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Therapeutic Modalities in the Management of COVID-19: A Worldwide Landscape

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ABSTRACT

Several strains of the novel Coronavirus have been identified and countries around the world are conducting research to identify, map and compare each type. Its infection can manifest with symptoms ranging from uncomplicated non-specific illness to a more damaging syndrome that include mild to moderate pneumonia (Covid-19 pneumonia broadly categorised into the phenotypes: L-type and H-type); Acute Respiratory Distress Syndrome; Sepsis and Septic shock. Although, this virus has a low mortality rate, the danger lies in its virulence and transmission dynamics. Until date, there has been no drug identified to be efficacious cure for this infection. Using the WHO (World Health Organization) guidelines as a base, various medical institutions are continuously updating their guidelines for the identification and therapeutic management of persons infected with Covid 19, with a strong emphasis on IPC measures. The guidelines also highlight detailed supportive treatment including supplemental oxygen therapy, ventilation, intubation and management of specific complications. The current treatment is tailored to patient centred management for the existing co-morbidities and appreciates a progress in the prognosis. The aim of this article is thus to review salient features of specific therapies being used now and summaries the different clinical trials being conducted so as to stay abreast of the possible treatment modalities.

KEYWORDS: COVID-19; Clinical trials; SARS COV-2; Therapeutic management

INTRODUCTION

Since December 2019, an outbreak of a new human virus has spread in many countries and has led to thousands of cases and deaths [1]. The novel coronavirus officially named as COVID-19 that started from Wuhan, China has spread to more than 211 countries & territories around the world [1]. Severe acute respiratory syndrome coronavirus-2 (SARS COV-2), the causative agent of COVID-19, was declared a pandemic by the World Health Organization on 11th March 2020 and is a major global health concern. Most people who are infected show mild respiratory symptoms that eventually disappear on their own, but some people develop more severe illness, like pneumonia [2]. The virus is spread through contact with an infected person or via respiratory droplets through coughs or sneezes. Although protective measures have been executed all throughout the world (such as isolation of confirmed and suspected cases, education about hand washing techniques and importance of wearing masks, prevention of large gatherings, & lockdowns) to reduce the spread of the virus, the need for an effective treatment is crucial to stop the pandemic and reduce the morbidity and mortality of COVID-19 [2]. Since the onset of the outbreak, researchers have suggested many agents that might have an efficacy against COVID-19. Different antiviral, antimicrobial, & immunomodulatory agents were included in the latest guidelines of various countries.

The management of symptoms may include the use of antipyretics or anti- inflammatory medicines for fever & mild pain and oxygen therapy for patients with respiratory distress and has asked to implement mechanical ventilation depending on the patient's clinical condition [3]. However, an array of drugs permitted for other conditions, as well as multiple investigational agents, are being studied for the treatment of COVID-19 in several clinical trials around the world [4-8]. The treatment protocols across various countries are very similar and most of them have suggested the study and use (as a part of compassionate use) of drugs like Hydroxychloroquine, Chloroquine phosphate, Remedesivir, and Lopinavir/Ritonavir [9,8-12]. There have been an increasing number of studies rapidly published online and in educational journals; however, there is limited and insufficient evidence specifically around the therapeutic management for COVID-19. The purpose of the review is to retrospectively study the various treatment modalities taking place for patients infected by the virus, in the worst affected countries of the world.

SARS-CoV-2: Virology and Drug Target

Corona virus has glycoprotein spikes on its surface, which gives the virus "Crown" like appearance, hence CORONA VIRUS [13]. This virus is supposed to have a ZOONOTIC origin. Genetically it has been revealed that Covid-19 genetically clusters with BETACORONA VIRUS, subgenus SERBACOVIRUS, together achieved with two bat-derived strains [4]. SARS-CoV-2 is named so because it is genetically similar to SARS Coronavirus, which was responsible for SARS outbreak 2002. SARS-CoV-2 is a single stranded RNA-enveloped virus, which targets its host cells through the viral structural spike(S) protein that binds to the angiotensin-converting enzyme 2 (ACE2) receptors. The ACE2 receptors are abundantly present in lungs and glandular cells of gastric, duodenal and rectal epithelium as well as endothelial cells and enterocytes of small intestine. ACE2 is also present in brain and there has been results showing effects of COVID-19 on brain. Encephalopathy has been reported in few patients after they have been detected with the virus by cerebrospinal fluid assay [14]. ACE2 receptors are largely present in the heart and are involved in heart function. A high incidence of thrombosis and venous thromboembolism has been noted in patients with severe COVID-19 in the ICUs. After binding to ACE2, the virus than uses the host cell receptor and endosomes to enter the cells and this is facilitated by a host type 2 transmembrane serine protease, TMPRSS2, via S protein. Clinical laboratory findings of COVID-19 resulted in high levels IL-2, IL-7 and IL-6, elevated levels of granulocyte-macrophage colony stimulating factor (GM-CSF) and tumor necrosis factor-alpha suggestive of cytokine release syndrome (18). People with COVID-19 have classical serum biomarkers, elevated C-reactive protein (CRP), lactate dehydrogenase (LDH), D-dimer and Ferritin.

REVIEW OF DRUGS AND THERAPIES

(Repurposed, Investigational & Adjunctive Therapies)

a) ANTIMALARIAL DRUGS

Hydroxychloroquine/chloroquine (with or without Azithromycin)

Hydroxychloroquine/chloroquine serves its antiviral activity by changing the pH of endosomes and is believed to prevent viral entry, transport, and post-entry events. They are prescription drugs that have been used for treatment of malaria and certain inflammatory conditions. The studies revealed that chloroquine might reduce glycosylation of ACE2; thereby preventing COVID-19 from effectively binding

to host cells [15-17]. In addition, chloroquine might block the production of pro-inflammatory cytokines thereby blocking the pathway that subsequently leads to acute respiratory distress syndrome (ARDS). These drugs are under investigation in clinical trials for pre-exposure or post-exposure prophylaxis of SARS-CoV-2 infection, and treatment of patients with mild, moderate, and severe COVID-19 [18,19]. According to NIH, there are insufficient clinical data to recommend either for or against using chloroquine or hydroxychloroquine for the treatment of COVID-19 [20].

Benefits: In the current available data based on clinical trials of Hydroxychloroquine, a somewhat higher proportion in the HCQ group experienced clinical improvement. However, the certainty in the evidence was rated as very low mainly due to small sample sizes (sparse data), co-interventions, and risk of bias due to methodological limitations.

Harm: A few studies described significant QT prolongation in patients treated with HCQ, some cases resulting in a QT increase to over 500 ms, which led to discontinuation of the HCQ treatment, illustrating the high risk for clinically relevant arrhythmias. Other side effects include headache, dizziness, nausea, vomiting, and stomach pain, loss of appetite and skin rash.

Conclusion: Hydroxychloroquine has showed effects in fighting pneumonia, improving lung imaging findings and providing short duration of disease time. The recommended dose for hydroxychloroquine for COVID-19 is 500 mg two times a day for 10 days recommended by experts. Because of the potential for toxicity, the NIH and IDSA guidelines panel recommends that the HCQ+AZ combination only be used in the context of a clinical trial. FDA issued an Emergency Use Authorisation (EUA) for the use of chloroquine and hydroxychloroquine for treatment of hospitalized adults and adolescents (weight ≥50 kg) with COVID-19 for whom a clinical trial is not available.

b) HIV PROTEASE INHIBITOR

Drugs - Lopinavir/Ritonavir

In studies conducted in China, Lopinavir and Ritonavir used in treatment of COVID-19 have showed no remarkable effects on the COVID-19 [21]. Lopinavir/ritonavir a drug approved for usage for the treatment of HIV, demonstrated in-Vitro activity against other novel corona viruses via inhibition of 3-chymotrypsin-like protease [21]. The most commonly studied lopinavir/ritonavir dosing regimen for treatment of COVID-19 is 400 mg/100 mg twice daily for up to 14 days. Other antiretrovirals, including protease inhibitors and integrase strand transfer inhibitors, were recognized by enzyme activity screening as having SARS-CoV-2 activity. In vitro cell models demonstrated activity of darunavir against SARS-CoV-2. The NIH and IDSA Panel recommends against the use of lopinavir/ritonavir or other HIV protease inhibitors (AIII) for the treatment of COVID-19, except in the context of a clinical trial [21].

Benefits: According to one RCT and two case studies analysed by the IDSA, treatment with lopinavir/ritonavir failed to show or exclude a beneficial effect on mortality, although failure of clinical improvement was lower in the study group that was treated with lopinavir.

Harm: lopinavir/ritonavir have shown effects like gastrointestinal adverse reactions, including anorexia, nausea, abdominal discomfort, or diarrhea. The risk of hepatic injury, pancreatitis, severe cutaneous eruptions, QT prolongation, and the potential for multiple drug interactions due to CYP3A inhibition, are all well documented with this drug combination.

Conclusion: The guidelines panel recommends the use of lopinavir/ritonavir only in the context of a clinical trial. Additional clinical trials or prospective outcome registries are needed for an approval of treatment with lopinavir/ritonavir and other HIV-1 protease inhibitors for patients with COVID-19

c) ANTIVIRAL DRUGS

Drugs- Remdesivir/Umifenovir/ Favipiravir

Remdesivir binds to the viral RNA-dependent RNA polymerase, inhibiting viral replication through premature termination of RNA transcription. This drug was also used as the emergency drug in first covid19 positive patient detected in the United States of America and there were improvements seen in the condition of the patient [22]. Umifenovir also known as Arbidol has showed more promising results as antiviral drug with a unique mechanism of targeting the S protein/ ACE2 interaction and inhibiting membrane fusion of the viral envelope [23,24]. The current dose of 200mg orally every 8 hours for influenza is being studied for COVID-19 treatment. This drug is currently being used for treatment of influenza in China with unsuccessful results.

Benefits and Harm: A recent case series of 53 patients with severe COVID-19 pneumonia who received remdesivir under a compassionate-use protocol reported clinical improvement

in 68% after a median follow-up of 18 days, with 13% mortality and a generally acceptable toxicity profile. Remdesivir can cause GI symptoms (e.g., nausea, vomiting), elevated transaminases, and prothrombin time elevation (without change in international normalized ratio [INR]).

Conclusion: NIH declared Remdesivir as an investigational antiviral drug for COVID19 and recommends it in the context of a clinical trial [25,26].

d) CORTICOSTEROIDS

Drugs- Dexamethasone/ Methylprednisolone/ Prednisone

Administration of corticosteroid treatment in Covid patients can most definitely said to be case based. Studies have shown that the use of a low dose of corticosteroids for "shock reversal" in patients having septic shock has improved their mortality rate and outcome [27]. However, evidence has also shown that there is little to no improvement and possible harm (due to immunosuppressive effects) in such a regimen when used for patients without ARDS [28]. ISDA suggests against the use of corticosteroids for patients admitted with COVID19 pneumonia whereas it recommends its use for patients with ARDS due to COVID19, but only in the context of clinical trials. Guidelines suggest a typical corticosteroid regimen in adults with COVID19and septic shock: Generally, IV Hydrocortisone 200 mg/day is administered in intermittent doses or as an infusion [29].

Benefits and Harms: Various studies were declared inconclusive by IDSA due to lack of critical information and variability seen in the treatments provided. Steroids and IL-6 inhibitors can be immunosuppressive and may increase risk of secondary infections. Steroids in certain cases have been seen to produce long-term side effect such as osteonecrosis.

Conclusion: According to IDSA and NIH, if a person is on a steroid (inhaled or systemic) for another indication (e.g., asthma), the steroid should be continued.

e) MONOCLONAL ANTIBODIES

Drugs- Sarilumab/ Bevacizumab/ Tocilizumab/ Nivolumab/ Leronlimab/ Itolizumab/ Gimsilumab/ Clazakizumab/ Meplazumab

Monoclonal antibodies synthesized in the laboratory mimic natural antibodies. Studies reporting on the pathogenesis of SARS and MERS-CoV suggest a release of proinflammatory cytokines including interleukins-6 (IL-6) during the clinical illness [30]. An antibody-based treatment has the potential to provide immediate effect in a COVID positive patient. The spike protein on the SARS-CoV-2 virus is the main target being explored for potential COVID-19 monoclonal antibodies [31]. The aim is to target the spike protein and the antibody will be able to neutralise and affect the capacity of the virus to infect healthy cells. A retrospective analysis of 20 severe cases of COVID-19 showed that treatment with tocilizumab led to a reduction in fever and lung lesion opacity, and recovered the percentage of lymphocytes in peripheral blood [32].

Benefits: According to the study, treatment with tocilizumab may have reduced mortality, as there were no deaths reported. However, this conclusion remains uncertain given the lack of a control group or adjustments for confounding factors.

Harm: This particular retrospective study did not report any serious adverse events. However, patients receiving tocilizumab are often at an increased risk of serious infections (bacterial, viral, invasive fungal infections, and tuberculosis) and hepatitis B reactivation. Cases of anaphylaxis, severe allergic reactions, severe liver damage and hepatic failure, and intestinal perforation have been reported after tocilizumab administration in patients without COVID-19.

Conclusion: The USA Guidelines panel recommends the use of Tocilizumab only in the context of clinical trials.

f) NUCLEOSIDE INHIBITORS

Drug-Ribavirin

Ribavirin is a guanine analogue that inhibits viral RNA-dependent RNA polymerase [33]. The clinical experiments with Ribavirin have shown remarkable results regarding its activity against COVID-19. However, its effect against SARS-CoV was limited, as it required high dosage to serve its anti-viral activity that is 1.2 g to 2.4 g orally every 8 hours and needed combination therapy. This drug can be given orally, intravenous and enteral routes.

Harm: Many studies conducted to check for the efficiency and side effects of this drug and few studies concluded that this drug has possible harm due to its adverse effects including HEMATOLOGIC and LIVER TOXICITY. Ribavirin causes severe hematologic toxicity and liver toxicity depending on the dose given. The high doses given in the treatment of SARS resulted in hemolyticanemia in patients, patients treated with Ribavirin plus Interferons for MERS required blood transfusion, in some, Ribavirin for SARS showed raise in transaminase elevation.

Ribavirin shows teratogenic activity and is contraindicated in pregnancy. Hence, Ribavirin given with combination therapy shows best results than given alone.

Conclusion: Ribavirin was used in the treatment of MERS and has shown good results but its efficiency to treat COVID-19 is still questionable and studies in china are being carried out to check its efficacy.

g) IMMUNOMODULATORS

Therapy-IFN Beta 1A & 1B/NK cells/PEG-IFN- Lamba

Interferons Alpha2b have been studied for nCoVs, most studies have shown its good results in combination therapy with drugs like Ribavirin, lopinavir and Ritonavir [34,35]. But delayed treatment will result in its decreased efficiency towards the disease same as other agents.

Harm: You should not use the combination of interferon alfa-2b and ribavirin if you have:

Severe kidney disease, blood cell disorders such as thalassemia or sickle cell anemia, allergy to interferons or ribavirin, if you are pregnant as interferon with ribavirin causes miscarriage, if you have liver disease as the combination causes cirrhosis or hepatitis, colitis and other intestinal problems.

Conclusion: The in-vitro data and animal data and the absence of clinical trials have been the reason to not include interferons currently as a treatment modality.

h) PASSIVE IMMUNE THERAPY

Therapy-Convalescent Plasma

Hyperimmune immunoglobulin or convalescent plasma is the serum specific antibodies of IgG for SARS-COVID and can be obtained from Co-Vid 19 patients who have recovered [36,37]. This was previously used in the treatment of MERS, SARS and H1N1 (2009) with favourable results. The IDSA guideline panel recommends COVID-19 convalescent plasma in the context of a clinical trial. Doctors are currently using this line of treatment on compassionate grounds. Cases where it was used on critically ill patients have proven to have promising results.

Benefits: IDSA identified a study that had one group of patients that were treated with convalescent plasma and another one as a control group. The study showed that there was 30% mortality in the control group as compared to no death in the group that was administered with the plasma treatment. A recent case series also showed five critically ill patients with laboratory confirmed COVID-19 (who had ARDS) improved after receiving plasma transfusion. Their body temperature came down to normal within 3 days (in 4 of 5 patients) and there were no detectable viral loads within 12 days. No serious adverse reactions or safety events were recorded following COVID-19 convalescent transfusion.

Harms: The risks associated with plasma transfusions such as fever, a small risk of infectious disease transmission, mild to severe allergic reactions, transfusion-related lung injury (TRALI) and transfusion associated circulatory overload (TACO).

Conclusion: Due to low overall certainty of evidence, additional research and clinical trials will be required before convalescent plasma is used as a confirmed treatment plan for COVID19.

i) MESENCHYMAL STEM CELL THERAPY

Currently, stem cell therapy has become a promising therapeutic field, which is showing various opportunities to cure incurable diseases [38]. MSCs has called for attention due to source potential, a high proliferation rate, the need of a less invasive procedure, and free of ethical issues. There is much superiority in using MSC therapy [39-41] in comparison with other treatments which includes - I) Easily access and can be isolated from various tissues such as bone marrow and adipose tissues, umbilical cord, dental pulp, menstrual-blood, buccal fat pad, foetal liver, etc. II) They are multipotent stem cells; III) MSCs can easily grow to clinical volume in the required period; IV) MSCs can be stored for repetitive therapeutic usage; V) Clinical trials of MSCs so far have not shown adverse reactions. In COVID-19 patients, the immune system produces large amounts of inflammatory factors in an overproduction of immune cells and cytokines.

j) KINASE INHIBITORS

Drugs - Nintedanibesilate/ Imatinib/ Ruxolitinib/ Baricitinib/ Acalabrutinib

Kinase Inhibitors have proven to be efficacious in various chemotherapy treatments because of their ability to inhibit phosphorylation of amino acids, thereby playing a critical role in preventing the progression of several cancers. A large number of trials are being conducted on Nintedanibesilate, which is a small molecule kinase inhibitor whose use has primarily been approved in treatment of idiopathic pulmonary

fibrosis [42,43]. Though results of the trials for their use in CoVid-19 are yet to come, these are highly targeted drugs and are being used in treating the comorbidities associated with the disease such as pulmonary fibrosis, hyperinflammation, pulmonary vascular leak, etc [44,45].

k) ANGIOTENSIN RECEPTOR BLOCKERS (ARB'S)

Drugs- Losartan/ Telmisartan/ Valsartan

American Heart Association, the Heart Failure Society of America and the American College of Cardiology all recommend that ACE inhibitors or ARBs should be continued in people who have an indication for these medicines. There are 6 clinical trials of the Angiotensin Receptor Blocker drugs and 2 trials on the drug Captopril (ACE Inhibitor) currently registered in the countries reviewed.

l) SYSTEMIC OXYGEN THERAPY

Therapy-Hyperbaric Oxygen

Hyperbaric oxygen therapy involves the administration of 100% oxygen in a pressurised room or via a tube. It's potential use in CoVid 19 patients is on the basis of its ability to generate an increase in the number of oxygen free radicals - stimulating the release of growth factors that can promote wound healing, diminish inflammatory response through a variety of mechanisms, ultimately improving neovascularisation and post-ischaemic tissue survival [46,47]. Preliminary evidence from China when used on patients suggested that when administered (once or in a series of treatments) hyperbaric oxygen therapy increased oxygen saturation in the blood and reversed disease progression. Though it remains relatively safe, possible side effects include lung damage, CNS or oxygen toxicity, middle ear barotrauma (MEB), and changes in vision [48-52].

m) VACCINES

According to COVID-19 tracker by raps.org (Last updated on June 01, 2020) , two vaccines are in between phases 2 and 3 one of which is Bacillus Calmette-Guerin (BCG) live-attenuated vaccine by University of Melbourne and Murdoch Children's Research Institute; Radboud University Medical Center; Faustman Lab at Massachusetts General Hospital and the other AZD1222 studied by The University of Oxford. The mRNA-1273 vaccine by Moderna is in phase 2 trial and Ad5-nCoV (by CanSino Biologics), INO-4800 (by Inovio Pharmaceuticals), BNT162 (by Pfizer and BioNTech), and PiCoVacc (by Sinovac) vaccines are in the 3rd phase of trials. Rest of the vaccines being studied is in a pre-clinical or at an early research phase. There are 9 interventional clinical trials on vaccines that are registered and ongoing in the countries reviewed in the article.

COUNTRY-WISE REVIEW OF ONGOING CLINICAL TRIALS

The search terms COVID-19 OR SARS-COV-2 on ClinicalTrials.gov showed 3265 registered clinical trials worldwide (as of January 1st 2020) of which 1919 were interventional studies (including recruiting, not yet recruiting and completed), 1236 were Observational studies and 18 were of the type Expanded Access. Out of these, 797 studies were in the Phase 4 of the clinical trial. The article aimed at reviewing and describing the ongoing Clinical trials in the major affected countries by COVID-19. The countries studied and researched upon are USA, Spain, Italy, France, Germany, UK, Iran, China and India.

A) USA

Hydroxychloroquine/chloroquine (with or without Azithromycin): A total of 59 out of 702 interventional studies were on the repurposed drug Hydroxychloroquine either individually, in combination or in comparison with other drugs like Chloroquine Sulfate, Azithromycin, Indomethacin, Dietary Supplement with Vitamin C/Zinc, lopinavir/ritonavir, Losartan and Ascorbic Acid. A single ongoing study was also seen on the drug chloroquine individually.

Lopinavir/Ritonavir: There are currently 7 ongoing trials on the drug Lopinavir/Ritonavir in combination with other drugs such as Hydroxychloroquine and Losartan.

Corticosteroids: According to ClinicalTrials.gov, there are 4ongoing trials of the drugs Methylprednisolone, Hydrocortisone, Auxora& RAPA-501-Allo.

Tocilizumab: 6 clinical trials are taking place in the United States of America on the immunomodulatory drug of Tocilizumab.

Convalescent Plasma: 39 clinical trials showing promising results are seen with respect to the treatment modality of Covalescent Plasma. Remdesivir: 22 ongoing clinical trials are seen with the antiviral drugs Remdesivir & Favipiravir.

Angiotensin Receptor Blockers (ARB's): Eight Clinical trials on ARBs are ongoing with drugs like Losartan and Telmisartan.

Mesenchymal Stem Cell Therapy: 10 ongoing clinical trials

are seen on the effect of mesenchymal stem cell therapy in successful treatment of COVID positive patients.

Vaccines: There are 56 interventional vaccine studies ongoing as of January 1st 2021.

B) SPAIN

A single trial of Acalabrutinib: An interventional randomized study included 428 individuals in Barcelona, Spain. Acalabrutinib- administered orally or receive delivery of emptied capsule via nasogastric (NG) or an enteral feeding tube.

A single trial of Indirect Endovenous Systemic Ozone: Interventional randomized study included 50 participants in SEOT Valencia, Spain. 200 ml at 40 mcg/ml of medical ozone / oxygen in 200 ml of patients' blood mixed in a homologated device for the procedure.

Inclusion criteria: COVID-19 patients detected with virus in oro/nasopharynx. Mild ill according to WHO numeric scale. Mild ill according to Berlin criteria. Non-intubated patients.

Exclusion criteria: Patient treated with systemic ozone in last 6 months. Patients having side effects with ozone. Glucose-6-dehydrogensase deficiency. Pregnant women.

12 trials of Sarilumab: Interventional randomized study conducted in 300 patients hospitalized with pneumonia. Age criteria was 18 years and above. Study conducted both in Italy and Spain.

C) ITALY

A single trial of ACE inhibitors, Angiotensin II Type-I Receptor Blockers: An observational study conducted by IRCCS Neuromed, Department of Epidemiology and Prevention, Italy, amongst 5000 participants. Patients who developed severe COVID-19 respiratory disease were included in this study. Control group included patients who did not develop severe COVID-19 respiratory disease.

2 trials of Hyper Immune Plasma: An interventional study amongst 49 individuals who were critically infected by COVID-49 was included in this trial by Catherine Klersy, Pavia, PV, Italy.

Inclusion criteria: Age above 18 years. Positive for RT-PCR for SARS-CoV-2 for less than 10 days. PCR increased by 3.5 with respect to baseline or > 18 mg/dl. Need for continuous ventilation or CPAP.

Exclusion criteria: Moderate to severe ARDS lasting more than 10 days. Proven hypersensitivity reaction to hemoderivatives or immunoglobulins. Consent not received. Administration of hyperimmune plasma at day 1 and based on clinical response on day 3 and 5.

D) FRANCE

In the article 'Clinical and virological data of the first cases of COVID-19 in Europe: a case series', the researchers give a history of usage of the drug Remdesivir for the first few COVID positive patients detected in France. The duration of drug delivery was different for each patient and the drug was discontinued for most of the patients after a few days due to mild side effects seen and due the fear of risk.

France currently has 593 clinical trials on the subject of COVID19 out of which 211 (after elimination of overlapping, serological tests and unrelated trials) are drug interventional studies. There are 7 trials studying Hydroxychloroquine, 5 trials on Corticosteroids, 3 ongoing studies on the antiviral drug Remdesivir, 9 studies on various immunomodulators (Nivolumab, Sarilumab& Tocilizumab), and various trials on Convalescent plasma, Hyperbaric oxygen, Dornase alpha inhalation solution, Mesenchymal stromal cells, and the drug captopril.

E) UNITED KINGDOM

Hydroxychloroquine: Four trials using hydroxychloroquine using (i) ChemoPROphyLaxIs For covId-19 infeCtious disease (the PROLIFIC trial) (ii) Platform Randomised trial of INterventions against COVID-19 In older people [53] (iii) An adaptive Phase 2/3, randomized, open-label study assessing efficacy and safety of hydroxychloroquine for hospitalized patients with moderate to severe COVID-19

Remdesivir: Seven trials studying use of Remdesivir include: (i) A Multicenter, Adaptive, Randomized Blinded Controlled Trial of the Safety and Efficacy of Investigational Therapeutics for the Treatment of COVID-19 in Hospitalised Adults [Remdesivir – active drug Triphosphate]. (ii) 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. (iii) A Phase 3 Randomized Study to Evaluate the Safety and Antiviral Activity of Remdesivir (GS-5734™) in Participants with Severe COVID-19.

Vaccine: 18 trials studying a vaccine ChAdOx1 nCoV-19 – A phase I/II study to determine efficacy, safety and immunogenicity of the candidate Coronavirus Disease (COVID-19) vaccine ChAdOx1 nCoV-19 in UK healthy adult volunteers.

Actilyse: One trial studying use of Actilyse (Alteplase) – A pilot, open label, phase II clinical trial of nebulised recombinant tissue-Plasminogen Activator (rt-PA)in patients with COVID-19 ARDS: The Plasminogen Activator COVID-19 ARDS (PACA) trial

SNG001: One trial studying use of SNG001 (IFNβ-1a for nebulisation) – A randomised double-blind placebo-controlled trial to determine the safety and efficacy of inhaled SNG001 (IFNβ-1a for nebulisation) for treatment of patients with confirmed SARS-CoV-2 infection (COVID-19)

Tocilizumab: Three trials studying use of Tocilizumab

(i) A Randomized, Double-Blind, Placebo-Controlled, Multicenter Study To Evaluate The Safety And Efficacy Of Tocilizumab In Patients With Severe Covid-19 Pneumonia.

Multiple therapeutics: 39 trials studying multiple therapeutics

(i) Preventing Pulmonary Complications in Surgical Patients at Risk of COVID-19: This trial is being conducted with Lopinavir-Ritonavir; Hydroxychloroquine (Plaquenil)

(ii) Randomised Evaluation of COVID-19 Therapy (RECOVERY): This trial is being conducted with Lopinavir/ritonavir, Dexamethasone, Hydroxychloroquine, Azithromycin, Prednisolone, Hydrocortisone, RoActemra (Tocilizumab)

(iii) ACCORD 2: A Multicentre, Seamless, Phase 2 Adaptive Randomisation Platform Study to Assess the Efficacy and Safety of Multiple Candidate Agents for the Treatment of COVID 19 in Hospitalised Patients: Bemcentinib, human immunoglobulin (Ig) G1 monoclonal antibody (mAb), Acalabrutinib, Zilucoplan, Heparin

(iv) Randomized, Embedded, Multifactorial, Adaptive Platform trial for Community-Acquired Pneumonia: Ceftriaxone, Moxifloxacin Hydrochloride, Levofloxacin Hemihydrate, Piperacillin-tazobactam, Ceftaroline, Amoxicillin-Clavulanate, Azithromycin, Clarithromycin, Hydrocortisone

F) GERMANY

Tocilizumab: 2 trials on the monoclonal antibody therapy Tocilizumab are being carried out –

(i) A prospective, randomized, double blinded placebo-controlled trial to evaluate the efficacy and safety of tocilizumab in patients with severe COVID-19 pneumonia

(ii) A Randomized, Double-Blind, Placebo-Controlled, Multicenter Study to evaluate the safety and efficacy of Tocilizumab in patients with severe Covid-19 Pneumonia

Remdesivir: Five trials on the anti-viral Remdesivir

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

A Phase 3 Randomized Study to Evaluate the Safety and Antiviral Activity of Remdesivir (GS-5734™) in Participants with Severe COVID-19

Convalescent plasma: One trial on convalescent plasma (i) A randomized, prospective, open label clinical trial on the use of convalescent plasma compared to best supportive care in patients with severe COVID-19

Hydroxychloroquine: Four trials on the anti-malarial Hydroxychloroquine (i) Randomized controlled trial of hydroxychloroquine versus placebo for the treatment of adult patients with acute coronavirus disease 2019 – COVID-19

Valsartan: One trial on the Angiotensin Receptor Blocker (i) Treatment of Sars-CoV2 infections (Covid19) with valsartan vs placebo, a three-armed randomized, partly blinded trial.

Sarilumab: Two trial on the Monoclonal antibody therapy (i) An adaptive phase 3, randomized, double-blind, placebo-controlled, study assessing efficacy and safety of sarilumab for hospitalized patients with COVID-19.

Multiple drugs: 13 trials on multiple drug therapies (i) Randomized, Embedded, Multifactorial, Adaptive Platform trial for Community-Acquired Pneumonia (REMAP-CAP).

The drugs whose therapeutic actions are being studied are - Levofloxacin, Hydrocortisone, Ceftriaxone, Azithromycin, Clarithromycin, Erythromycin, Amoxicilline-Clavulante, Piperacillin-Tazobactam, Roxithromycin, Ceftaroline, Moxifloxacin, Oseltamivir Phosphate, Lopinavir/Ritonavir, Anakinra, Interferon Beta-1a.

Vaccine: 13 trials were conducted (i)A Multi-site Phase I/II, 2-Part, Dose-Escalation Trial Investigating the Safety and Immunogenicity of four Prophylactic SARS-CoV-2 RNA Vaccines

Against COVID-2019 Using Different Dosing Regimens in Healthy Adults. Human trials for this m-RNA vaccine have begun as of April 23rd, 2020. There are 4 candidates available for trial: BNT162a1, BNT162b1, BNT162b2, BNT162c2. The BNT162 targets the Spike protein and Receptor Binding Domain (RBD) of SAR-CoV-2.

G) IRAN

According to the Article "An Algorithmic Approach to Diagnosis and Treatment of Coronavirus Disease 2019 (COVID-19) in Children: Iranian Expert's Consensus Statement", certain drugs and their dosages have been mentioned for the management of the virus specifically in children. Treatment for patients who were admitted in intensive care unit included combined antiviral agents and immunomodulators [oseltamivir + hydroxychloroquine + Kaletra (lopinavir + ritonavir)] ± ribavirin and if necessary, antibiotics were used according to the patient's situation. There are various ongoing drug trials in the pursuit of finding an effective treatment against the virus. The 17 ongoing clinical trials include 15 drug interventions.

H) CHINA

Chloroquine phosphate/ Hydroxychloroquine: Total 45 trials have been conducted by China for Chloroquine phosphate/Hydroxychloroquine.Amulticenter, single-blind, randomized controlled clinical trial at Beijing you'an Hospital, Capital Medical University.

Hyperbaric oxygen therapy: Nine clinical trials have been seen to be taking place for Hyperbaric oxygen Therapy. Dr.Zhong Mangling published promising results with hyperbaric oxygen therapy at the Department of Hyperbaric Oxygen in Wuhan Yangtze River Shipping General Hospital. The COVID-19 patients were treated with hyperbaric oxygen for 90-120mins with a dose of 1.4 to 1.fi ATA. The results were encouraging as the patients showed remarkable results in fighting hypoxemia COVID-19 can cause.

Natural Killer cells (NK): A total of 10 Clinical trial conducted. At the First Affiliated Hospital of Xinxiang Medical University participants will receive conventional treatment plus twice a week of NK cells (0.2*10E7 NK cells/kg body weight). The eligibility criteria for this experiment will be male or female of age between 18-65 years, pneumonia which is judged by radiograph or computed tomography and laboratory confirmation of NCP infection by reverse-transcriptase polymerase chain reaction (RT-PCR) from any diagnostic sampling source.

The exclusion criteria will be patients who is pregnant or breastfeeding, patient with HIV, HBV or HCV infection, malignancy, psychosis, patients participating in other clinical trials and the patients with inability to provide informed consent or to comply with test requirements.

Nintedanibesilate soft capsules: 13 trials of Nintedanibesilate soft capsules have been seen in China. A single-center, randomized, placebo-controlled trial at Tongji Hospital of Tongji Medical College, Huazhong Science and Technology University conducted in the treatment of pulmonary fibrosis in healed moderate to severe patients of novel coronavirus pneumonia (COVID-19).Nintedanibis used to treat idiopathic pulmonary fibrosis. Nintedanib cloth sulfonate soft capsule treatment: according to the drug manual recommendation, give nintedanib cloth sulfonate soft capsule 150mg twice daily with an interval of about 12 hours each time. Continuous medication for 8 weeks. Changes were seen in forced vital capacity (FVC) after treatment compared to baseline.

Inclusion criteria for this study group 18-70 years old individuals regardless of gender, infection with novel coronavirus confirmed by throat swab nucleic acid test, CT examination of patients with multiple fibrotic shadows in both lungs and signed informed consent.

Exclusion criteria were previous history of chronic bronchitis, emphysema, interstitial lung disease or pulmonary heart disease, people with active peptic ulcer, mental illness and pregnancy and lactation.

Allogeneic Human Dental Pulp Mesenchymal Stem Cells: There is a single ongoing trial in china for this treatment modality. To treat severe novel coronavirus pneumonia (COVID-19) patients at Renmin Hospital of Wuhan University. Intravenous injection of 3.0x10e7 human dental pulp stem cells solution (30ml) on day 1, day 4 and day 7, based on routine treatment of COVID-19.

Intravenous saline injection (Placebo)- Intravenous injection of 3ml of 0.9% saline on day 1, day 4 and day 7, based on routine treatment of COVID-19. The estimated completion of the study is to be noted by 31 May 2021, which started at 31 December 2020.

Two clinical trials with Heparin anticoagulation and high dose vitamin C treatment: Shanghai Hospital Management and Zhongnan Hospital for COVID-19. Low-molecular-weight-heparin 1 to 2 mg/kg per day, continued until the patient's D-dimer level returned to normal. Once fibrinogen

degradation product (FDP) ≥ 10 microgram/ml and D-dimer ≥ 5 microgram/ml, switch to unfractionated heparin. Vitamin C is administered at a dose of 50 to 100 mg/kg per day and continued until significant improvement in the oxygenation index.

20 trials with Anti-CD147 Humanized Meplazumab injection: To treat 2019-nCoV pneumonia at Tang-Du Hospital. The primary drug used is meplazumab. The secondary drug used is methylprednisolone. Remarkable end point results were achieved.

Two vaccines available in china for COVID-19- a) Sinopharm b) Sinovac. Both vaccines are to be proven 79% effective and are to be stored in 2-8 degrees Celsius.

I) INDIA

Hydroxychloroquine: Four trials studying Chloroquine or Hydroxychloroquine include: (i) An open labelled RCT to study the effect of Chloroquine in addition to standard therapy in COVID-19 patients. (ii) To study Topical Chloroquine Nasal Drops in early stage COVID019 and its impact on viral load and cure rates. (iii)An open labelled, RCT to study Hydroxychloroquine for the prevention of new infection and also its adverse outcomes. (iv) Usage of Hydroxychloroquineand Azithromycin In Indicated Confirmed Covid-19 Positive Cases for Its Efficacy in Early Negative Conversion- Pilot Observational Study AIIMS Raipur

Convalescent Plasma: Four trials studying Convalescent Plasma include: (i) A single arm clinical trial to evaluate the safety and efficacy of convalescent plasma in COID-19 patients. (ii) An RCT to study the safety and efficacy of Convalescent Plasma Therapy in Severely Sick COVID-19 Patients. (iii)A Phase II, Open Label, Randomized Controlled Trial to Assess the Safety and Efficacy of Convalescent Plasma to Limit COVID-19 Associated Complications in Moderate Disease. (iv) An Open Label Randomised Control Trial on Passive Immunization with Convalescent Plasma in Severe Covid-19 Disease.

BCG vaccine: Three trials studying BCG are: (i) A Multicentre, Phase III, Double Blind, Randomised, Placebo- Controlled Study to Evaluate the efficacy of recombinant BCG VPM1002 in reducing infection incidence and disease severity of SARS_ COV-2/COVID-19 among high risk subjects. (ii) A double blind randomised parallel group, Placebo-controlled trial to study the effect of BCG- Denmark (Green Signal) on prevention of COVID 19 infection in health care workers. (iii)A non-randomised Phase 2 Clinical Trial for the Evaluation of BCG as potential therapy for CoVID-I9

Homeopathy: (i) A cluster, randomized trial proving the efficacy of Homeopathic treatment in prevention and cure of COVID-19 [Arsenic Album 30]. (ii) A Clinical Trial to ascertain the effect of Homoeopathic Medicines in prevention of outbreak of symptoms in asymptomatic Corona virus and suspected Corona virus patients [Arsenic Album, Bryonia Alba, Gelsemium, AntimoniumTartaricum, CrotalusHorridus]. (iii) A Clinical Trial to Study the Efficacy of Homoeopathic Medicine in Prevention and Cure of Corona Virus Disease 19 [Arsenic Album 30]. (iv) Homoeopathy as adjuvant in management of Covid-19 infection. (v) Randomized, Parallel Group, Active Controlled trial on effects of homeopathic medicine made from cadamba on COVID-19.

Ayurveda: The Ayurvedic remedies make use of various medicinal plants that have benefits in controlling fever and other flu like symptoms. 3 trials studying therapies of alternative medicine include: (i) A single arm trial for Evaluation of effect of composite AYUSH treatment as Prophylaxis of COVID-19 Study. (ii) A Randomized controlled Single blinded prospective multi-centre clinical trial to investigate the safety and efficacy of ZingiVir-H as an adjuvant therapy in hospitalized adults diagnosed with coronavirus disease 2019 (COVID-19) [Ayurvedic remedies –Samshamanivati, Sudarshan Ghana Vati, Khadiradivati, MurrchitaTilataila and Homeopathic medicine – Arsenic album 30]. (iii) A Non-randomized, Active Controlled study to assess the effectiveness of Ayurvedic formulation in addition to standard of care in COVID-19 positive patients in a tertiary hospital.

Imatinib: 1 trial studying Imatinib – Efficacy of Imatinib in mild SARS CoV2 infection: A randomized study. Imatinib is a tyrosine kinase inhibitor. In-vitro studies carried out have shown it to be a potent inhibitor for SARS and MERS.

Ivermectin: Ivermectin is an anti-parasitic drug that has erstwhile been used in the treatment of parasitic infestations such as Onchocerciasis, Filariasis, Pin worms, Head lice and Rosacea. Ivermectin potentiates GABA neurotransmission responses. In-vitro studies done have revealed that it also displays an anti-viral action through specifically inhibiting IMPα/β1-mediated nuclear import. There is a single non-randomised active controlled trial to study the effectiveness of Ivermectin with standard of care treatment versus standard of care treatment for COVID-19 cases.

SSV Formulation: One trial studying a nutraceutical

formulation – SSV Formulation- An open labelled trial to evaluate the safety and efficacy of SSV Formulation to boost immunity in quarantine patients of COVID-19. Not much is known about the exact formulation of this nutraceutical.

Co-infection with Mycobacterium: (i) A Randomized, Parallel Group, Placebo Controlled Clinical Trial of Mycobacterium w in critically ill COVID 19 Patients.

Niclosamide: (i)A randomise trial to evaluate the effect of Oral Niclosamide in mild and very mild COVID-19 cases.

Itolizumab: (i) A Multi-Centre, Open label, Two Arm Randomized, Pivotal Phase 2 Trial to Study the Efficacy and Safety of Itolizumab in COVID-19 Complications.

CONCLUSION

COVID-19, the pandemic, has created a ravage in the world by being so contagious in its manner. The number of clinical trials conducted, as highlighted in Table 1, in order to investigate or obtain a potential treatment line for this pandemic highlights both the need and the capability to be able to come up with a high quality research in the middle of such pandemic. Unfortunately, no therapies have been proven one-hundred percent effective till date and the research of the potential treatment plan is still in progress. But with the help of supportive therapies and few trusted drugs, the treatment of COVID-19 has become possible to some extent. The advancement in preparation of vaccines has also contributed a lot to the hope towards cure of the disease. China, India, The United States Of America, United Kingdom, and many other countries are successful in putting vaccines for trial for COVID-19. The clinical trials mentioned above are current on-going trails as of January 1st 2021. The drugs like Hydroxychloroquine, Lopinair/Ritonavir, Nintedanibesilate, Bevacizumab, Sarilumab, Ribavirin, Convalescent plasma therapy and Hyperbaric oxygen therapy are widely and commonly used in many countries for trails in the treatment of COVID-19 due to their promising results to an extent. Tocilizumab has been proven effective in many studies to treat severe COVID-19 as it has shown promising results. The scientists are working day and night to obtain an effective vaccine or drug in order to control and stopping the pandemic as soon as possible. Keeping in mind the low effectiveness of many drugs to fight coronavirus, social distancing, maintaining personal hygiene and sanitization and maintaining immunity levels is the only and best way to control the spread of the disease.

A Summary of the Interventional Clinical Trials being conducted by country

D DRUG/THERAPY	DESCRIPTION	USA	SPAIN	ITALY	FRANCE	GERMANY	UK	IRAN	CHINA	INDIA
Captopril	ACE Inhibitor	-	-	1	1	-	-	-	-	-
Homeopathic medicines (Arsenic Album 30, Camphora, Bryonia Alba, Helleborus Niger, JusticiaAdhatoda, Cadamba)	Alternative therapy	-	-	-	-	-	-	-	-	5
Ayurvedic medicines (Yashtimadhu, Ayush-64, Ashwagandha, Guduchi and Pippali, Zingivir-H)	Alternative therapy	-	-	-	-	-	-	-	-	3

Ozone Therapy	Alternative therapy	-	1	-	-	-	-	-		-
Losartan	Angiotensin Receptor Blocker	5	-	-	-	-	-	-	-	-
Telmisartan	Angiotensin Receptor Blocker	1	-	-	-	-	-	-	-	-
Valsartan	Angiotensin Receptor Blocker	-	-	-	-	1	-	-	-	-
Favipiravir	Anti-viral	2	-	-	-	-	-	1	7	-
Remdesivir	Anti-viral	20	-	-	3	5	7	-	2	-
Umifenovir	Anti-viral	-	-	-	-	-	-	-	-	-
Azithromycin	Anti-biotic	13	-	-	-	-	-	3	-	-
Heparin	Anti-coagulant	14	-	-	2	-	-	-	2	-
Tranexamic acid	Anti-fibrinolytic	2	-	-	-	-	-	-	-	-
Colchicine	Anti-gout	1	-	-	-	-	1	1	-	-
Niclosamide	Anti-helminthic	2	-	-	-	-	-	-	-	1
Aescin	Anti-inflammatory/	-	-	-	-	-	-	-	-	-
Anti-oedematous	-	-	1	-	-	-	-	-	-	-
Hydrochloroquine-sulfate/ Chloroquine	Anti-malarial	59	-	-	-	4	4	-	45	4
Ivermectin	Anti-parasitic	3	-	-	-	-	-	-	-	1
Atovaquone	Anti-protozoal	2	-	-	-	-	-	-	-	-
Povidone-Iodine	Anti-septic	6	-	-	-	-	-	-	-	1
Vazegapant	CGRP receptor antagonist	1	-	-	-	-	-	-	-	-
DRUG	**DESCRIPTION**	**USA**	**SPAIN**	**ITALY**	**FRANCE**	**GERMANY**	**UK**	**IRAN**	**CHINA**	**INDIA**
Dexamethasone	Corticosteroid	2	-	-	2	-	-	-	-	-
Methylprednisolone	Corticosteroid	2	-	-	-	-	-	-	8	-
Prednisone	Corticosteroid	1	-	-	-	-	-	-	-	-
Linagliptin	DPP4 Inhibitor	1	-	-	-	-	-	-	-	-
Dornasealfa	Enzyme	1	-	-	-	-	-	-	-	-
(Biosynthetic DNase1)	3	-	-	-	-	-	-	-	-	-
Deferoxamine	Heavy metal antagonist	-	-	-	-	-	-	1	-	-
Lopinavir/Ritonavir	HIV protease inhibitor	7	-	-	-	-	-	-	14	-
Oestrogen	Hormone therapy	1	-	-	-	-	-	-	-	-
IFN Beta 1A & 1B	Immunomodulators	-	-	-	-	-	1	2	-	-
NK cells	Immunomodulators	8	-	1	-	-	-	-	10	-
PEG-IFN- Lamba	Immunomodulators	-	-	-	-	-	-	-	-	-
Sirolimus	Immunosuppressant	4	-	-	-	-	-	-	-	-
Acalabrutinib	Kinase Inhibitor	-	1	-	-	-	-	-	-	-
Captopril	ACE Inhibitor	-	-	1	1	-	-	-	-	-
Baricitinib	Kinase Inhibitor	-	-	-	-	-	-	-	-	-
Imatinib	Kinase Inhibitor	1	-	-	-	-	-	-	-	1
Nintedanibesilate	Kinase Inhibitor	-	-	-	-	-	-	-	13	-
Ruxolitinib	Kinase Inhibitor	1	-	-	-	-	-	-	-	-

Bevacizumab	Monoclonal Antibodies	-	-	1	-	-	-	-	20	-
Clazakizumab	Monoclonal Antibodies	5	-	-	-	-	-	-	-	-
Gimsilumab	Monoclonal Antibodies	1	-	-	-	-	-	-	-	-
Itolizumab	Monoclonal Antibodies	-	-	-	-	-	-	-	-	1
Leronlimab	Monoclonal Antibodies	2	-	-	-	-	-	-	-	-
Meplazumab	Monoclonal Antibodies	-	-	-	-	-	-	-	-	-
Nivolumab	Monoclonal Antibodies	-	-	-	2	-	-	-	-	-
Sarilumab	Monoclonal Antibodies	2	27	-	1	2	-	-	-	-
Tocilizumab	Monoclonal Antibodies	6	-	-	3	2	3	-	-	-
Tradipitant	Nerokinin-1 antagonist	-	-	-	-	-	-	-	-	-
Ribavirin	Nucleoside inhibitors	1	-	-	-	-	-	-	26	-
Convalescent plasma	Passive Immune Therapy	39	-	2	3	1	-	-	2	4
Leflunomide	Pyrimidine synthesis inhibitor	2	-	-	-	-	-	-	-	-
Selinexor	Selective inhibitor of nuclear transport (SINE)	-	-	-	-	-	-	-	-	-
Nitric oxide inhalation	Selective Pulmonary vasodilator	7	-	-	-	-	-	-	-	-
DRUG	**DESCRIPTION**	**USA**	**SPAIN**	**ITALY**	**FRANCE**	**GERMANY**	**UK**	**IRAN**	**CHINA**	**INDIA**
Fluvoxamine	Selective serotonin reuptake inhibitor	2	-	-	-	-	-	-	-	-
Dapagliflozin	SGLT2 inhibitors	-	-	-	-	-	-	-	-	-
Human amniotic fluid	Stem cell therapy	3	-	-	-	-	-	-	-	-
Mesenchymal	Stem cell therapy	12	-	-	2	-	-	1	1	-
Hyperbaric Oxygen	Systemic oxygen therapy	2	-	-	1	-	-	-	9	-
SSV formulation	Traditional therapy (Indian)	-	-	-	-	-	-	-	-	1
BCG vaccine	Vaccine (re-purposed)	2	-	-	1	-	-	-	-	3
Mycobacterium w	Vaccine (re-purposed)	-	-	-	-	-	-	-	-	1
Vaccine(s)	Vaccine (new)	49	-	-	-	13	18	-	2	-
Aviptadil	Vasoactive intestinal polypeptide	1	-	-	-	-	-	-	-	-
Vitamin C	Nutritive Agent	8	-	-	-	-	-	-	2	-
Actilyse	Thrombolytic	-	-	-	-	-	1	-	-	-

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CONFLICT OF INTEREST

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