

Remdesivir 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. Remdesivir 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 completion 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, favipiravir 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.

<table>
<thead>
<tr>
<th>Registration Number</th>
<th>Title/Institution</th>
<th>Sample size</th>
<th>Date of approval</th>
<th>Estimated completion time</th>
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<tr>
<td>ChiCTR2000030894</td>
<td>Favipiravir Combined With Tocilizumab in the Treatment of novel coronavirus pneumonia (COVID-19) - A Multicenter, Randomized, Controlled Trial Peking University First Hospital</td>
<td>150</td>
<td>2020/03/16</td>
<td>2020-06-25</td>
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<tr>
<td>ChiCTR2000030254</td>
<td>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</td>
<td>150</td>
<td>2020/02/26</td>
<td>2020-05-31</td>
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<tr>
<td>ChiCTR2000029600</td>
<td>Clinical study for safety and efficacy of Favipiravir in the treatment of novel coronavirus pneumonia (COVID-19) The Third People’s Hospital of Shenzhen</td>
<td>240</td>
<td>2020/02/06</td>
<td>2020-03-20</td>
</tr>
<tr>
<td>ChiCTR2000029548</td>
<td>Randomized, open-label, controlled trial for evaluating 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</td>
<td>90</td>
<td>2020/02/04</td>
<td>2020-04-29</td>
</tr>
<tr>
<td>ChiCTR2000029544</td>
<td>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</td>
<td>30</td>
<td>2020/02/03</td>
<td>2020-06-03</td>
</tr>
</tbody>
</table>
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 completion 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.

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

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.
**LOPINAVIR/РИТОНАВИР**

**Background**

Lopinavir/ритонавир 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/ритонавир 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-ритонавир in addition to standard care, or standard care alone. Treatment with lopinavir-ритонавир 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-ритонавир treatment beyond standard care.

**Ongoing trials**

One trial NCT04307693 comparing the safety and efficacy of lopinavir/ритонавир 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’s 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 coronavirus 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 completion 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 immunoglobulin (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.

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**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.**

<table>
<thead>
<tr>
<th>No.</th>
<th>NTC Number</th>
<th>Title</th>
<th>Status</th>
<th>Participants</th>
<th>Date of start</th>
<th>Date of completion</th>
<th>Country</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>NCT04333355</td>
<td>Safety in Convalescent Plasma Transfusion to COVID-19</td>
<td>Not yet recruiting</td>
<td>20</td>
<td>April 15, 2020</td>
<td>December 20, 2020</td>
<td>Mexico</td>
</tr>
<tr>
<td>2</td>
<td>NCT04340050</td>
<td>COVID-19 Convalescent Plasma</td>
<td>Recruiting</td>
<td>10</td>
<td>April 10, 2020</td>
<td>December 31, 2020</td>
<td>USA</td>
</tr>
<tr>
<td>3</td>
<td>NCT04343261</td>
<td>Convalescent Plasma in the Treatment of COVID 19</td>
<td>Not yet recruiting</td>
<td>15</td>
<td>April 10, 2020</td>
<td>April, 2021</td>
<td>USA</td>
</tr>
<tr>
<td>4</td>
<td>NCT04347681</td>
<td>Potential Efficacy of Convalescent Plasma to Treat Severe COVID-19 and Patients at High Risk of Developing Severe COVID-19</td>
<td>Not yet recruiting</td>
<td>40</td>
<td>April 12, 2020</td>
<td>April 12, 2021</td>
<td>USA</td>
</tr>
<tr>
<td>No.</td>
<td>NTC Number</td>
<td>Title</td>
<td>Status</td>
<td>Participants</td>
<td>Date of start</td>
<td>Date of completion</td>
<td>Country</td>
</tr>
<tr>
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<tr>
<td>5</td>
<td>NCT04345991</td>
<td>Efficacy of Convalescent Plasma to Treat COVID-19 Patients, a Nested Trial in the CORIMUNO-19 Cohort</td>
<td>Not yet recruiting</td>
<td>120</td>
<td>April 14, 2020</td>
<td>June 21, 2020</td>
<td>Saudi Arabia</td>
</tr>
<tr>
<td>6</td>
<td>NCT04346446</td>
<td>Efficacy of Convalescent Plasma Therapy in Severely Sick COVID-19 Patients</td>
<td>Recruiting</td>
<td>20</td>
<td>April 14, 2020</td>
<td>June 30, 2020</td>
<td>India</td>
</tr>
<tr>
<td>6</td>
<td>NCT04342182</td>
<td>Convalescent Plasma as Therapy for COVID-19 Severe SARS-CoV-2 Disease (CONCOVID Study)</td>
<td>Recruiting</td>
<td>426</td>
<td>April 8, 2020</td>
<td>July 1, 2020</td>
<td>Netherlands</td>
</tr>
<tr>
<td>7</td>
<td>NCT04345679</td>
<td>Anti COVID-19 Convalescent Plasma Therapy</td>
<td>Not yet recruiting</td>
<td>20</td>
<td>April 14, 2020</td>
<td>April 1, 2021</td>
<td>Hungary</td>
</tr>
<tr>
<td>8</td>
<td>NCT04343755</td>
<td>Convalescent Plasma as Treatment for Hospitalized Subjects With COVID-19 Infection</td>
<td>Recruiting</td>
<td>55</td>
<td>April 9, 2020</td>
<td>April, 2020</td>
<td>USA</td>
</tr>
<tr>
<td>9</td>
<td>NCT04327349</td>
<td>Investigating Effect of Convalescent Plasma on COVID-19 Patients Outcome: A Clinical Trial</td>
<td>Enrolling by invitation</td>
<td>30</td>
<td>March 28, 2020</td>
<td>September 30, 2020</td>
<td>Iran</td>
</tr>
<tr>
<td>10</td>
<td>NCT04332800</td>
<td>Convalescent Plasma for Patients with COVID-19: A Pilot Study</td>
<td>Not yet recruiting</td>
<td>1200</td>
<td>April 1, 2020</td>
<td>December 31, 2020</td>
<td>Colombia</td>
</tr>
<tr>
<td>11</td>
<td>NCT04332835</td>
<td>Convalescent Plasma for Patients with COVID-19: A Randomized, Open Label, Parallel, Controlled Clinical Study</td>
<td>Not yet recruiting</td>
<td>80</td>
<td>April 1, 2020</td>
<td>December 31, 2020</td>
<td>Colombia</td>
</tr>
<tr>
<td>12</td>
<td>NCT04343523</td>
<td>Convalescent Plasma Therapy vs. SOC for the Treatment of COVID19 in Hospitalized Patients</td>
<td>Recruiting</td>
<td>278</td>
<td>April 3, 2020</td>
<td>July, 2020</td>
<td>Spain</td>
</tr>
<tr>
<td>14</td>
<td>NCT04344535</td>
<td>Convalescent Plasma vs. Standard Plasma for COVID-19</td>
<td>Enrolling by invitation</td>
<td>500</td>
<td>April 8, 2020</td>
<td>August 31, 2021</td>
<td>USA</td>
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<tr>
<td>15</td>
<td>NCT04344015</td>
<td>COVID-19 Plasma Collection</td>
<td>Recruiting</td>
<td>2000</td>
<td>April 13, 2020</td>
<td>April 12, 2021</td>
<td>USA</td>
</tr>
<tr>
<td>16</td>
<td>NCT04292340</td>
<td>Anti-SARS-CoV-2 Inactivated Convalescent Plasma in the Treatment of COVID-19</td>
<td>Recruiting</td>
<td>15</td>
<td>February 1, 2020</td>
<td>December 31, 2020</td>
<td>China</td>
</tr>
<tr>
<td>17</td>
<td>NCT04334876</td>
<td>Rapid SARS-CoV-2 IgG Antibody Testing in High Risk Healthcare Workers</td>
<td>Not yet recruiting</td>
<td>340</td>
<td>April 1, 2020</td>
<td>January 1, 2021</td>
<td>USA</td>
</tr>
<tr>
<td>18</td>
<td>NCT04323800</td>
<td>Efficacy and Safety Human Coronavirus Immune Plasma (HCIP) vs. Control (SARS-CoV-2 Non-immune Plasma) Among Adults Exposed to COVID-19</td>
<td>Not yet recruiting</td>
<td>150</td>
<td>May 1, 2020</td>
<td>January, 2023</td>
<td>USA</td>
</tr>
<tr>
<td>19</td>
<td>NCT04345289</td>
<td>Efficacy and Safety of Novel Treatment Options for Adults With COVID-19 Pneumonia</td>
<td>Not yet recruiting</td>
<td>1500</td>
<td>April 20, 2020</td>
<td>June 15, 2021</td>
<td>Netherlands</td>
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<tr>
<td>20</td>
<td>NCT04346589</td>
<td>Convalescent Antibodies Infusion in Critically Ill COVID 19 Patients</td>
<td>Not yet recruiting</td>
<td>10</td>
<td>April, 2020</td>
<td>June, 2020</td>
<td>Italy</td>
</tr>
<tr>
<td>21</td>
<td>NCT04348877</td>
<td>Plasma Rich Antibodies from Recovered Patients From COVID19</td>
<td>Not yet recruiting</td>
<td>20</td>
<td>April 20, 2020</td>
<td>December, 2020</td>
<td>Egypt</td>
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<tr>
<td>22</td>
<td>NCT04344077</td>
<td>COVID-19 Plasma Collection</td>
<td>Not yet recruiting</td>
<td>2800</td>
<td>April 15, 2020</td>
<td>April 1, 2025</td>
<td>USA</td>
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<tr>
<td>23</td>
<td>NCT04342195</td>
<td>Acquiring Convalescent Specimens for COVID-19 Antibodies</td>
<td>Recruiting</td>
<td>12</td>
<td>March 5, 2020</td>
<td>March, 2021</td>
<td>USA</td>
</tr>
</tbody>
</table>
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.

Funding
None.

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Univadis from MedScape Available at: https://www.univadis.it/viewarticle/covid-19-italy-launches-an-independent-trial-on-tocilizumab-715741 [accessed 15 April 2020].


