Weekly update

Research & development of products to treat COVID-19

Updated 6 May 2020

Disclaimer

No product against COVID-19 is approved. This document does not provide guidance on what medicines to take. Please avoid self-prescription and always refer to your doctor before making any treatment decision.

This document provides a selection of updates on the research and development of treatments for COVID-19. Those highlights are for the information of patient organisations/groups, advocates and people living with a rare disease. EURORDIS takes reasonable steps to verify the accuracy of the information presented. This document does not constitute, and shall not be deemed or construed as, any approval or endorsement by EURORDIS of such product or entity.
## Contents (click to navigate in document) New this week in red

A ‘must-read’ introduction .............................................................................................................. 3
Resources ........................................................................................................................................ 4
Products in development ................................................................................................................. 4
Summary Table ............................................................................................................................... 5
Products to reduce SARS-CoV2 viral growth ................................................................................. 6
  Azithromycin .................................................................................................................................. 6
  Blood donation ............................................................................................................................... 7
  Favipiravir ..................................................................................................................................... 10
  Hydroxychloroquine to treat coronavirus infected patients ...................................................... 11
  Hydroxychloroquine to prevent infection by coronavirus .......................................................... 15
  Interferon-Beta-1a ...................................................................................................................... 16
  Lopinavir / ritonavir ..................................................................................................................... 16
  Polyclonal antibodies .................................................................................................................. 18
  Remdesivir (has results) .............................................................................................................. 18
Products to treat inflammation and/or respiratory illness .......................................................... 20
  Tocilizumab (with first positive results) .................................................................................... 20
Products withdrawn from this document ...................................................................................... 22
Studies of interest .......................................................................................................................... 23
  Discovery Trial (results expected 14/05) .................................................................................. 24
  Solidarity trial .............................................................................................................................. 25
  For all other clinical trials ........................................................................................................... 26
A ‘must-read’ introduction

This document provides a selection of updates on the research and development of treatments for COVID-19. Those highlights are for the information of patient organisations/groups, advocates and people living with a rare disease. EURORDIS takes reasonable steps to verify the accuracy of the information presented. This document does not constitute, and shall not be deemed or construed as, any approval or endorsement by EURORDIS of such product or entity.

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EURORDIS has a role in disseminating up-to-date information that could be useful for people living with a rare disease, who are exposed to the SARS-coV2 virus infection. Some rare diseases constitute an aggravated risk when infected by C-19. Some products being studied for C-19 are already approved or used off-label for some rare diseases, with potential information confusion and shortages risks. In other rare diseases, some products being studied for C-19 may have medicinal products interactions with medicines used in the care of these diseases. All good reasons to inform patient advocates with curated though raw information material to empower their respective actions. EURORDIS’s Task Force on Drug Information, Transparency and Access (DITA) was tasked to prepare and regularly update this document. This task force is composed of EURORDIS volunteers and staff.

This document is an editorial selection and highlights the most recent developments for products being currently tested in phase III clinical trials, measuring their efficacy and toxicity. It is by no mean an exhaustive list of all therapeutic research. To avoid repeating the same situation than for the last Ebola outbreak, where the evaluation of potential treatments could not be completed (not enough participants as the trials were started too late), clinical trials against COVID-19 were authorised very soon after the epidemic started. The priority is to enrol participants in authorised trials.

**For any questions or clarification please contact François Houÿez:**

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Resources

- World Health Organization: [https://www.who.int/blueprint/priority-diseases/key-action/Table_of_therapeutics_Appendix_17022020.pdf?ua=1](https://www.who.int/blueprint/priority-diseases/key-action/Table_of_therapeutics_Appendix_17022020.pdf?ua=1)
  All trials for COVID-19: [https://www.who.int/docs/default-source/coronaviruse/covid-19-trials.xls?sfvrsn=a8be2a0a_6&ua=1](https://www.who.int/docs/default-source/coronaviruse/covid-19-trials.xls?sfvrsn=a8be2a0a_6&ua=1)
- The NIH register of clinical trials includes 210 clinical trials to treat COVID 19 (as of 30 March 2020). You can consult here: [https://clinicaltrials.gov](https://clinicaltrials.gov)
- A recent review of the most advanced research was published here: Research and Development on Therapeutic Agents and Vaccines for COVID-19 and Related Human Coronavirus Diseases. Cynthia Liu et al. ACS Cent. Sci., 315-331. Published 12/03/2020 [https://pubs.acs.org/doi/10.1021/acscentsci.0c00272](https://pubs.acs.org/doi/10.1021/acscentsci.0c00272)
- Video on the pathophysiology of the virus, the dynamic of the pandemic and how to fight it [https://youtu.be/BtNgoyqVOY](https://youtu.be/BtNgoyqVOY)

Products in development

![TREATMENTS](image)

**Treatment Goal**
End purpose of drug being developed

**In Development**

Preclinical

![Phase of Development (Clinical Trials)](image)

**Figure 1: Source visual capitalist 7 April 2020**
## Summary Table

<table>
<thead>
<tr>
<th>Authorisation holder or developer</th>
<th>Generic forms</th>
<th>Mechanism of action for COVID-19</th>
<th>Number of recruiting trials worldwide (enrolment target)</th>
<th>Of which randomised trials (enrolment target)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Azithromycin</strong></td>
<td>Yes</td>
<td>Some broad-spectrum antiviral activity in vitro. Often added to Hydroxychloroquine in trials and compassionate use programmes</td>
<td>9 (3,144)</td>
<td>8 (3,064)</td>
</tr>
<tr>
<td><strong>Blood donation</strong></td>
<td>NA</td>
<td>Antibodies from healed COVID-19 patients, re-injected to active COVID-19 patients</td>
<td>14 (1,741)</td>
<td>7 (1,326)</td>
</tr>
<tr>
<td><strong>Favipiravir</strong></td>
<td>Toyama Chemical</td>
<td>Broad antiviral activity against RNA viruses. Targets RdRp (the RNA-dependent RNA polymerase), leading to inaccurate viral RNA synthesis</td>
<td>7 (676)</td>
<td>6 (626)</td>
</tr>
<tr>
<td><strong>Interferon-Beta</strong></td>
<td>Several MAHs in the EU/EEA</td>
<td>It could help controlling the inflammatory response during COVID-19</td>
<td>7 (7,010)</td>
<td>6 (5,096)</td>
</tr>
<tr>
<td><strong>Hydroxychloroquine</strong></td>
<td>21 different MAHs in EU/EEA</td>
<td>Its antiviral effect against SARS virus were discovered in vitro back in 2006. It interferes with ACE2 glycosylation. By blocking ACE2, Hydroxychloroquine might prevent the virus entry into the cells</td>
<td>60 (54,609)</td>
<td>51 (52,184)</td>
</tr>
<tr>
<td><strong>Lopinavir / ritonavir</strong></td>
<td>9 different MAHs in EU/EEA</td>
<td>Several HIV protease inhibitors such as lopinavir produce strong interaction with SARS-CoV-2 main protease in Silico</td>
<td>23 (28,488)</td>
<td>20 (28,348)</td>
</tr>
<tr>
<td><strong>Polyclonal antibodies</strong></td>
<td>Takeda, Regeneron</td>
<td>Antibody concentrates from convalescent patients' plasma</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Remdesivir (has results)</strong></td>
<td>Gilead Sciences</td>
<td>Broad-spectrum antiviral, with activity against RNA viruses such as coronaviruses. It targets the SARs-coV- RNA-dependent RNA polymerase needed for the virus replication</td>
<td>11 (23,599)</td>
<td>10 (23,598)</td>
</tr>
<tr>
<td><strong>Tocilizumab (has results)</strong></td>
<td>Roche</td>
<td>Some patients with severe COVID-19 might have a cytokine storm syndrome. Hyper-inflammation could be treated with therapies with proven safety profiles</td>
<td>17 (3,293)</td>
<td>13 (2,783)</td>
</tr>
</tbody>
</table>
Products to reduce SARs-coV2 viral growth

Azithromycin

Rational

Proposed as an add-on treatment for its action against bacterial pneumopathies, and also as it showed some broadspectrum antiviral activity in vitro.

Clinical experience against COVID-19

Twenty cases treated in a French study (uncontrolled) with a possible reduction of the viral load at Day 6, with lower levels than compared to untreated patients in the literature. No conclusion can be drawn as this viral load reduction could indicate natural healing and not a treatment effect.

Status

Tested in combination with Hydroxychloroquine or other products in many trials, in particular:

- Australia: NCT02735707
- Brazil: NCT04329572, NCT04321278 and NCT04322123
- Canada: NCT04324463
- Denmark: NCT04322396
- France: Marseille IUH
- Pakistan: NCT04328272
- USA, Utah: NCT04329832

And various studies in China.

Availability

This antibacterial product is authorised as a broad-spectrum antibiotic, is now in the public domain as an antibiotic since 2005 and marketed by hundreds of different companies.

- To be prescribed and dispensed by a doctor at the hospital.
- Largely available, several producers.

Caution

Absolute contraindications to azithromycin include hypersensitivity to azithromycin, erythromycin, chlorithromycin, dirithromycin, josamycin, midecamycin diacetate, everolimus, pimecrolimus, sirolimus, temsirolimus, fidaxomicine and other products.

There is a long list of contraindications and you should always discuss them with the prescribing doctor.

Consult your national regulatory agency to find more information on the safety of Azithromycin.

1 Refers to number in NIH registry: [www.clinicaltrials.gov](http://www.clinicaltrials.gov)
Blood donation

Rational

They consist in antibodies from COVID-19 patients who recovered, re-injected to patients with the active form of COVID-19.

The use of convalescent plasma was recommended as an empirical treatment during outbreaks of Ebola virus in 2014, and a protocol for treatment of Middle East respiratory syndrome Coronavirus with convalescent plasma was established in 2015. This approach with other viral infections such as SARS-CoV, H5N1 avian influenza, and H1N1 influenza also suggested that transfusion of convalescent plasma was effective for COVID-19.2

Timeline

May see some use and anecdotic results immediately, but research could take months. Some preliminary results might be published I May 2020.

Clinical experience against COVID-19

The clinical experience is limited, and there will be more information after studies and results from treatment in USA and other countries, as FDA recently approved the use of convalescent plasma in critically ill patients with COVID 19.

Status

China

One study was conducted in China, Shenzhen Third People's Hospital. Cross-sectional and longitudinal blood samples were collected from 8 SARS-CoV-2 – infected subjects during the early outbreak in Shenzhen. The diverse and potent neutralising antibodies identified here are promising candidates for prophylactic and therapeutic SARS-CoV-2 interventions.3

The results highlight the possibility that antibodies from convalescent plasma may have contributed to the clearance of the virus and the improvement of symptoms. In the current study, all patients received antiviral agents, including interferon and lopinavir/ritonavir, during and following convalescent plasma treatment, which may have contributed to the viral clearance observed.

In Wuhan, April 17, over 500 patients with COVID-19 have been treated by the plasma of recovered cases so far. The Wuhan Blood Center has collected nearly 380,000 ml of plasma from 1,101 recovered patients for treating COVID-19 patients. The plasma was sent to 13 designated hospitals.4

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2 Chenguang Shen, PhD; Zhaoqin Wang, PhD; Fang Zhao, PhD; et al. Treatment of 5 Critically Ill Patients With COVID-19 With Convalescent Plasma. March 27, 2020. doi:10.1001/jama.2020.4783
4 Xinhu, Editor: huaxi, Over 500 COVID-19 patients treated by convalescent plasma in Wuhan, 2020-04-17 , Published online: http://www.xinhuanet.com/english/2020-04/17/c_138986074.htm
USA

The Mayo clinic serves as the lead institution for the US programme. Trials have started in different sites, to investigate whether the plasma treatment is better as prophylaxis before infection, in early stages of illness to prevent escalation or as a last attempt to save the critically ill.

A project for convalescent plasma is already looking for donors after FDA allowed testing on the 24th of March (National COVID-19 Convalescent Plasma Project). Other countries are joining what began as a grassroots endeavour by doctors and scientists. "We brought in the United Kingdom over the weekend. Ireland, too," said Casadevall, who co-wrote the paper March 13.

France

France is starting a trial with convalescent plasma (07/04). "Coviplasm": this is the name of this clinical study using convalescent plasma. 60 patients to be included in this trial conducted in Paris region, Eastern Region and Burgundy, sponsored by InSERM.

Donors: 200 patients who recovered for more than 14 days. Call to donors by EFS. Each donation: 600 millilitres plasma for, total needed 600 units of 200 millilitres plasma, for 30 participants, 30 other receiving SOC (randomised).

The first results could be known very quickly, within two to three weeks only. If they were positive, it would be necessary to be able to collect a lot of convalescent plasma from the healed people: the French Blood Establishment is preparing for it.

Netherland

Another large trial was started in the Netherlands, with 426 participants, using the same approach:

Convalescent Plasma as Therapy for Covid-19 Severe SARS-CoV-2 Disease (CONCOVID Study) (NCT number): NCT04342182

Estimated start: 08.04.2020 and estimated study completion date: 01.07.2020.

United Kingdom

The NHS is recruiting online.

Industry initiatives

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5 Mayo Clinic, Expanded Access to Convalescent Plasma for the Treatment of Patients With COVID-19, 20 April 2020, Published online: https://www.uscovidplasma.org/
6 Tim McDonnell. If you’ve recovered from Covid-19, here’s one way you might be able to help others. Published online 30.03.2020: https://qz.com/1828563/how-to-help-others-if-youve-recovered-from-covid-19/
Microsoft is launching a self-screening tool for people to check whether they qualify to donate their plasma in the hopes of creating a treatment for those with COVID-19, according to a company blog post. The tool is part of the company’s work with a group called the CoVig-19 Plasma Alliance.\(^\text{11}\)

**Availability**

The FDA approved use of convalescent plasma in strict conditions and under the Emergency Authorisation Status. The container label of COVID-19 convalescent plasma units must include the following statement, "Caution: New Drug--Limited by Federal (or United States) law to investigational use." (21 CFR 312.6 (a))\(^\text{12}\)

Eligible patients for use under expanded access provisions:

- Must have laboratory confirmed SARS-coV-2 infection
- Must have severe or immediately life-threatening COVID-19, for example:\(^\text{13}\)
  - Severe disease is defined as:
    - Dyspnea
    - respiratory frequency ≥ 30/min
    - blood oxygen saturation ≤ 93%
    - partial pressure of arterial oxygen to fraction of inspired oxygen ratio < 300, and/or
    - lung infiltrates > 50% within 24 to 48 hours
  - Life-threatening disease is defined as:
    - respiratory failure
    - septic shock, and/or
    - multiple organ dysfunction or failure
- Must provide informed consent

**Caution**

Plasma transfusions are generally safe and well-tolerated by most patients, but can cause allergic reactions and other side effects. It is also not known if patients with COVID-19 might have other types of reactions to convalescent plasma.\(^\text{14}\)

Among plasma donors (people who fully recovered from COVID-19), there are some people also infected with HIV (they were infected before). Like for organ donations, discussions are taking place for HIV people to donate their blood to other HIV people suffering from COVID-19 (USA, Switzerland), but not to other COVID-19 patients.

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\(^\text{14}\) US Food and Drugs Administration, Investigational COVID-19 Convalescent Plasma - Emergency INDs Frequently Asked Questions. 26.03.2020, available online: [https://www.fda.gov/media/136470/download](https://www.fda.gov/media/136470/download)
Favipiravir

Rational

Medicine authorised as Avigan, Toyama Chemical, in Japan and China for flu (influenza). The active substance belongs to a class of products called pyrazinecarboxamide derivative, with an broad antiviral activity against many RNA viruses.\(^{15}\)

It targets the RdRp (the RNA-dependent RNA polymerase), its mechanism of action consists in a purine nucleoside that acts as an alternate substrate leading to inaccurate viral RNA synthesis.

Clinical experience against COVID-19

In February 2020, Favipiravir was studied in China for experimental treatment of COVID-19. On March 17, Chinese officials suggested the drug had been effective in treating COVID-19.

Limited clinical experience has been reported supporting the use of favipiravir for COVID-19. In a prospective, randomised, multcenter study, favipiravir (n = 120) was compared with Arbidol (n = 120) for the treatment of moderate and severe COVID-19 infections. Differences in clinical recovery at day 7 were observed in patients with moderate infections (71.4% favipiravir and 55.9% Arbidol, \(P = .019\)). No significant differences were observed in the severe or severe and moderate (combined) arms.\(^{16}\)

Status

22 March 2020: AIFA approved the drug for experimental use against COVID-19 and has begun conducting trials in 3 regions most affected by the disease. AIFA reminded the public that the existing evidence in support of this drug is scant and preliminary.

China: A study on 80 patients comparing it to lopinavir/ritonavir found that it significantly reduced viral clearance time to 4 days, compared to 11 days for the control group, and that 91.43% of patients had improved CT scans with few side effects. Limitation: not a randomized double-blinded placebo-controlled clinical trial.\(^{17,18}\)

Three clinical trials are planned or in progress in China:


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**Availability**

Authorised only in Japan and China

**Caution**

Teratogenic product, restricted use.

**Hydroxychloroquine to treat coronavirus infected patients**

Advice for patients with lupus taking Hydroxychloroquine:

1. Do not stock up on Hydroxychloroquine.
2. If you anticipate the need for Hydroxychloroquine soon, talk to your pharmacy to pre-order, and clearly mention that this is as treatment for your lupus. Do not ask for more than you need (i.e. 1 box)
3. Ask your doctor to mention on the prescription that this is for your lupus. In some countries, this will help prioritise supply.
4. If you do not have Hydroxychloroquine anymore:
   - While Hydroxychloroquine is an essential part of your treatment, if you have regularly taken it over the past weeks, it will keep its protective effect for an extended period, even if you cannot take it during a limited period. Strictly follow your Rheumatologist's guidance, both in the period where you might not have access to Hydroxychloroquine, and when you receive your next box.
   - Ask your pharmacist how long it can take to be delivered. In most cases, the delay should not be longer than 48 to 72 hours.
   - If your pharmacist cannot obtain it from their usual suppliers: ask your pharmacist to get in contact with the local provider office ("Marketing authorisation holder") on a possible emergency procedure for on-label usage
   - Get in contact with your rheumatologist and ask for guidance. In some countries, your doctor might also be able, if necessary, to meet your needs via hospital controlled supply
   - Do NOT self-adjust any of your medication: do not stop Cortisone, nor immune-suppressant, nor Hydroxychloroquine treatments, unless you get instructed to do so by your doctor.

**Rational**

Hydroxychloroquine is an anti-malarial treatment. It was first authorised in 1947, and since then prescribed to millions of travellers as a prophylactic or curative treatment against Malaria. It is also largely used against lupus (systemic lupus erythematosus) by some 5 million people around the world. It is on the World Health Organization's List of Essential Medicines, the safest and most effective medicines needed in a health system.

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Its antiviral effect against SARS virus were discovered in vitro back in 2006.\(^2\) It interferes with ACE2 glycosylation. The interaction between the viral S protein and ACE2 on the host cell surface is of significant interest since it initiates the infection process. By blocking ACE2, Hydroxychloroquine might prevent the virus entry into the cells.

Chinese researchers started exploring its efficacy and safety in 2020 among patients infected with SARs-coV-2 virus.

**Clinical experience against COVID-19**

Some doctors are combining Hydroxychloroquine with azithromycin, an antibiotic. Much of the published evidence comes from a very small French study conducted by Prof Didier Raoult in Marseille (80 patients, not randomized) and reports from China. Larger, more rigorous clinical trials are starting, but they will take more time.

Initially, Prof Raoult looked at the SARS-coV\(_2\) viral load decline in patients who had been treated with Hydroxychloroquine or Hydroxychloroquine plus Azithromycin.\(^2\) There is a marked viral load decline but in the absence of any control group, it cannot be imputed to the treatment. Spontaneously, the viral load declines in most patients, hospitalised or not, and then the patients heal.

Two other French studies concluded the opposite: “we found no evidence of a strong antiviral activity or clinical benefit of the combination of Hydroxychloroquine and azithromycin for the treatment of our hospitalized patients with severe COVID-19”.\(^2\) In China, another trial with few patients but randomised (30 patients randomised to Hydroxychloroquine plus standard of care or to standard of care) showed no difference in virological outcomes. At day 7, virological clearance was similar, with 86.7% vs 93.3% clearance for the Hydroxychloroquine group and standard care group, respectively (p>.05).\(^2\)

Another multicentre study in China, randomised, between Hydroxychloroquine and standard of care, with a total of 150 participants, failed to show any difference at day 28, both in terms of virological and clinical results.\(^2\)

A French retrospective study in advanced patients (hospitalised and receiving oxygen) with a total of 181 patients, 84 had received Hydroxychloroquine, and 97 did not. They looked at the risk of being transferred to an Intensive Care Unit within 7 days of treatment, or death from any cause. There were no statistical differences between the two groups in that primary endpoint. Meanwhile, 8 of the Hydroxychloroquine-treated patients had electrocardiogram changes that

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\(^2\) Hydroxychloroquine in patients with COVID-19: an open-label, randomized, controlled trial. Wei Tang et al. medRxiv 2020.04.10; doi: https://doi.org/10.1101/2020.04.10.20060558. This article is a preprint and has not been peer-reviewed
required them to be taken off the drug. The authors conclude that these results “do not support the use of Hydroxychloroquine in patients hospitalised for a documented SARS-CoV-2 pneumonia”. 25

Now, there are many more trials underway, but when looking over the actual controlled data for Hydroxychloroquine, the case for this product is not very encouraging.

Dr. Joe Brewer in Kansas City, Mo., uses Hydroxychloroquine in two ways: to treat patients and as prophylaxis to protect health-care workers from infection.

Status

Hydroxychloroquine is marketed under different brand names, with more than 21 marketing authorisation holders in the EU, and is in the public domain.

France and Italy published decrees26,27 for the use of Hydroxychloroquine to treat COVID 19 (off-label use) under strict conditions:

- Hydroxychloroquine to be prescribed to patients with COVID-19 and to be dispensed in hospitals, and then it can be continued at home if needed
- Treatment is reimbursed or covered, no co-payment
- Hydroxychloroquine can only be dispensed in a community pharmacy if prescribed by prescribed by a rheumatologist, internal medicine doctor, dermatologist, nephrologist, neurologist, paediatrician (for lupus or other chronic conditions)

Clinical trials

See Discovery trial in next Chapter

Availability

**Warning: there are reports of wrong doses or wrong product when purchasing Hydroxychloroquine online**

Measure for chronic patients to access Hydroxychloroquine & lopinavir/ritonavir and for seriously complicated COVID-19 patients with regards priority access to these off-label treatment:

- Belgium: Community pharmacies can only dispense the medicine to chronic patients. When submitting an order request to the wholesaler, they need to motivate this. Community pharmacies can also compound Hydroxychloroquine capsules in case Plaquenil® would not be available or in case

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25 No evidence of clinical efficacy of Hydroxychloroquine in patients hospitalized for COVID-19 infection with oxygen requirement: results of a study using routinely collected data to emulate a target trial. Matthieu Mahevas et alo. medRxiv 2020.04.10; doi: https://doi.org/10.1101/2020.04.10.20060699. This article is a preprint and has not been peer-reviewed

26 https://www.legifrance.gouv.fr/affichTexte.do?cidTexte=JORFTEXT000041755775&dateTexte=&oldAction=rechJO&categorieLien=id&idJO=JORFCONT000041755510&fbclid=IwAR0iH21u38s0CZ--RYy9NaubKYdSV3GFVcdQFEdF3gi0i3TYCVuiP9x33Xx8l

27 https://www.gazzettaufficiale.it/eli/id/2020/03/17/20A01706/SG
a different dosage is prescribed. For COVID-19 these medicines can only be prescribed and dispensed in hospitals.

- Denmark: The Danish Medicines Agency has decided that pharmacies can only supply these medicines if prescribed by hospital doctors and specialist doctors and only for patients with certain diagnoses and only if these patient are in continuous treatment with these medicines.
- France: Community pharmacists are requested by the ANSM to dispense these drugs only on medical prescription in their usual indications, this in order to secure their access to patients who benefit from it for their chronic treatment. They can also compound Hydroxychloroquine capsules if needed. Hospitals can prescribe and dispense it to treat COVID-19, with a protocol to collect data.

With an increasing demand, and a ban on the export of the active substance in India (where the active substance is manufactured), there are some tensions on the supply. As a remedy, hospital pharmacists are compounding Hydroxychloroquine as magistral preparation.

Patients using Hydroxychloroquine to treat lupus or other chronic conditions are advised to contact their doctors if they have difficulties renewing their medicines.

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**Tensions on Hydroxychloroquine supply:** as the demand for Hydroxychloroquine is increasing, and some 5 million patients are taking worldwide to treat inflammatory diseases, some countries report tensions on its availability. This does not mean there is a shortage. **Pharmacists and patients should not stockpile Hydroxychloroquine.**

**Italy:** For Hydroxychloroquine against COVID-19, dispensed in hospitals, AIFA recommends pharmacists to deliver half packages to save supply. Package s of Hydroxychloroquine usually contain 30 pills, when for a typical course at the recommended maximal dose (up to 7 days), a maximum of 16 pills is needed. The dispensation of a full pack to a patient would waste half the pills it contains. In order to save 50% of pills, it is advised to divide the content of a pack into 2, and to deliver a blister of 15 pills to patients.


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**Special care if you have this rare condition**

Myasthenia Gravis (MG): there are rare reports of developed MG after initiation of Hydroxychloroquine or of exacerbation of myasthenic symptoms.

Retinopathy: long-term use of Hydroxychloroquine associated with small risk of retinopathy.

In both cases, Hydroxychloroquine to be prescribed by a medical doctor in a hospital setting, after evaluation of the patient’s condition and risks.

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Caution: must be prescribed by a specialised doctor as

Absolute contraindications to Hydroxychloroquine include

- known hypersensitivity to Hydroxychloroquine or chloroquine, amino-4 quinolines, amodiaquine, mefloquine, glafenine, floctafenine, antrafenine
- retinopathy
- age < 6 years
- lactation
- patients taking imipramine, mirtazapine, fluoxetine citalopram, escitalopram, hydroxyzine, clomipramine, sertraline, venlafaxine, clozapine, quetiapine, risperidone, aripiprazole, promethazine, haloperidol, cyamemazine, domperidone, and piperaquine because of increased risk of arrhythmia and torsades de pointes

Relative contraindications or cases in which it is not recommended include

- hepatic porphyria
- hypersensitivity to lactose
- abnormalities of galactose metabolism
- lactase deficiency
- digestive malabsorption / intolerance syndrome due to the presence of lactose as an excipient
- psychoactive products such as cocaine, amphetamines, cannabis (can induce arrhythmia). Methadone or buprenorphine also
- This risks also exist with tramadol

Monitoring arrhythmia risk

It is important to get a baseline ECG to be able to measure changes. This starting point measurement could be from a standard 12-lead ECG, telemetry or a smartphone-enabled mobile ECG device.\textsuperscript{30}

See Mayo Clinic Guidance on the Risk of QTc Prolongation From Off-Label COVID-19 Treatments.\textsuperscript{31}

**Hydroxychloroquine to prevent infection by coronavirus**

Hydroxychloroquine is now also tested to prevent the infection in individuals who were exposed to the virus (as post-exposure prophylaxis)

UCLA is one of seven sites participating in a clinical trial investigating whether Hydroxychloroquine can prevent infection with COVID-19. The multi-site study led by the University of Washington in collaboration with six other university centres, is now enrolling 2,000 participants who are close contacts of persons who are confirmed or suspected to be infected with COVID-19.

Trial participants are randomly assigned to take Hydroxychloroquine or a placebo over two weeks, and nasal swab samples are collected and tested daily to confirm new COVID-19 infections across the two groups. Sandoz, a Novartis division, has donated the Hydroxychloroquine doses for the study.

\textsuperscript{30} On March 20, 2020, the Food and Drug Administration (FDA) granted emergency approval of AliveCor’s Kardia 6L mobile ECG device as the only FDA-approved mobile device for QTc monitoring with COVID-19. The mobile device’s ability to remotely provide the patient’s heart rhythm and QTc value does not require an extra ECG technician to take the measurement in person, thus saving increased exposure to COVID-19 and the need for more personal protective equipment.

The $9.5 million trial looking at post-exposure preventive therapy for COVID-19 is part of an initiative launched by the Bill & Melinda Gates Foundation, Wellcome, and Mastercard to speed development and access to therapies against the respiratory virus that has spread throughout the world.32

**Interferon-Beta-1a**

**Rational**

The possible use of Interferon-β to treat patients with COVID-19 was first proposed by Chinese researchers, who published a list of treatments possibly effective: Remdesivir, Lopinavir / ritonavir, lopinavir / ritonavir combined with interferon-β, convalescent plasma, and monoclonal antibodies.33 It could help controlling the inflammatory response during COVID-19.

**Clinical evidence against COVID-19**

Interferon-Beta associated to lopinavir / ritonavir is tested in several trials, in particular:

- **NCT04331899** United States (120 participants) uses Peginterferon
- **NCT04315948** France (Discovery trial) 3,200 participants
- **2020-001023-14** United Kingdom 400 participants

**Status**

Interferon-Beta-1a is already authorised to treat multiple sclerosis (Avonex®, Rebif®, Pregidy®...), as a chronic treatment. When used long-term, it is contra-indicated in patients who have severe depression or have thoughts of suicide.

**Lopinavir / ritonavir**

**Rational**

It is a combination of 2 HIV protease inhibitors, ritonavir being used as a booster to enhance lopinavir activity. Several HIV inhibitors such as lopinavir, ritonavir, and saquinavir produce strong interaction with the active site of SARS-CoV-2 main protease in silico.34 From SCIENCE, “The combination can inhibit the protease of other viruses as well, specifically coronaviruses. It has shown efficacy in marmosets infected with the MERS virus, and has also been tested in SARS and MERS patients, though results from those trials are ambiguous.” In advanced COVID19 patients, the lack of efficacy was probably due to the fact it was used too late.

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It targets coronavirus main protease 3CLpro, a protease for the proteolysis of viral polyprotein into functional units. And also PLpro, papain-like protease PLpro a protease for the proteolysis of viral polyprotein into functional units.

**Timelines**

Early results (interim analysis) expected in April 2020.

**Clinical experience against COVID-19**

Clinical experience against COVID-19One Chinese trial showed no benefit, but it enrolled too few patients for statistical analysis (underpowered). In adults with severe COVID-19 hospitalised in Wuhan, China, treatment using a combination of antiviral drugs –lopinavir–ritonavir (HIV/AIDS therapies) –provided no benefit.35

**Status**

It is authorised in most countries to treat HIV infection. It benefits from a voluntary License, WHO Patent Pool.

**Clinical research to treat COVID-19**

Phase III Discovery trial (see chapter 2 on clinical trials). This is a multi-centre clinical trial, adaptive, randomised, open trial of the safety and efficacy of treatments for COVID-19 in hospitalised adults.

The interim trial results will be monitored by a Data Monitoring Committee and if at any stage evidence emerges that any one treatment arm is definitely inferior then it will be centrally decided that that arm will be discontinued. Conversely, if good evidence emerges while the trial is continuing that some other treatment(s) should also be being evaluated, then it will be decided that one or more extra arms will be added while the trial is in progress. The primary objective of the study is to evaluate the clinical efficacy and safety of different investigational therapeutics relative to the control arm in patients hospitalized with COVID-19, the primary endpoint is the subject clinical status (on a 7-point ordinal scale) at day 15.

Adverse events related to treatments used against coronavirus disease 2019 (CovidTox) is a sub-study of the Discovery Trial and will analyse data in 1000 patients.

There are 16 trials registered on clinicaltrials.gov: China, Hong Kong, Republic of South Korea, Saudi Arabia, Canada, Egypt, Thailand…36

Today, there are 27 studies listed on clinicaltrials.gov with at least one arm that includes lopinavir/r. Two studies are listed as completed, neither with results posted yet.

NCT04276688 is complete, Hong Kong, with 127 participants: Lopinavir/ritonavir + ribavirin + Interferon-Beta compared to Lopinavir/ritonavir. It started on 10 Feb.

NCT04346147 has completed recruitment. It is in Madrid, with 165 participants, 3 arms:

- Lopinavir/ritonavir + Hydroxychloroquine
- Hydroxychloroquine + imatinib

Hydroxychloroquine + baricitinib
It started on 13 April, results expected to report by August 2020.
There is one trial at Oxford with LOP/RIT and dexamethasone (EUDRACT 2020-001113-21).^37

**Polyclonal antibodies**

**Rational**

TAK-888: Takeda initiated the development of an anti-SARS-CoV-2 polyclonal hyper-immune globulin (H-IG) to treat high-risk individuals with COVID-19, while also studying whether Takeda’s currently marketed and pipeline products may be effective treatments for infected patients.\(^38\)

Testing of antibody concentrates from convalescent patients' plasma by Takeda could take 10-12 months to complete.

**Remdesivir**

**Rational**

Remdesivir is an investigational broad-spectrum antiviral, developed by Gilead Sciences as a treatment for Ebola virus disease and Marburg virus infections, with antiviral activity against other single stranded RNA viruses such as respiratory syncytial virus, Junin virus, Lassa fever virus, Nipah virus, Hendra virus, and the coronaviruses (including MERS and SARS viruses).

It targets the SARS-coV- RNA-dependent RNA polymerase for replicating viral genome.

Intellectual property rights: Gilead Sciences owns the patent US20170071964 for a “Preparation of amino acid-containing nucleotides and methods for treating arenaviridae and coronaviridae virus infections.”\(^39\)

**First results**

**NIH Clinical Trial Shows Remdesivir Accelerates Recovery from Advanced COVID-19**

Preliminary results indicate that patients who received remdesivir had a 31% faster time to recovery than those who received placebo (p<0.001). Specifically, the median time to recovery was 11 days for patients treated with remdesivir compared with 15 days for those who received placebo. Results also suggested a survival benefit, with a mortality rate of 8.0% for the group receiving remdesivir versus 11.6% for the placebo group (p=0.059).\(^40\)

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\(^{37}\) https://www.clinicaltrialsregister.eu/ctr-search/trial/2020-001113-21/GB


\(^{39}\) ACS Cent. Sci. 2020, 6, 315–331

Clinical experience against COVID-19

No firm results so far. Some clinical trials have been stopped, due to the difficulty to enrol patients (China, when the epidemic was declining).

In late January 2020, Gilead began laboratory testing of remdesivir against SARS-CoV-2. It was administered to the first U.S. patient confirmed to be infected by SARS-CoV-2, in Snohomish County, Washington, for "compassionate use" after he progressed to pneumonia. While no broad conclusions can be made based on the single treatment, the patient's condition improved dramatically the next day, and he was eventually discharged.41

On 6 February 2020, clinical trials of remdesivir began in China. On 15 April, two main trials in China were suspended, one for moderate cases, the other for severe ones (both could not enrol enough participants: clinicaltrials.gov identifiers NCT04252664 and NCT04252664).

WHO announced the launch of a large four-arm pragmatic clinical trial (SOLIDARITY trial) that includes one group of patients treated with Remdesivir.

In Europe, the DISCOVERY trial is also exploring the efficacy and safety of remdesivir in hospitalised patients.

Gilead's own severe Covid-19 trial includes 2,400 participants from 152 different clinical trial sites all over the world (clinicaltrials.gov identifier NCT04292899). Its moderate Covid-19 trial includes 1,600 patients in 169 different centres, also all over the world (clinicaltrials.gov identifier NCT04292730). These are NIAID's double-blind placebo-controlled studies.

Gilead is expecting results by mid-May 2020 in patients with severe COVID-19 diseases. It compares treatment outcomes and safety following 5 or 10 days of remdesivir treatment versus standard of care.42

A fuller picture on remdesivir is expected any day now. Gilead has said that it will release data from one of its U.S. trials by the end of this week. As designed, the only randomisation is the duration of treatment: either five days or 10 days of drug. Without a true control group of patients, many experts say, it will be difficult to determine whether remdesivir is effective. Collecting data quickly can actually slow things down if studies are not designed in a way that gives clear, definitive answers.

Status

USA: On 20 March, FDA Commissioner Stephen Hahn confirmed the compassionate use programme. On 24+3 March 2020, Gilead suspended access to remdesivir for compassionate use (excepting cases of critically ill children and pregnant women), for reasons related to supply, citing the need to continue to provide agent for testing in clinical trials.

42 https://s3-us-west-1.amazonaws.com/groupsioattachments/21255/73228606/50969/0?AWSAccessKeyId=AKIAJECNKOVMCCU3ATNQ&Expires=1587729314&Signature=PV%2B9MODqj0CEu1FiS9k2CF52Q0%3D&response-content-disposition=inline%3B+filename%3D%22Gilead+Statement+04.23.2020.pdf%22
On 1 May 2020, the FDA issued an Emergency Use Authorization for Remdesivir.\(^\text{43}\)

Czech Republic: On 17 March 2020, remdesivir was provisionally approved for use for COVID-19 patients in a serious condition.

**Products to treat inflammation and/or respiratory illness**

**Tocilizumab (with first positive results)**

**Rational**

Tocilizumab, is a monoclonal antibody, a type of protein that has been designed to recognise and attach to a specific target (called an antigen) in the body. Tocilizumab attaches to the receptor for a messenger molecule or ‘cytokine’ called interleukin-6 (IL6). This messenger is involved with inflammation and is found at high levels in patients with rheumatoid arthritis, systemic juvenile idiopathic arthritis, juvenile idiopathic polyarthritis, giant cell arteritis and cytokine release syndrome. Tocilizumab reduces the inflammation and other symptoms of these diseases.

Accumulating evidence suggests that a subgroup of patients with severe COVID-19 might have a cytokine storm syndrome. A recent study recommends identification and treatment of hyper-inflammation using existing, approved therapies with proven safety profiles to address the immediate need to reduce the rising mortality. Therapeutic options include selective cytokine blockade (e.g. Anakinra or Tocilizumab)\(^\text{44}\).

**Clinical experience against COVID-19**

In February 2020, first clinical trials in China investigated Tocilizumab as experimental treatment of pneumonia in COVID-19. On April 10\(^\text{th}\) 2020, 43 trials are registered by WHO. Different populations are investigated: patients with inflammatory rheumatic diseases, patients with advanced or metastatic cancer and COVID-19 (not listed here).

**First results**

**CORIMUNO-TOCI-19 trial – NCT04331808, France. INSERM, APHP**

Participants were hospitalised for moderate or severe COVID-19 pneumonia which did not require Intensive Care at admission (no mechanical ventilation). Treatment outcome was a composite endpoint, participants needing mechanical or non-invasive ventilation, or death after 14 days of treatment.

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\(^{44}\) Puja Mehta, Daniel F McAuley, Michael Brown, Emilie Sanchez, Rachel S Tattersall, Jessica J Manson et al. "COVID-19: consider cytokine storm syndromes and immunosuppression” – The Lancet - Published: March 16, 2020 - DOI: [https://doi.org/10.1016/S0140-6736(20)30628-0](https://doi.org/10.1016/S0140-6736(20)30628-0)
A total of 129 were randomised: 65 with standard of care and Tocilizumab, 64 with standard of care only. Fewer participants treated with Tocilizumab needed assisted ventilation or died (statistically significant difference).

Due to the exceptional circumstances, investigators and sponsors decided to communicate on these results before they could be peer-reviewed, for ethical reasons.45

Treatment of COVID-19 Patients With anti-interleukin Drugs (COV-AID)
Recruiting. 342 participants. A phase 3 Prospective, Randomized, Factorial Design

Treatment group 1: Anakinra
Treatment group 2: Siltuximab
Treatment group 3: Anakinra + Siltuximab
Treatment group 4: Tocilizumab
Treatment group 5: Anakinra + Tocilizumab
Treatment group 6: standard of care (control group)

NCT04330638, Belgium.

A Study to Evaluate the Safety and Efficacy of Tocilizumab in Patients With Severe COVID-19 Pneumonia (COVACTA)
Recruiting. 330 participants. Phase 3 randomized, Double-Blind, Placebo-Controlled

Treatment group: Tocilizumab
Control group: IV placebo

Sponsor is Roche, RoActemra (Tocilizumab) MAH. NCT04317092

Favipiravir Combined With Tocilizumab in the Treatment of Corona Virus Disease 2019
Recruiting. 150 participants. Randomized with Parallel Assignment open label study.

Treatment group 1: Favipiravir Combined With Tocilizumab
Treatment group 2: Favipiravir
Treatment group 3: Tocilizumab

NCT04310228, China. Results expected by May 2020.

Combined Use of Hydroxychloroquine, Azithromycin, and Tocilizumab (TOCOVID)
Recruiting. 276 participants, children and adults. A phase 2 Randomized, Multicentre, open-label study. Parallel Assignment.

Treatment group: Tocilizumab associated with Hydroxychloroquine and azithromycin.
Control group: Hydroxychloroquine and azithromycin.

Primary outcome: In-hospital mortality + need for mechanical ventilation

NCT04332094, Spain.

Status

Tocilizumab is available as a solution to be injected under the skin and as a concentrate for making a solution for infusion (drip) into a vein to treat rheumatic diseases under the brand name RoActemra® by Roche in Europe.

Caution

The most serious side effects are serious infections, complications of diverticulitis and allergic reactions. For the full list of side effects, see the Summary of product characteristics. Tocilizumab must not be used in patients who have an active, severe infection. Doctors should monitor patients carefully for signs of infection during treatment, and should prescribe Tocilizumab with caution in patients who have had recurring or long-term infections, or diseases that could increase the risk of infections, such as diverticulitis or diabetes. One study shows that infections can occur without fever.46

Availability

Tocilizumab can only be obtained in hospital pharmacies with a prescription and treatment should be started by a doctor who has experience in the diagnosis and treatment of the relevant condition. The drug must be stored in the refrigerator and kept at cold temperatures if transported from hospital to home.

Products withdrawn from this document

As trials both for Fingolimod and Thalidomide did not start, and given the toxicity of both products, they were withdrawn from this review.

Studies of interest
This section will be updated on a weekly basis. Only a selection of clinical trials can be discussed.

Discovery Trial (results expected 15/05)\textsuperscript{47}

EudraCT Number: 2020-000936-23

**Objective:** to evaluate the efficacy and safety of four experimental therapeutic strategies which might be effective against COVID-19

**Principal investigator:** Florence Ader, infectiologist, Infectious and Tropical Diseases Department of the Croix-Rousse Hospital of Lyon University Hospital and researcher at the CIRI International Research Centre in Infectiology (Inserm/CNRS / Claude Bernard University Lyon 1)

**Sponsors:** INSERM, COMBACTE, PREPARE and RECOVER

**Adaptive trial design:** ineffective experimental treatments can very quickly be dropped and replaced by other molecules that emerge from research efforts

**Number of participants:** 3200, 800 in France (20 centres)

**Starting date:** 22 March 2020

**Update:** as of 29 March, 123 enrolled in France (objective 800) in 7 centres (objective: 20).\textsuperscript{48} As of 5 April, 600 enrolled in France.

As of 1 May, around 740 / 800 enrolled in France.

**Participating countries:** Belgium, France, Germany, Luxembourg, the Netherlands, Spain, Sweden, and the United Kingdom

First interim analysis: around 5 April 2020

Final analysis: when all participants treated for 15 days

**First Results are expected around 15 May 2020.**

\textsuperscript{47} Launch of a European clinical trial against COVID-19

Design: randomized, open-label trial (participants will know which treatment they receive).

Arms:

- standard of care
- standard of care plus remdesivir
- standard of care plus lopinavir and ritonavir
- standard of care plus lopinavir, ritonavir and interferon beta
- standard of care plus hydroxy-chloroquine

Inclusion: patients should have Clinical assessment (evidence of rales / crackles on exam) AND SpO2 ≤ 94% on room air, OR requiring mechanical ventilation and/or supplemental oxygen, which might be a too late stage.

Interpretation: A normal, healthy person should have an SPO2 of between 94 and 99 percent while breathing normal room air. Someone with an upper respiratory infection or disease should have an SPO2 above 90. If this level falls below 90, the person will require oxygen to maintain brain, heart and other organ function. Normally, if a person has an SPO2 below 90, they run the risk of developing hypoxemia or low blood oxygen saturation. Symptoms may include shortness of breath, especially during brief exercise or even while you are at rest. Many people also experience low blood oxygen levels when they are sick, have a blood clot in their lungs, have a collapsed lung, or a congenital heart defect.

Solidarity trial

http://www.isrctn.com/ISRCTN83971153

Sponsor
World Health Organization

Participating countries
Argentina, Bahrain, Canada, France, Iran, Norway, South Africa, Spain, Switzerland and Thailand have confirmed that their participation.

USA and United Kingdom are not involved.

Arms: similar to European Discovery Trial, chloroquine instead of hydroxychloroquine

- standard of care
- standard of care plus remdesivir
- standard of care plus lopinavir and ritonavir

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standard of care plus lopinavir, ritonavir and interferon beta
standard of care plus chloroquine

Starting date: 26 March 2020

Inclusion

Adults (aged over 18 years) hospitalized with definite COVID-19 and not already receiving any of the study drugs. Patients invited to join the study will be those who are admitted to a collaborating hospital

For all other clinical trials

You can consult the Anti-Cancer Fund database:

http://www.redo-project.org/COVID-19db

Paris hospitals (39 hospitals) participate in many clinical trials, read here (in French):