This first report focuses on clinical trials:

1. The World Health Organization (WHO) announced a large global trial, called ***SOLIDARITY*****,** where antiviral compound **remdesivir;** the malaria medications **chloroquine and hydroxychloroquine**; a combination of two HIV drugs, **lopinavir and ritonavir**; and that same combination plus **interferon-beta**, will be tested. Enrolment of patients is through the WHO website, but the drugs must be available at the hospital, the website will randomize the patient to one of the drugs available or to the local standard care for COVID-19.
2. **Hydroxychloroquine and Azithromycin** as a treatment of COVID-19
3. Early, low-dose and short-term application of **corticosteroid treatment** in patients with severe COVID-19 pneumonia:
4. Antiviral membrane fusion inhibitors, **Favipiravir versus Arbidol** for COVID-19.
5. **Ciclesonide**, an inhaled corticosteroid used to treat asthma and allergic rhinitis.
6. **Meplazumab, a monoclonal anti-CD147 antibody, treats COVID-19 pneumonia**.
7. Roche's **Tocilizumab**
8. **Cell therapy- Mesenchymal Stem Cells**
9. **RECOVERY trial**

A review of registered Chinese (chictr.org.cn) and US (clinicaltrials.gov) databases for clinical trials for COVID-19 upto Match 7th 2020 by Belhadi et al. on MedRxiv 2020.03.18.20038190; doi: https://doi.org/10.1101/2020.03.18.20038190 showed out of the 353 studies identified, 115 clinical trials were selected for data extraction. Phase IV trials were the most commonly reported study type (n=27, 23%). **The most frequently assessed therapies were: stem cells therapy (n=23 trials), lopinavir/ritonavir (n=15), chloroquine (n=11), umifenovir (n=9), hydroxychloroquine (n=7), plasma treatment (n=7), favipiravir (n=7), methylprednisolone (n=5), and remdesivir (n=5).**

Clinical trials

1. **SOLIDARITY:** On Friday March 20th 2020, the World Health Organization (WHO) announced a large global trial, called SOLIDARITY, to find out whether any can treat infections with the new coronavirus for the dangerous respiratory disease. It's an unprecedented effort—an all-out, coordinated push to collect robust scientific data rapidly during a pandemic. The study, which could include many thousands of patients in dozens of countries, has been designed to be as simple as possible so that even hospitals overwhelmed by an onslaught of COVID-19 patients can participate.

   WHO is focusing on what it says are the four most promising therapies: an experimental antiviral compound called **remdesivir;** the malaria medications **chloroquine and hydroxychloroquine**; a combination of two HIV drugs, **lopinavir and ritonavir**; and that same combination plus **interferon-beta**, an immune system messenger that can help cripple viruses. Some data on their use in COVID-19 patients have already emerged—the HIV combo failed in a small study in China—but WHO believes a large trial with a greater variety of patients is warranted.

   Enrolling subjects in SOLIDARITY will be easy. When a person with a confirmed case of COVID-19 is deemed eligible, the physician can enter the patient's data into a WHO website, including any underlying condition that could change the course of the disease, such as diabetes or HIV infection. The participant has to sign an informed consent form that is scanned and sent to WHO electronically. After the physician states which drugs are

available at his or her hospital, the website will randomize the patient to one of the drugs available or to the local standard care for COVID-19.

“After that, no more measurements or documentation are required,” says Ana Maria Henao Restrepo, a medical officer at WHO’s Emergencies Programme. Physicians will record the day the patient left the hospital or died, the duration of the hospital stay, and whether the patient required oxygen or ventilation, she says. “That’s all.”

The design is not double-blind, the gold standard in medical research, so there could be placebo effects from patients knowing they received a candidate drug. But WHO says it had to balance scientific rigor against speed. The idea for SOLIDARITY came up less than 2 weeks ago, Henao Restrepo says, and the agency hopes to have supporting documentation and data management centers set up next week. “We are doing this in record time,” she says.

On Sunday, INSERM, the French biomedical research agency, announced it will coordinate an add-on trial in Europe, named Discovery, that will follow WHO’s example and will include 3200 patients from at least seven countries, including 800 from France. That trial will test the same drugs, with the exception of chloroquine. Other countries or groups of hospitals could organize add-on studies as well, Heneo-Restrepo says. They are free to do additional measurements or observations, for instance on virology, blood gases, chemistry, and lung imaging. “While well-organized additional research studies of the natural history of the disease or of the effects of the trial treatments could well be valuable, they are not core requirements,” she says.

The list of drugs to test was first put together for WHO by a panel of scientists who have been assessing the evidence for candidate therapies since January, Heneo-Restrepo says. The group of selected drugs that had the highest likelihood of working, had the most safety data from previous use, and are likely to be available in supplies sufficient to treat substantial numbers of patients if the trial shows they work.

Source: Science magazine https://www.sciencemag.org/news/2020/03/who-launches-global-megatrial-four-most-promising-coronavirus-treatments?fbclid=IwAR25ChrKbKvjn0N3qSRrcg9tWhQ40TLM-jgqurOUfiSzLhWiBH-dhJ-rFaw#

Remdesivir

The most promising COVID-19 antiviral is remdesivir, which gets incorporated into viral RNA and prevents it being synthesised, halting viral replication. Remdesivir inhibited SARS-CoV-2 replication in laboratory studies and was tested in one patient with COVID-19 in US. The patient’s symptoms improved following intravenous remdesivir administration; however, more clinical data is required before the drug can be approved for use.

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The University of Oxford is testing the **anti-malaria drug, hydroxychloroquine** on 3,000 high-risk coronavirus patients to see if it can alleviate the worst of the symptoms. This trial is aimed at those people who are at higher risk of complications but are not yet that sick that they need to go to hospital. We’re hoping to find drugs that might prevent that kind of disease progression to help them get better quicker,” Professor Chris Butler, of Oxford University, told BBC Radio 6. A separate trial, also by Oxford University, will test hydroxychloroquine on patients who are so ill they have already been taken to hospital.

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2. **Hydroxychloroquine and Azithromycin as a treatment of COVID-19**: preliminary results of an open-label non-randomized clinical trial

Philippe GAUTRET, Jean Christophe LAGIER, Philippe PAROLA, Van Thuan HOANG, Line MEDDED, Morgan MAILHE, Barbara DOUDIER, Johan COURJON, Valerie GIORDANENGO, Vera ESTEVES VIEIRA, Herve TISSOT DUPONT, Stephane HONORE, Philippe COLSON, Eric CHABRIERE, Bernard LA SCOLA, Jean Marc ROLAIN, Philippe BROUQUI, Didier RAOULT Sr.

medRxiv 2020.03.16.20037135; doi: https://doi.org/10.1101/2020.03.16.20037135

Method: Patients were included in a single arm protocol to receive 600mg of hydroxychloroquine daily and their viral load in nasal swabs was tested daily. Depending on their clinical presentation azithromycin was added to the treatment.

36 out of 42 patients meeting the inclusion criteria in this study that had at least six days of follow-up at the time of the present analysis. A total of 26 patients received hydroxychloroquine and 16 were control patients. Patients were included in a single arm protocol to receive 600mg of hydroxychloroquine daily and their viral load in nasal swabs was tested daily. Depending on their clinical presentation, azithromycin was added to the treatment. Untreated patients from another centre and cases refusing the protocol were included as negative controls. Presence and absence of virus (PCR method only) at day 6-post inclusion was considered the end point.

Results: hydroxychloroquine is efficient in clearing viral nasopharyngeal carriage of SARS-CoV-2 in COVID-19 patients in only three to six days, in most patients. A significant difference was observed between hydroxychloroquine-treated patients and controls starting even on day3 post-inclusion. However, 4 of the 26 treated patients were not recovering. Thus, one should be careful about these preliminary results.

Now published in: Philippe Gautret, Jean-Christophe Lagier, Philippe Parola, Van Thuan Hoang, Line Meddeb, Morgane Mailhe, Barbara Doudier, Johan Courjon, Valérie Giordanengo, Vera Esteves Vieira, Hervé Tissot Dupont, Stéphane Honoré, Philippe Colson, Eric Chabrière, Bernard La Scola, Jean-Marc Rolain, Philippe Brouqui, Didier Raoult. Hydroxychloroquine and azithromycin as a treatment of COVID-19: results of an open-label non-randomized clinical trial. International Journal of Antimicrobial Agents. 2020,105949. ISSN 0924-8579, https://doi.org/10.1016/j.ijantimicag.2020.105949 Retraction watch on this paper..

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3. **Early, low-dose and short-term application of corticosteroid treatment in patients with severe COVID-19 pneumonia**: single-center experience from Wuhan, China

Yin Wang, Weiwei Jiang, Qi He, Cheng Wang, Baoju Wang, Pan Zhou, Nianguo Dong, Qiaoxia Tong

medRxiv 2020.03.06.20032342; doi: https://doi.org/10.1101/2020.03.06.20032342

Forty-six hospitalized patients with severe COVID-19 pneumonia hospitalized at

Wuhan Union Hospital from January 20 to February 25, 2020, were retrospectively reviewed.

The patients were divided into two groups based on whether they received corticosteroid treatment. The clinical symptoms and chest computed tomography(CT) results were compared

A total of 26 patients received intravenous administration of methylprednisolone with a dosage of 1-2mg/kg/d for 5-7 days, while the remaining patients not. There was no significant difference in age, sex, comorbidities, clinical or laboratory parameters between the two groups on admission. The average number of days for body temperature back to the normal range was significantly shorter in patients with administration of methylprednisolone when compared to those without administration of methylprednisolone (2.06±0.28 vs. 5.29±0.70, P=0.010).

The data indicate that in patients with severe COVID-19 pneumonia, early, low dose and short-term application of corticosteroid was associated with a faster improvement of clinical symptoms and absorption of lung focus.

4. **Favipiravir versus Arbidol for COVID-19**: A Randomized Clinical Trial

Chang Chen, Jianying Huang, Zhenshun Cheng, Jianyuan Wu, Song Chen, Yongxi Zhang, Bo Chen, Mengxin Lu, Yongwen Luo, Jingyi Zhang, Ping Yin, Xinghuan Wang

medRxiv 2020.03.17.20037432; doi: https://doi.org/10.1101/2020.03.17.20037432

Objective: To compare the efficacy and safety of favipiravir and arbidol to treat COVID-19 patients on 7 day′s clinical recovery rate.

Design: Prospective, multicenter, open-label, randomized superiority trial in February, 2020. Setting: Multicenter study. Participants: Patients with confirmed COVID-19 admitted to 3 hospitals from Feb 20, 2020 to Mar 12, 2020.

Interventions: Conventional therapy + favipiravir or arbidol. The patients with chest CT imaging and laboratory-confirmed COVID-19 infection, aged 18 years or older were randomly assigned to receive favipiravir or arbidol. Safety data were collected for a further 1 weeks′ follow-up.

Results: Total 236 patients with COVID-19 were enrolled in the full analysis set (FAS), 120 patients were assigned to favipiravir group (116 assessed) and 120 to arbidol group (120 assessed). In FAS cohort, for ordinary patients with COVID-19, 7 day′s clinical recovery rate was 55.86% in the arbidol group and 71.43% in the favipiravir group (P = 0.0199).

For ordinary COVID-19 patients and COVID-19 patients with hypertension and/or diabetes, the time of fever reduction and cough relief in favipiravir group was significantly shorter than that in arbidol group (both P < 0.001), but there was no statistical difference was observed of auxiliary oxygen therapy or non-invasive mechanical ventilation rate (both P > 0.05).

Trial Registration: sChictr.org.cn, number ChiCTR200030254.

5. **Identification of antiviral drug candidates against SARS-CoV-2 from FDA-approved drugs**

Sangeun Jeon, Meehyun Ko, Jihye Lee, Inhee Choi, Soo Young Byun, Soonju Park, David Shum, Seungtaek Kim

bioRxiv 2020.03.20.999730; doi: https://doi.org/10.1101/2020.03.20.999730

Method: screen a panel of FDA-approved drugs to identify antiviral drug candidates for the treatment of COVID-19 and suggest the identified drug candidates may be considered for therapeutic development.

Approximately 3,000 FDA- and IND-approved drug library against SARS-CoV to identify antiviral drug candidates (manuscript in preparation). Since the SARS-CoV and SARSCoV-2 are very similar (79.5% sequence identity), the drugs which show antiviral activity against SARS-CoV are expected to show similar extent of antiviral activity against SARS-CoV-2.

A total of 35 drugs were selected from the earlier SARS-CoV screening results. In addition, fifteen drugs were included based on recommendations from infectious diseases specialist.

Setting: Vero cells were used and each drug was added to the cells prior to the virus infection.

Result: At 24 h after the infection, the infected cells were scored by immunofluorescence analysis with an antibody specific for the viral N protein of SARS-CoV-2. niclosamide, an antihelminthic drug, exhibited very potent antiviral activity against SARS-CoV-2 (IC50 = 0.28 µM).

Niclosamide inhibits SKP2 activity, which enhances autophagy and reduces MERS-CoV replication

ciclesonide is another interesting drug candidate for further development although its antiviral potency was much lower (IC50 = 4.33 µM) than niclosamide. It is an inhaled corticosteroid used to treat asthma and allergic rhinitis. A recent report by Matsuyama et al. corroborated our finding of ciclesonide as a potential antiviral drug against SARS-CoV-2 12. A treatment report of three patients who were infected by SARS-CoV-2 in Japan (https://www3.nhk.or.jp/nhkworld/en/news/20200303_20/) warrants further clinical investigation of this drug in patients with COVID-19.

6. **Meplazumab treats COVID-19 pneumonia**: an open-labelled, concurrent controlled add-on clinical trial

Huijie Bian, Zhao-Hui Zheng, Ding Wei, Zheng Zhang, Wen-Zhen Kang, Chun-Qiu Hao, Ke Dong, Wen Kang, Jie-Lai Xia, Jin-Lin Miao, Rong-Hua Xie, Bin Wang, Xiu-Xuan Sun, Xiang-Min Yang, Peng Lin, Jie-Jie Geng, Ke Wang, Hong-Yong Cui, Kui Zhang, Xiao-Chun Chen, Hao Tang, Hong Du, Na Yao, Shuang-Shuang Liu, Lin-Na Liu, Zhe Zhang, Zhao-Wei Gao, Gang Nan, Qing-Yi Wang, Jian-Qi Lian, Zhi-Nan Chen, Ping Zhu

medRxiv 2020.03.21.20040691; doi: https://doi.org/10.1101/2020.03.21.20040691

A small open label, single center human clinical trial NCT04275245on using Meplazumab a monoclonal anti-CD147 antibody as add-on therapy to treat COVID-19 pneumonia. No toxicity was reported.

Aim: assess the efficacy and safety of meplazumab, a humanized anti-CD147 antibody, as add-on therapy in patients with COVID-19 pneumonia.

Methods: All patients received recommended strategy from Diagnosis and Treatment for 2019 Novel Coronavirus Diseases released by National Health Commission of China.

Eligible patients were add-on administered 10 mg meplazumab intravenously at days 1, 2, and 5. Patients hospitalized in the same period were observed as concurrent control.

The endpoints include virological clearance rate, case severity, chest radiographic, and laboratory test.

Results: 17 patients were enrolled and assigned to meplazumab group between Feb 3, 2020 and Feb 10, 2020. 11 hospitalized patients served as concurrent control. Baseline characteristics were generally balanced across two groups. Compared to control group, meplazumab treatment significantly improved the discharged (p=0.006) and case severity (p=0.021) in critical and severe patients. The time to virus negative in meplazumab group was reduced than that in control group (median 3, 95%CI[1.5-4.5] vs. 13, [6.5-19.5]; p=0.014, HR=0.37, 95%CI[0.155-0.833]).

The percentages of patients recovered to the normal lymphocyte count and CRP concentration were also increased remarkably and rapidly in meplazumab group. No adverse effect was found in meplazumab-treated patients.

Interpretation: Meplazumab efficiently improved the recovery of patients with SARS-CoV-2 pneumonia with a favorable safety profile.

Related publication: : SARS-CoV-2 invades host cells via a novel route: CD147-spike protein

Ke Wang, Wei Chen, Yu-Sen Zhou, Jian-Qi Lian, Zheng Zhang, Peng Du, Li Gong, Yang Zhang, Hong-Yong Cui, Jie-Jie Geng, Bin Wang, Xiu-Xuan Sun, Chun-Fu Wang, Xu Yang, Peng Lin, Yong-Qiang Deng, Ding Wei, Xiang-Min Yang, Yu-Meng Zhu, Kui Zhang, Zhao-Hui Zheng, Jin-Lin Miao, Ting Guo, Ying Shi, Jun Zhang, Ling Fu, Qing-Yi Wang, Huijie Bian, Ping Zhu, Zhi-Nan Chen

bioRxiv 2020.03.14.988345; doi: https://doi.org/10.1101/2020.03.14.988345

7. Roche, has announced plans to initiate a global phase III study and collect data on Actemra's (**tocilizumab**) potential utility in severe COVID-19 pneumonia patients.

8. **Mesenchymal Stem Cells** have immunomodulatory properties, so they release bioactive agents, such as cytokines, to modify the immune response. COVID-19 can stimulate a terrible inflammation cytokine storm in the lungs, such as IL-2, IL-6, IL-7, GSCF, IP10, MCP1, MIP1A, and TNFα, followed by edema, dysfunction of the air exchange, acute respiratory distress syndrome, acute cardiac injury and secondary infection (Huang et al. (2020), The Lancet, 395:497-506), which may led to death. Therefore, avoiding, preventing or attenuating the cytokine storm may be the key for the treatment of COVID-19 infected patients. MSCs, owing to their powerful immunomodulatory ability, may have beneficial effects of preventing or attenuating the cytokine storm.

   A clinical trial was undertaken in China on patients with pneumonia due to COVID-19. *Prof. Georgina Ellison-Hughes of KCL is a co-author on the paper*.
   One million MSCs per kilogram of weight were intravenously transplanted into seven patients and results were observed over 14 days. Before the transplantation, all

patients had COVID-19 pneumonia with symptoms of high fever, weakness, shortness of breath and low oxygen saturation. Results showed that all symptoms had disappeared by two to four days after the transplantation. The oxygen saturations rose to ≥ 95% at rest, without or with oxygen uptake. This was not the case in the 3 placebo control patients. Among the MSC-treated patients, one severe and two common patients were able to make a recovery and be discharged 10 days after treatment.

The study found improvement was particularly dramatic for an elderly male patient in a severe critical condition. This is because the mesenchymal stem cells restored the balance of the immune system, which becomes over-activated as it tries to kill the virus. It produces a large amount of inflammatory factors, leading to the severe cytokine storm. The MSCs modulate this cytokine storm and once the immune function was restored, the patients were able to make a recovery.

http://www.aginganddisease.org/article/0000/2152-5250/ad-0-0-216.shtml

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9. **RECOVERY trial https://www.recoverytrial.net/** has recruited over 5,000 patients in 165 NHS hospitals around the UK in a month. Patients are randomly allocated one of the drugs (or a placebo). There are already 500 to 900 patients on each of the drugs being tested and 2,000 in the control groups. Led by Oxford University, Peter Horby, Professor of Emerging Infectious Diseases and Global Health and Martin Landray, Professor of Medicine and Epidemiology at the Nuffield Department of Population Health.

   Drugs being used:
   - **Hydroxychloroquine**, anti-malaria drug.
   - **Azithromycin**, an antibiotic.
     NB: if there is any effect in patients given these drugs alone, compared with those given no drugs, they can be combined later.
   - **lopinavir-ritonavir**, two antiretroviral drugs used in HIV treatment.
   - **low-dose dexamethasone**, a type of steroid typically used to reduce inflammation.
   - **Tocilizumab** - interleukin 6 antagonist, used in rheumatoid arthritis and to treat cytokine storm.

In discussions to introduce convalescent sera, and as experimental drugs come along, Recovery will include those too.

As of April 17th 2020.

This report was contributed to by Georgina M. Ellison-Hughes and Anna Bajur