universität wien

DIPLOMARBEIT/ DIPLOMA THESIS

Titel der Diplomarbeit / Title of the Diploma Thesis

„COVID-19 treatment approaches“

verfasst von / submitted by

Elham Riefaie

angestrebter akademischer Grad / in partial fulfilment of the requirements for the degree of

Magistra der Pharmazie (Mag. pharm.)

Wien, 2020 / Vienna, 2020

Studienkennzahl lt. Studienblatt / degree programme code as it appears on the student record sheet:	A 449
Studienrichtung lt. Studienblatt / degree programme as it appears on the student record sheet:	Pharmazie
Betreut von / Supervisor:	Prof. Mag. Dr. Anna Weinzinger

Abstract

The sudden outbreak of the ongoing COVID-19 pandemic lead to researchers working with rapid speed to prevent the further spread of the virus SARS-CoV-2. As of the 23rd July 2020, 298 treatments and 199 vaccines are under development. This thesis aims to summarize and give an overview of the present pre-clinical research and clinical trials of potential candidates for COVID-19 treatments and vaccines.
The required information has been taken from online databases like PubMed, Science, Nature, PNAS and Cell. Papers included were published between December 2019 and July 2020.
The current results indicate the most promising outcomes for dexamethasone as a treatment and ChAdOx1 nCoV-19 as a vaccine. Further research is needed to identify safe and effective treatments and vaccines for COVID-19.

Key words: COVID-19, SARS-CoV-2, coronavirus, pandemic, treatment, vaccine

Abstrakt

Der plötzliche Ausbruch der derzeitigen COVID-19-Pandemie führte dazu, dass Forscher mit hoher Geschwindigkeit daran arbeiten, die Ausbreitung des Virus SARS-CoV-2 zu stoppen. Mit Stand vom 23. Juli 2020 befinden sich 298 Behandlungen und 199 Impfstoffe in Entwicklung. Diese Diplomarbeit soll die aktuelle präklinische Forschung und die klinischen Studien zu potenziellen COVID-19-Behandlungen und Impfstoffen zusammenfassen und einen Überblick schaffen.
Die erforderlichen Informationen wurden von Online-Datenbanken wie Pubmed, Science, Nature, PNAS und Cell entnommen. Die enthaltenen Publikationen wurden zwischen Dezember 2019 und Juli 2020 veröffentlicht.
Die Ergebnisse weisen auf vielversprechende Ergebnisse für Dexamethason als Behandlung und ChAdOx1 nCoV-19 als Impfstoff hin. Weitere Forschung ist erforderlich, um eine sichere und wirksame Behandlung und Impfstoffe gegen COVID-19 zu identifizieren.

Schlüsselbegriffe: COVID-19, SARS-CoV-2, Coronavirus, Pandemie, Therapie, Impfstoff

Acknowledgement

First and foremost, I would like to thank my supervisor, Professor Mag. Dr. Anna Weinzinger at the University of Vienna, who, despite the current circumstances due to COVID-19, made it possible for me to write this thesis. Despite social distancing and a short notice registration for the thesis on my part, she managed to supervise me, let me participate in journal clubs and was always ready with the perfect advice for my questions.

I also wish to express my sincere appreciation for the love and continuous support of my family and friends. Especially to my mum, Amina; my dad, Hassan; and my siblings. This achievement would not have been possible without them being by my side. Thank you.

Table of contents

Table index

List of figures

List of abbreviations

SARS	Severe acute respiratory syndrome
MERS	Middle East respiratory syndrome
MERS-CoV	Middle East respiratory syndrome related coronavirus
SARS-CoV	Severe acute respiratory syndrome coronavirus
COVID-19	Coronavirus disease 2019
nCoV	Novel coronavirus
HCoVHKU1	Human coronavirus HKU1
HCoV-OC43	Human coronavirus OC43
UTR	Untranslated region
Nsps	Nonstructural proteins
ORF	Open reading frame
RdRp	RNA-dependent RNA polymerase
N protein	Nucleocapsid protein
E protein	Envelope protein
S protein	Spike protein
M protein	Matrix protein
ACE2	Angiotensin converting enzyme 2
RBD	Receptor binding domain
TMPRSS2	Transmembrane Serine Protease 2

M^{pro}	Main protease
RNA	Ribonucleic acid
mRNA	Messenger RNA
ER	Endoplasmic reticulum
D	Aspartic acid
G	Glycine
RT-PCR	Reverse transcription polymerase chain reaction
LDH	Lactate dehydrogenase
IL	Interleukin
CRP	C-reactive protein
AST	Aspartate aminotransferase
ALT	Alanine aminotransferase
BUN	Blood urea nitrogen
ECG	Electrocardiogram
PT time	Prothrombin time
PTT time	Partial thromboplastin time
X-ray	Energetic High-Frequency Electromagnetic Radiation
CT	Computed tomography
ARDS	Acute respiratory distress syndrome
SaO2	Oxygen saturation
COPD	Chronic obstructive pulmonary disease
BMI	Body mass index
IgG	Immunoglobulin G
ECMO	Extracorporeal membrane oxygenation
6 HB	Six helical bundle

HR	Heptad repeat
H3N2	Hemagglutinin protein influenza
DMSO	Dimethyl sulfoxide
IFN	Interferon
EC_{50}	Half maximal effective concentration
TNF	Tumor necrosis factor
HIV	Human immunodeficiency virus
CYP	Cytochrome P
IC_{50}	Half maximal inhibitory concentration
EC90	90% maximal effective concentration
SpO2	Peripheral capillary oxygen saturation
FDA	Food and Drug Administration
GABA	Gamma-aminobutyric acid
IMP	Importin
DNA	Deoxyribonucleic acid
PH	Power of hydrogen
ED_{50}	Effective dose for 50% of the population
Ms	Milliseconds
WHO	World Health Organization
FDA	Food and Drug Administration
JAK-STAT	Janus Kinase-Signal Transducer and Activator of Transcription
MAPK	Mitogen-activated protein kinase
NF-kB	Nuclear factor kappa-light-chain-enhancer of activated B cells
ICU	Intensive care unit

PaO2	Partial pressure of oxygen, arterial
FiO2	Fraction of inspired oxygen
PLT	Platelet
INR	International normalized ratio
RCT	Randomized controlled trial
CI	Confidence interval
HR	Hazard ratio
IQR	Interquartile range
WCC	White cell count
P	Probability
LPV/r	Lopinavir-Ritonavir
HCQ	Hydroxychloroquine
SOC	Standard of care
LD	Low dose
HD	High dose
PF Ratio	PaO2/FiO2 ratio
PBO	Placebo
H1N1	Hemagglutinin Type 1 and Neuraminidase Type 1
ADE	Antibody-dependent enhancement
HBV	Hepatitis B virus
HCV	Hepatitis C virus
Dpoi	Days post onset of illness
IgA	Immunoglobulin A
CCR5	Chemokine receptor 5
Ang	Angiopoietin

Mab	Monoclonal antibody
HEK cells	Human embryonic kidney cells
HACE2	Human angiotensin converting enzyme 2
Calu 3 cells	Cultured human airway epithelial cells
Fc region	Fragment crystallizable region
LALA Mutation	Leu234Ala, Leu235Ala mutation
CGMP	Current good manufacturing practices
VAERD	Vaccine associated enhanced respiratory disease
BCG	Bacillus Calmette–Guérin
HPV	Human papilloma virus
VSV	Vesicular stomatitis virus
Ad5	Adenovirus 5
PittCOVacc	Pittsburgh coronavirus vaccine
ND50	50% neutralizing dose
I.V.	Intravenous
N/A	Not applicable
CPAP	Continuous positive airway pressure
SOFA	Sequential organ failure score
CTCAE	Common terminology criteria for adverse events
NPS	Nasopharyngeal swab
IFNAR	Interferon- alpha/beta receptor
IU	International units
ChAdOx1	Chimpanzee adenovirus Oxford 1
MenACWY	Meningococcal conjugate vaccine
VEGF	Vascular endothelial growth factor

Introduction

Since the SARS and MERS outbreak, the fear of another outbreak was always present. The SARS epidemic started in China in 2002 and infected 8422 people and lead to 916 deaths. The ß-coronavirus SARS- CoV was followed by another ß-coronavirus known as MERS-CoV in 2012. The epidemic started in Saudi Arabia and infected 3000 people and lead to 858 deaths. (S. Pandey et al., 2020; Sarvepalli, 2020)

The newly emerged zoonotic severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) is the cause of COVID-19. In December, 2019 a cluster of pneumonia cases with symptoms such as diarrhea, elevated body temperature, cough and myalgia, was discovered in Wuhan, China. Most cases were traced back to the Huanan Seafood Wholesale Market and the causes for the symptoms were not known. (Hamed, 2020)
On January 12, the WHO named the condition, coronavirus disease 2019 and the virus was firstly named 2019-nCoV and was later changed to SARS-CoV-2, since it shows 79,5% genome homology and overall several similarities to SARS-CoV-1. (A. Pandey et al., 2020a)
Since then, COVID-19 started spreading rapidly through human to human transmission and on March 11, 2020 was announced a pandemic by the World Health Organization. (https://www.who.int/news-room/detail/27-04-2020-who-timeline---covid-19) As of July 30, 2020, there are approximately 17,218,757 confirmed cases and 670,956 deaths due to COVID-19. 10,729,972 patients recovered and 5,817,829 patients are currently infected. (https://www.worldometers.info/coronavirus/)

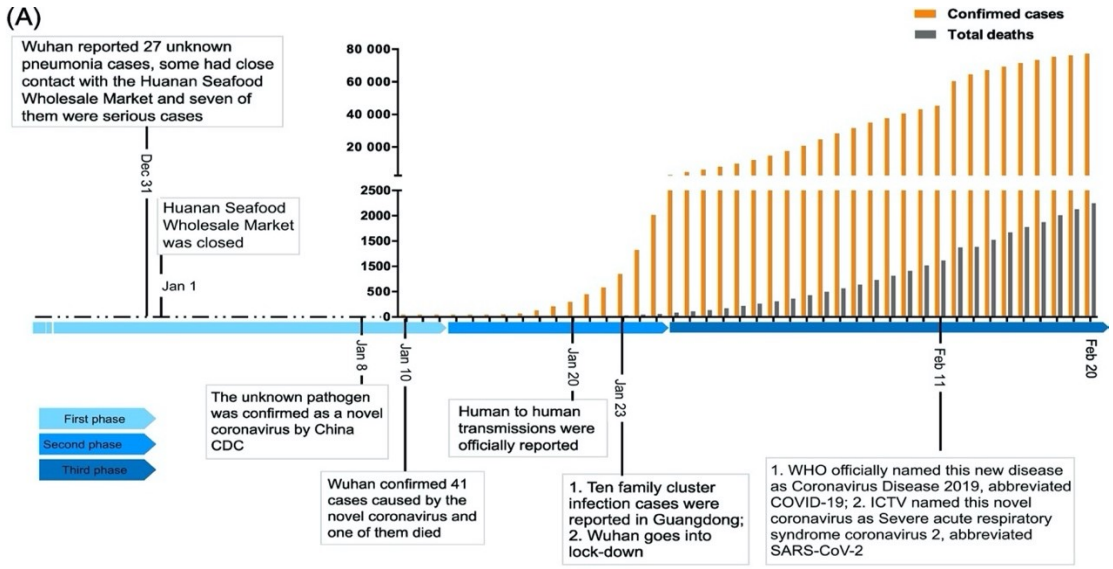

Figure 1 Timeline of events and transmission in the beginning of the COVID-19 pandemic
(Sun et al., 2020)

COVID-19, SARS and MERS

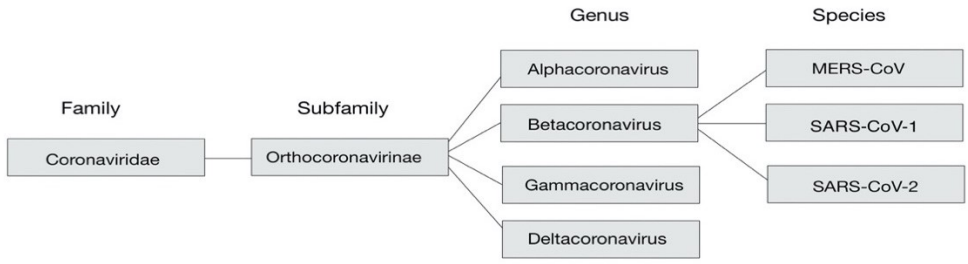

Figure 2 Coronaviruses

Prior to the COVID-19 outbreak, six human coronaviruses were known. Two α-coronaviruses, which include HCV-NL63 and HCoV229E and four ß-coronaviruses SARS-CoV, MERS-CoV, HCoVHKU1 and HCV-OC43. SARS and MERS have developed into epidemics in 2003 and 2012. (A. Pandey et al., 2020a) Similarities of SARS-CoV-2 to MERS- CoV and SARS-CoV are specified in Table 1.

Table 1 Comparison of SARS-CoV-2 to SARS-CoV and MERS-CoV

Virus	Origin region	Phylogenetic root	Host/ intermediate host	Entry receptor	Fatality rate	R0*
SARS-CoV-2	Wuhan, China	Class 1, Cluster 2a	Bats/ intermediate host is not identified	ACE-2 receptor	2.3%	2-2.5
SARS-CoV	Guangdong China, 2002-2003	Class 1, Cluster 2b	Bats/ dromedary camels or palm civets	ACE-2 receptor	9.5%	1.7- 1.9
MERS-CoV	Saudi Arabia	Class 2	Bats/ palm civets or camels	DDP4 receptor	34.4%	0.7

Source: (A. Pandey et al., 2020)
**R0: Basic reproduction number*

SARS-CoV-2 structure

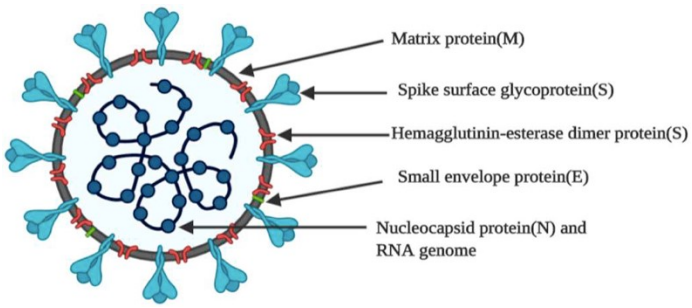

Figure 3 SARS-CoV-2 structure
Source: (A. Pandey et al., 2020)
Permission: Licensed Content from Elsevier, permission through Copyright Clearance Center's Rightslink ® service, License Number: 4873611428808

RNA genome

The virions diameter is 125 nm and the length of the genome varies from 26-32 kb. SARS-CoV-2 is a coronavirus and belongs to the family of Coronaviridae more precisely to the Betacoronavirus genus and is a single-stranded and positive-sense RNA virus. Corona is Latin for crown and refers to the spikes on the virus interface resulting in the form of a crown. The genome contains a 3' poly A tail and 5' cap. At the 3' and 5' end flanking untranslated regions (UTRs) are present. The genome includes 16 non-structural proteins (nsps) that are encoded at the 5' end by ORF (open reading frame). Nsps include the RNA dependent RNA polymerase (RdRp), viral proteases and helicase. The structural proteins like nucleocapsid (N), envelope (E), spike (S) and membrane (M) at the 3'end is encoded by different ORFs towars the 3'end. The S protein plays a role in receptor binding and fusion of the cells. The E protein is responsible for viral release and viral morphogenesis, while the N protein regulates viral RNA synthesis. The M protein plays a critical role for viral assembly and binds the nucleocapsid. (S. Kang et al., 2020; A. Pandey et al., 2020a)

Spike protein

The spike protein is present on the surface of SARS-COV-2 and is a fusion protein that is heavily glycosylated. It consists of an ectodomain, a transmembrane domain and an intracellular segment. The ectodomain is split into the S1 and S2 subunit, that form homotrimers as shown in Figure 4. The S1 subunit is essential for ACE2 receptor binding and stabilizes the prefusion state since it contains the receptor binding domains (RBD) and the S2 subunit is responsible for viral envelope fusion with the membrane of the host cell. During the internalization of the virion, the S protein undergoes priming by TMPRSS2 (serine protease) of the host cell. Other proteases like cathepsin B an L are only needed when TMPRSS2 is absent. Furthermore, studies showed that SARS-CoV-2 does not fully depend on human proteases for cell entry but is already preactivated by proprotein convertase furin. This permits the cell entry of SARS-CoV-2 with getting around the surveillance of the immune system. The receptor binding domain of SARS-COV-2 was found to bind with a 10-time higher affinity to the ACE-2 receptor than SARS-CoV-1. The wide and fast spread of COVID-19 can be lead back to those characteristics of SARS-CoV-2. (Jaume et al., 2011; A. Pandey et al., 2020a; Sun et al., 2020; Walls et al., 2020)

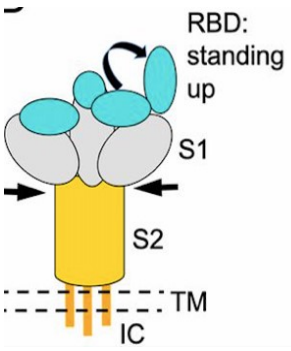

Figure 4 Structure of the spike protein
Source: (Shang et al., 2020)
Permission: CC-BY license

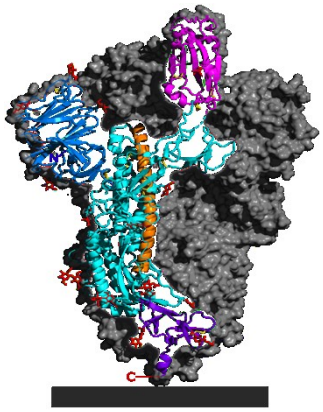

Figure 5: "SARS-CoV-2 spike homotrimer with one protein subunit highlighted. The ACE2 binding domain is magenta."
Source:https://en.wikipedia.org/wiki/Severe_acute_respiratory_syndrome_coronavirus_2#/media/File:6VSB_spike_protein_SARS-CoV-2_monomer_in_homotrimer.png
Permission: Creative Commons CC0 1.0 Universal Public Domain Dedication

Main protease

The main protease M^{pro}, also known as 3C- like protease is essential for replication and proteome production. It is auto-cleaved and splits the polyprotein into nsps at LeuGIn (Ser, Ala, Gly). (A. Pandey et al., 2020a)

RNA dependent RNA polymerase

The key enzyme of transcription and replication of SARS-CoV-2 is the RNA dependent RNA polymerase encoded by nsp12. It catalyses viral genomic RNA production by forming complexes with nsps such as nsp 7 and 8. (A. Pandey et al., 2020a)

Pathogenesis

The viral RNA is released after membrane fusion into the cytoplasm. Translation of the RNA results into two polyproteins. Proteases cleave the polyproteins into 16 nsps that assemble the RNA replicase-transcriptase complex. After the transcription, resulting into subgenomic RNA, subgenomic mRNA is produced and translated into various structural proteins. The nucleocapsid is formed when the viral genomic RNA is conjoined with the structural proteins. The viral particles are released as primary virions from the ER-Golgi into the infected cells. (Li et al., 2020)

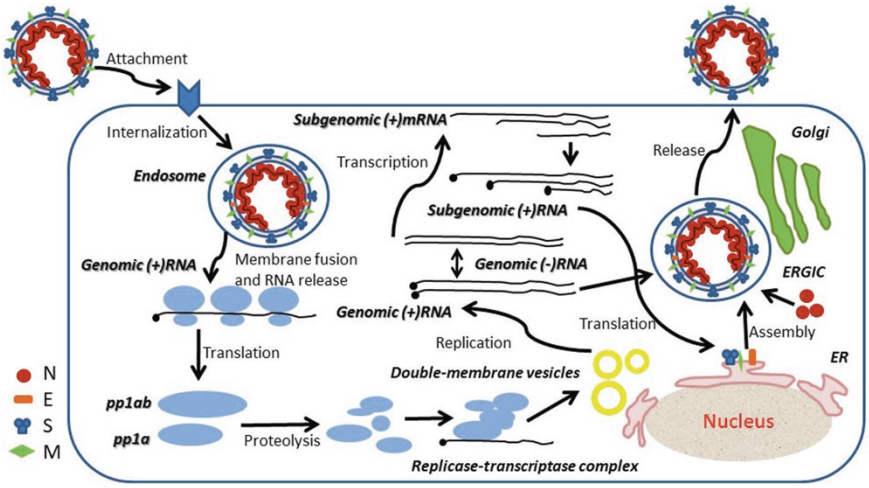

Figure 6 SARS-CoV-2 cycle
Source: (Li et al., 2020)
Permission: Licensed Content Springer Nature, permission through Copyright Clearance Center's Rightslink ® service, License Number: 4873631217758

SARS-CoV-2 causes respiratory and gastrointestinal infections and can also affect the liver, brain, heart and kidney. The virus can be inactivated by lipid solvents such as ethanol, chloroform, chlorine, peracetic acid and ether. (S. Kang et al., 2020)

Potential hosts

Previous coronaviruses such as SARS- CoV and MERS- CoV emerged from bats and the intermediate hosts were palm civet cats in SARS and dromedary camels in MERS. SARS-CoV-2 presents 96% similarity to the genome of bat coronavirus RaTG13, suggesting that it emerged from bats and through an intermediate host it was transmitted to humans, that is still unknown. (S. Kang et al., 2020) Metagenomic data also discovered similarity of SARS-CoV-2 to Pangolin-CoV. (T. Zhang et al., 2020)

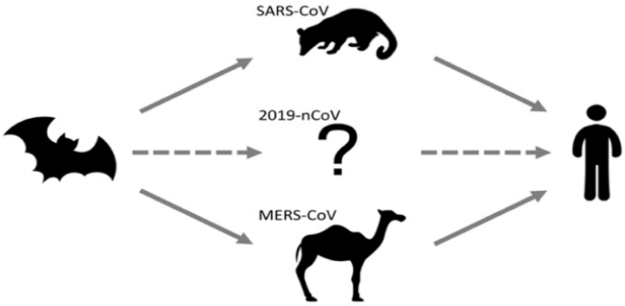

Figure 7 SARS-CoV-2 unknown intermediate host
Source: (Y. Xu, 2020)
Permission: Licensed content from Elsevier, permission through Copyright Clearance Center's Rightslink ® service, License Number: 4873640168610

Transmission

The main routes of transmission include close contact and respiratory droplets from infected patients that are exhaled through breathing, sneezing, coughing and speaking. contact with infected surfaces followed by touching of the face, more specifically contact with mucous membranes like the mouth, nose or eyes. Furthermore, transmission through aerosols is also possible. The fast spread of COVID-19 can be traced back to airborne transmission by asymptomatic patients, since aerosols can remain infectious for hours especially indoors and be inhaled into the lungs. Furthermore, patients can transmit the virus before developing immune response and symptoms due to the rapid replication of SARS-CoV-2 leading to fast spread to the pharynx. This pre-symptomatic shedding of the virus makes individuals contagious for several days before onset of symptoms, since the incubation period can extend from 2 to 14 days. Furthermore, a case with an incubation period of 27 days, another case with 19 days and a case with 24 days incubation period were reported. Asymptomatic patients can spread the virus and remain contagious up to 21 days. 79% of the cases in Wuhan China were estimated to be the result of transmission by asymptomatic individuals. This makes the lower fatality rate of COVID-19 a cause for higher infectibility. Airborne transmission is not yet acknowledged, and more studies are needed, however growing evidence shows that droplets from coughs and sneezes can create aerosols and remain airborne and accumulate for long periods of time especially in closed spaces. In addition, droplets of intense coughs or sneezes can cover distances of more than 6 meters. SARS-CoV-2 is less likely to be infectious for a long time in open-air conditions, because it is sensitive to ultraviolet radiation of the sun, temperature, atmospheric aerosols and humidity. Transmission by asymptomatic individuals makes intense testing essential to identify those patients and to isolate them. After evidence for airborne transmission was revealed, the use of masks for everyone was recommended, since they reduce the number of droplets and viral concentrations remarkably. The beneficial effects of masks have been demonstrated in countries such as Hong Kong, South Korea, Taiwan and Singapore, that maintained a low number of cases by requesting citizens early on to wear masks in all public spaces and providing masks for every citizen. Besides of SARS- CoV-2s ability to stay infectious for long periods of time in the air, the rigid structure of the outer protein coat enables the virus to can remain on surfaces such as plastic and steel for up to 6 hours. (Bai et al., 2020; Guan et al., 2020; S. Kang et al., 2020; S. Pandey et al., 2020; Prather et al., 2020; Sarvepalli, 2020)

Data shows that the variant of SARS-CoV-2 with a mutation of the spike, the D614G amino acid change, is the dominant form in the current pandemic. The G614 variant was demonstrated to be more infectious than D614 and therefore spreading faster. However, there is no supporting proof that G614 is correlated with higher mortality rates. Spike mutations

have to be monitored intensively, because of the spike's significance for vaccine development and therapies based on antibodies. (Korber et al., 2020)

Diagnostics

The only test used currently for COVID-19 confirmation is reverse transcription polymerase chain reaction (RT-PCR). Specimens for a test include sputum, nasal swab, oropharyngeal or nasopharyngeal swab, nasal wash, bronchoalveolar lovage, pleural fluid. False negative with RT-PCR occur in 20 to 30% of the cases. (https://www.lecturio.com/covid-19-coronavirus-disease-2019/)

Laboratory and radiological findings also play an important role for diagnosis:

- Inflammatory markers such as ferritin, LDH, IL-6, CRP, procalcitonin and lactate are elevated in most patients.
- Count of white blood cells: Lymphopenia, leukopenia and leukocytosis are common in COVID-19 patients.
- Liver markers assessment of AST and ALT
- Renal function assessment of BUN, urea and creatinine
- Assessment of cardial function by ECG and troponin
- Haematosis tests: Patients often exhibit prolonged PT and PTT times. Furthermore, D-Dimer is elevated.
- Chest X-ray and CT: Most common are ground glass opacities, bronchovascular thickening, lymphadenopathy, and lesions that are mostly peripheral, bilateral and distributed in the lower lobe.

Clinical manifestation

The most common symptoms include fever, cough, headache, cough, fatigue and muscle pain. Diarrhea, myocarditis, elevated troponin levels and myalgia occur less frequently. Severe cases develop dyspnea or/and hypoxemia, multiple organ failure, ARDS, coagulopathy or septic shock. Lesions in the lungs appear in the majority of cases. (S. Kang et al., 2020) Blood examinations demonstrate leucopenia, lymphopenia, thrombocytopenia, increased levels of lactic dehydrogenase, α-hydroxybutyric dehydrogenase, aspartate aminotransferase, creatinine, c-reactive protein (CRP), alanine transaminase, interleukin-6 and γ- glutamyl transpeptidase. Severe cases suffer from liver damage, acute respiratory distress syndrome, kidney failure, septic shock, acidosis multiple organ failure, pneumonia and elevated cytokine storms. Chest radiographies demonstrated ground-glass opacities, diffused patch consolidation, pneumothorax, focal consolidation and labor consolidation. The most frequent cause of death is severe bilateral pneumonia leading to respiratory failure. (S. Pandey et al., 2020; Sarvepalli, 2020)

Acute Respiratory Distress Syndrome (ARDS) leads to elevated cytokine storms and is the primary death cause for COVID-19. (Nile et al., 2020)

About 15% suffer from severe infection, 5% from critical infection and 5.5.% from fatal infection. Mild infection clinically manifests in fever, lethargy, dry cough, muscle pain and dehydration. Severe infection leads to symptoms including breathing difficulties, hemoptysis, high fever and pain in the chest. Complications include sepsis, pneumonia, organ failure and acute respiratory distress syndrome. (https://www.lecturio.com/covid-19-coronavirus-disease-2019/)

Asymptomatic patients make up more than half of COVID-19 patients and are capable to infect others. However, it is not proven how long they remain contagious. Mild cases present symptoms similar to the flu such as nasal congestion, fatigue, sore throat, myalgia, diarrhea, abdominal pain, muscle pain, nausea, headache and dermatological symptoms. Saturation of oxygen (SaO2) is above 93%. Patients with mild symptoms recover within 2 weeks. Patients with severe course of COVID-19 rely on intensive care and mechanical ventilation after developing respiratory crackles, chest paint, dyspnea and anorexia. SaO2 sinks under 93%. Critical cases often exhibit ARDS and the recovery time ranges from 3 to 6 weeks. (https://www.lecturio.com/covid-19-coronavirus-disease-2019/)

Table 2 Signs and symptoms at admission of 99 COVID-19 patients

Fever	83%
Cough	82%
Shortness of breath	31%
Muscle ache	11%
Confusion	9%
Headache	8%
Sore throat	5%
Rhinorrhea	4%
Chest pain	2%
Diarrhea	2%
Nausea and vomiting	1%
More than one sign or symptom	90%
Fever, cough and shortness of breath combined	15%

Source: (N. Chen et al., 2020)

Differential Diagnosis

Table 3 Differential Diagnosis COVID-19, Influenza and common cold

Clinical signs	COVID-19	Influenza	Common cold
Incubation period	2-14 days	1-4 days	< 3 days
Onset	Progressive	Abrupt	Abrupt
Fever	Very frequent	Very frequent	Rare
Dry cough	Very frequent (mild to severe)	Very frequent (mild to severe)	Frequent (usually mild, sometimes productive)
Fatigue	Frequent	Very frequent	Rare or mild
Myalgia	Frequent	Very frequent	Mild
Sneezing	Occasionally	Rare or mild	Very frequent
Nasal congestion	Rare or mild	Frequent	Very frequent
Headache	Occasionally	Very frequent	Rare or mild
Sore throat	Occasionally	Occasionally	Very frequent
Diarrhea	Occasionally	Occasionally	Rare
Dyspnea	Frequent	Rare	Never

Source: https://www.lecturio.com/covid-19-coronavirus-disease-2019/

Mortality

For individuals with diabetes it is more likely to suffer from a more severe course of COVID-19, because SARS- CoV-2 causes elevated release of catecholamines and glucocorticoids and therefore to elevated blood glucose levels. Another study demonstrated hypoglycemia in type 2 diabetes patients and therefore a spike of pro- inflammatory monocytes and platelet

reactivity leading to raised cardiovascular mortality. These metabolic disorders in diabetic patients resulting in immune response reduction and therefore severe complications. (Hamed, 2020)

75% of COVID-19 patients who died in China and Italy suffered from hypertension. This is partly explained by the increased expression of ACE2 in patients with hypertension due to blood pressure medications such as ACE inhibitors and angiotensin blockers. (Hamed, 2020)

Obesity is linked to decreased functional capacity, expiratory reserve volume and respiratory system compliance, resulting into severe COVID-19 course and complications with ventilation due to decreased pulmonary function. (Hamed, 2020)

Table 4 Mortality rate by age

Age	Number of deaths	Share of deaths
0-17 years	3	0,04%
18-44 years	309	4,5%
45-64 years	1581	23,1%
65-74 years	1683	24,6%
75+ years	3263	47,7%
Total	6839	100%

Source: (New York City Health, 2020)

Risk factors include serious heart conditions including heart failure, cardiomyopathies, coronary artery disease, COPD, obesity (BMI > 30), sickle cell disease , solid organ transplantation, asthma, cerebrovascular disease, , chronic kidney disease, hypertension, type 2 diabetes, smoking, immune deficiencies and liver disease. (https://www.cdc.gov/coronavirus/2019-ncov/need-extra-precautions/evidence-table.html)

Table 5 Mortality in relation to preexisting conditions

Preexisting condition	Mortality rate- confirmed cases	Mortality rate- all cases
Diabetes	9.2%	7.3%
Cardiovascular disease	13.2%	10.5%
Hypertension	8.4%	6.0%
Chronic respiratory disease	8.0%	6.3%
Cancer	7.6%	5.6%

Source: https://www.worldometers.info/coronavirus/coronavirus-age-sex-demographics/

Children are at lower risk for severe COVID-19 course. 55% of children infected with COVID-19 are either asymptomatic or show mild symptoms. Less than 1% of children exhibit critical symptoms. (https://www.lecturio.com/covid-19-coronavirus-disease-2019/) However, a high number of Kawasaki disease symptoms in children was linked to SARS-CoV-2 IgG antibodies. (Moreira, 2020)

Prevention

Washing hands often with for at least 30 seconds or sanitizing hands with sanitizer with a minimum of 60% alcohol. Furthermore, it is important to not touch the eyes, nose or mouth with unwashed hands. Face masks and minimum distance of 1-2m also reduce transmission and crowded areas should be avoided. Social distancing is an important measurement taken by most governments. (https://www.lecturio.com/covid-19-coronavirus-disease-2019/)

Immunity

According to the WHO it is still unknown if a SARS-CoV-2 infection can provide long-term immunity, since other coronaviruses are able to reinfect individuals after approximately a year. (Galanti & Shaman, 2020) Even if patients develop antibodies, there are reports of individuals testing positive for SARS-CoV-2 after recovering from COVID-19. However, it is still under investigation if these cases are false positives or lingering infections. (Omer et al., 2020)

Methods

The presented work consists of a literature survey, due to the COVID-19 crisis. The aim of the present diploma thesis is to achieve an overview of current treatment and vaccine developments for COVID-19. Sources and databases used include PubMed.gov, clinicaltrials.gov, sciencemag.org, cell.com, pnas.org and nature.com. Studies and articles from December 2019 to 20th July, 2020 were collected and included in this diploma thesis.

Treatment approaches

Currently no specific treatment or vaccine is available for the newly emerged coronavirus SARS-CoV-2. Supportive care and standard care are based on symptoms and include oxygen therapy and ventilator support, extracorporeal membrane oxygenation (ECMO), antimicrobials, corticosteroid and vasopressors. (A. Pandey et al., 2020b)
Potential therapeutic targets include the spike protein, the serine protease TMPRSS2, proteases such as the papain-like protease and 3C-like protease and the RNA dependent RNA polymerase. (Li et al., 2020)

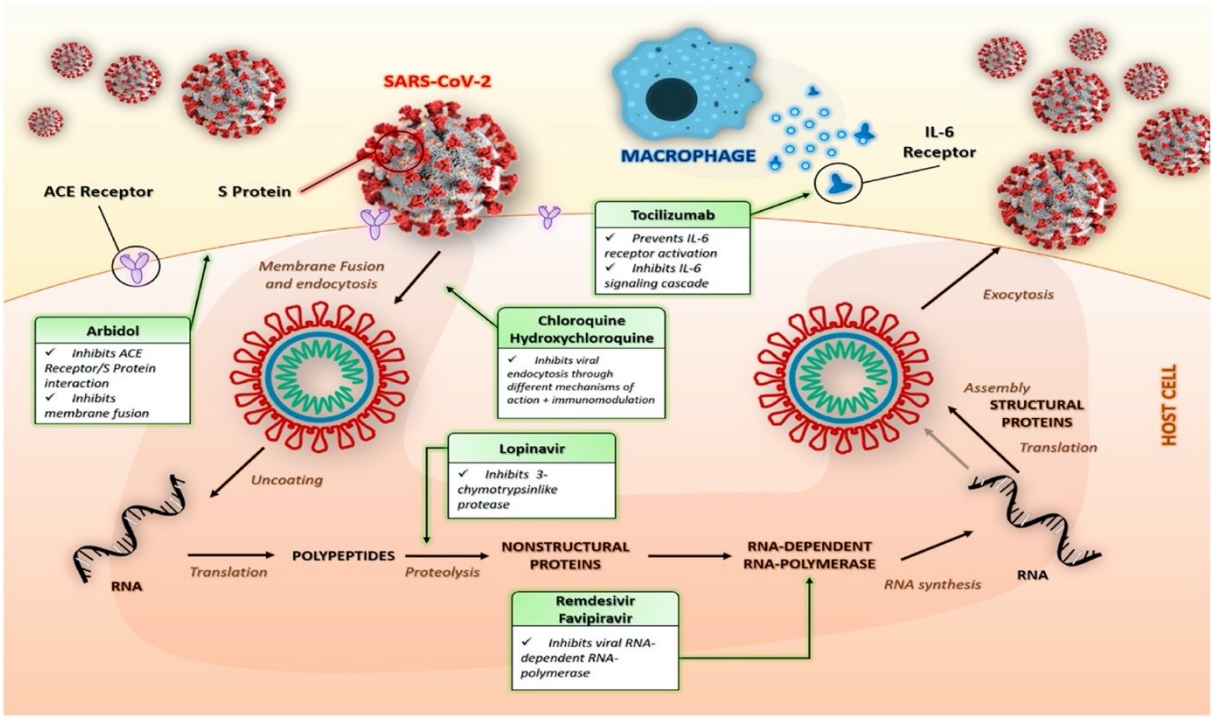

Figure 8: The main targets of various drugs for COVID-19 therapy
Source: (Nittari et al., 2020)
Permission: Licensed Content from Elsevier, permission through Copyright Clearance Center's Rightslink ® service, License Number: 4873730119825

Inhibition of SARS- CoV-2 fusion and entry

SARS- CoV- 2 Entry

The viral entry of SARS- CoV-2 depends on the spike protein. In particular the receptor binding domain (RBD) on the surface unit, S1, which attaches to a cellular receptor and thereby to the surface of target cells. The entry receptor is angiotensin- converting- enzyme- 2 (ACE 2), which the RBD protein binds to with high affinity. (Tai et al., 2020)
After host cell entry, the heptad repeat 1 and 2 form a six- helical bundle (6- HB), which enables membrane fusion of target and virus cell. (Xia, Zhu, et al., 2020)
Furthermore, spike protein priming by cellular proteases, like the cellular serine protease TMPRSS2, are needed for viral entry into cells. (Hoffmann et al., 2020)
In consequence, it is important to specify the RBD protein as an expected target for the inhibition of SARS- CoV-2 entry into target cells. (Tai et al., 2020) Regions like HR1 are highly conserved and therefore a target that would not cause drug- resistant mutations. Furthermore, SARS- CoV-2 shows a superior quantity of membrane fusion to SARS- CoV, indicating that the fusion mechanism is an essential target for treatment of COVID-19. (Xia, Liu, et al., 2020)

Xia et al. found that a designed drug, EK1, was troubling viral 6- HB formation by targeting the HR1 domain of the spike protein. The effect was enhanced by 240-fold when EK1C4, a lapidated form of EK1, was used. (Xia et al., 2019)

Arbidol (Umifenovir)

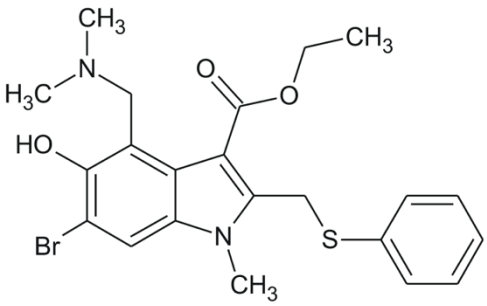

Figure 9 Chemical structure of Arbidol
Source: https://de.wikipedia.org/wiki/Datei:Arbidol.svg
Permission: Creative Commons CC0 1.0 Universal Public Domain Dedication

Mechanism of action and antiviral effect

The exact mechanism of arbidol, an indole- derivate, is still not well- known. The mechanism is based on inhibiting the viral fusion and entry, by blocking contact between virus and target cells. There is also evidence, that it enhances the humoral immune response, by releasing chemokines like interferon and macrophages. It is used for treatment in China and Russia or treatment and prevention of influenza because of its inhibiting effect on the hemagglutinin fusion machinery. (Deng et al., 2020)
Arbidol targets aromatic amino acids, viral proteins and host factors. Arbidol inhibited viral attachment and vesicle trafficking in Hepatitis C virus. (X. Wang et al., 2020)
Analysis of the protein sequence of SARS- CoV- 2 and influenza virus reveal that that a short region of the spike glycoprotein domain from SARS- CoV-2 matches the influenza virus hemagglutinin protein (H3N2). Since the spike glycoprotein is essential for cell adhesion and entry through ACE2, arbidol is a potential target. (Vankadari, 2020)

Efficacy in COVID-19

Time-of-addition experiments demonstrated that arbidol inhibited entry and post- entry stages of SARS- CoV- 2 by an inhibition rate of 75 and 55 %. In addition, the expression of viral nucleoprotein was decreased. Furthermore, arbidol reduced binding efficiency of SARS-CoV-2 to Vero E6 cells by 67 % compared to control by DMSO and therefore raised the quantity of unbound virus to 156 %. (X. Wang et al., 2020)

Molecular and structural studies demonstrated that the binding site for arbidol in SARS- CoV-2 is the spike glycoprotein and its trimerization, which is required for cell attachment and entry. "Blocking the trimerization of spike glycoprotein also leads in the formation of naked or unmatured virus which are least infectious." Furthermore, they demonstrated the similarity to the amino acids in the binding and trimerization domains of influenza virus. (Vankadari, 2020)

Deng et al.'s study compared the effect of lopinavir and arbidol with lopinavir alone in patients with COVID-19. The group that was treated additionally with arbidol was bound to a notable superior negative conversion of SARS- CoV-2, more negative stool tests and improved chest CT scans. (Deng et al., 2020)

Zhu et al.'s study also shows the superior impact of lopinavir by comparing its effect to a group treated with lopinavir and ritonavir. 14 days after admission no patients treated with arbidol alone showed positive SARS- CoV- 2 test results in comparison to 44,1 % in the lopinavir/ ritonavir group. (Z. Zhu et al., 2020)

A randomized and controlled trial treated 35 mild/moderate SARS- CoV- 2 patients with arbidol and compared them to a group of 34 patients treated with lopinavir and to 17 patients who received no antiviral medication. No difference in clinical improvement was found between the groups and only little improvement was found for arbidol. Limitations of this study include its small size, lack of blindness, and that no severe ill patients were included. (Yueping Li, 2020)

A retrospective, multicenter study included 141 patients and divided them into patients who received INF-α2b and patients who were administered a combination of arbidol and INF-α2b. No significant difference was presented when the groups were compared. The median time to negative PT- PCR test results was 27.4 days in the arbidol/INF-α2b group and 23.8 days in the INF-α2b group. However, the time to CT improvement was reduced in the combination group compared to patients in the INF-α2b only group. (P. Xu et al., 2020)

A meta-analysis included 12 studies adding up to 1052 patients and systematically reviewed them. Results show that even if arbidol was linked to a higher negative PCR rate after 14 days of treatment, it was not associated to a negative nucleus acid conversion time, duration of hospitalization, negative rate after 7 days or palliation of cough or fever after 7 days. The review found no evidence supporting that arbidol improves outcomes in COVID-19 patients. (Huang et al., 2020)

Adverse effects

No significant side effects were documented for arbidol. But most patients demonstrated increased levels of bilirubin and digestive upsets. (Deng et al., 2020)

Conclusion

The study of Deng et al. is a nonrandomized, retrospective and small sized study. Zhu et al's study is also retrospective with a small number of patients. Therefore, it is difficult to know if arbidol shortened the time span of positive RNA tests in the patients or if this would have been the natural duration of COVID-19 in their cases either way. Even if the results seem promising, more careful studies (with fewer limitations) are needed to evaluate the antiviral mechanism of arbidol on SARS- CoV-2.

Disruption of replication

Lopinavir and Ritonavir

Mechanism of action

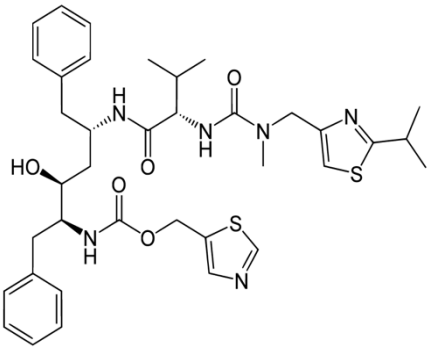

Figure 11 Chemical structure of Ritonavir
Source: https://en.wikipedia.org/wiki/Ritonavir
Permission: Creative Commons CC0 1.0 Universal Public Domain Dedication

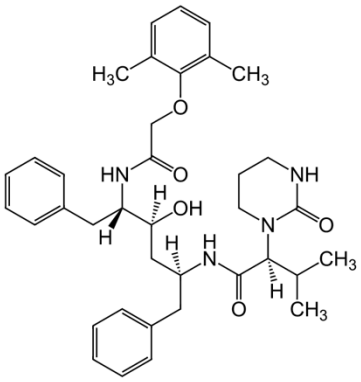

Figure 10 Chemical structure of Lopinavir
Source: https://en.wikipedia.org/wiki/Lopinavir
Permission: Creative Commons CC0 1.0 Universal Public Domain Dedication

A protease inhibitor, called lopinavir is commonly administered with Ritonavir because it prolongates the half- life of lopinavir by inhibiting CYP-450. Furthermore, this combination is correlated with less adverse effects. (Yueping Li, 2020)

Effect on other viruses

The administration of lopinavir with ritonavir has demonstrated a favorable effect in HIV-1 patients for ten years. Furthermore, it expressed antiviral effects on MERS-CoV, in vitro. (Yueping Li, 2020)
In vitro studies also demonstrated antiviral effect of lopinavir against SARS- CoV-1 with an EC_{50} of 4.1 µg/mL and in MERS- CoV with an EC_{50} of 10.8 µg/mL.

Lopinavir/ Ritonavir and COVID-19

A pharmacokinetic study demonstrated that the same dose administered in HIV patients was twice as high in COVID-19 patients. This was linked to cytokine storms of IL-6, IL-1 and TNF α leading to downregulation of CYP 450. (Schoergenhofer et al., 2020)
In vitro studies demonstrated the antiviral effect of lopinavir against SARS- CoV-2 at an IC_{50} of 26µM. (Cattaneo et al., 2020)
Lopinavir/ritonavir demonstrated a clearly lower cytopathic effect in Vero cells compared to hydroxychloroquine, which lead to damaged cells. Furthermore, viral titers decreased drastically in the lopinavir/ritonavir patients ($p< 0.001$) in comparison to control and hydroxychloroquine group. (C. K. Kang et al., 2020)
In a randomized and controlled trial 99 COVID-19 patients with harsh symptoms were administered lopinavir/ ritonavir and compared to 100 participants who received standard care. Results for lopinavir/ ritonavir demonstrated no advantageous difference neither in mortality, duration of clinical improvement nor in detectable viral RNA loads. (B. Cao et al., 2020)
Ye et al. demonstrated in patients receiving lopinavir/ritonavir a decrease of fever in comparison to patients receiving only adjuvant drugs for pneumonia. (Cattaneo et al., 2020)
A retrospective study including 120 mildly ill COVID-10 patients treated 78 patients with lopinavir/ritonavir and observed shortened duration of SARS- CoV-2 RNA shedding. The

average length of viral shedding in the lopinavir/ritonavir group was 22 days in comparison to 28.5 days in participants receiving only standard care. However, no disparities in shedding duration between patients receiving lopinavir/ ritonavir longer than 10 days after the occurrence of symptoms and participants receiving no treatment. (Yan et al., 2020)
In a retrospective study in France 13 patients received ritonavir/ lopinavir and were compared to 17 patients receiving hydroxychloroquine/ azithromycin and to 15 patients receiving no antiviral treatment. At the 6^{th} day of follow- up 5 patients (38%) in the lopinavir/ritonavir group tested negative for SARS-CoV- 2 compared to 3 patients (18%) in the hydroxychloroquine/ azithromycin group and 2 patients (20%) in the control group. The last follow- up showed a survival rate of 92 % in the lopinavir/ ritonavir group, 88 % in the hydroxychloroquine/azithromycin group and 67 % in the non- treatment group. No significant difference between the groups were concluded from these results, especially in ARDS patients none of the treatments resulted in significantly faster viral clearance. (Hraiech et al., 2020)
A study in the New England Journal assigned 199 patients either to standard care or lopinavir/ ritonavir. In both groups the average time to clinical improvement was 16 days. Furthermore, 13 patients terminated treatment with lopinavir/ ritonavir because of gastrointestinal adverse effects. (Valk et al., 2020)
In a retrospective study of 203 patients treated with lopinavir/ritonavir exhibited shortened duration of viral shedding. (Zuo et al., 2020)
A controlled, randomized trial in China treated 199 patients either with lopinavir/ritonavir or with standard care. Lopinavir/ritonavir achieved not significant but numeric decrease of fatality and length of hospital and intensive care stay. However, no difference in viral load was demonstrated between both groups. (Doggrell, 2020)
The latest findings of one of the biggest trials, the Recovery trial, stated that lopinavir-ritonavir does not benefit COVID-19 patients. The 28- day fatality rate was 22.1% in patients receiving lopinavir-ritonavir compared to 21.3% in participants who received standard care. Besides the incapability of lopinavir-ritonavir to improve survival, no benefit regarding time to discharge from the hospital, or mechanical ventilation requirement was demonstrated. (Griffin, 2020)

Adverse effects

Patients treated with lopinavir and Ritonavir, because of adverse gastrointestinal reactions like diarrhea, gastritis, abdominal pain and nausea. (B. Cao et al., 2020)
An increase in transaminase levels and ALT levels were noticed in COVID-19 patients treated with remdesivir. Furthermore, abnormalities in liver function and enzymes occurs. However, it is not clarified if these adverse effects are due to remdesivir or the result of COVID-19 infection. (Jorgensen et al., 2020)

Remdesivir

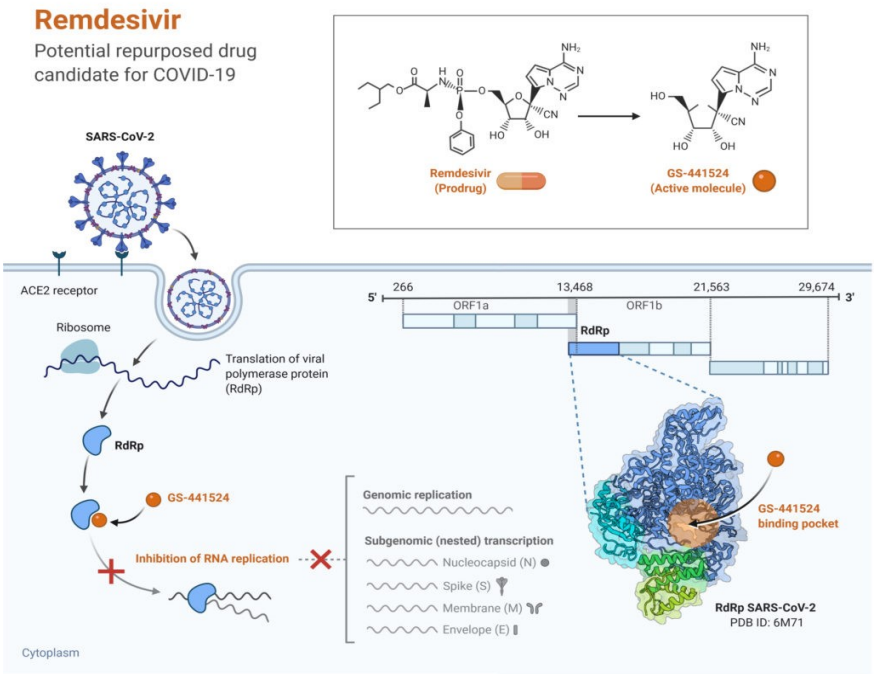

Figure 12 Remdesivir mechanism of action in COVID-19
Source: https://microbenotes.com/remdesivir/
Permission: granted from Author

Mechanism of action

Remdesivir, also known as GS-5734 was designed by Gilead Sciences in partnership with the CDC. The goal was to develop an antiviral medication for RNA viruses that have the capability to cause pandemics. (Eastman et al., 2020)
The RNA- dependent RNA polymerase inhibitor, remdesivir is an adenosine analogue prodrug, which leads to early RNA synthesis discontinuation and disruption of replication after integrating into viral RNA strands by competing with adenosine triphosphate. Even though coronaviruses are able to proofread their RNA strands and identify nucleoside analogs, the antiviral impact of remdesivir is not weakened. (Amirian & Levy, 2020)
After intravenous administration of remdesivir, transformation to an intermediate metabolite and lastly to nucleoside analogue takes place. (Yang, 1996)

Remdesivir and other viruses

Remdesivir demonstrates antiviral activity for various RNA viruses like filoviruses and coronaviruses. (Yang, 1996)
In vitro studies have demonstrated the antiviral effect of remdesivir in both coronaviruses MERS- CoV and SARS- CoV. In vivo studies of MERS- CoV in mice showed therapeutic and prophylactic effects by disrupting replication and therefore improving pulmonary function and survival duration. Likewise, in SARS- CoV mouse models, remdesivir lead to lower viral loads in the lungs. Furthermore, remdesivir showed protection from Nipah virus in African green monkeys. (Amirian & Levy, 2020).
Clinical data includes a nurse with Ebola meningoencephalitis that was treated and cured with remdesivir in Scotland without any adverse effects. Furthermore, there is data of 175 Ebola patients that were administered remdesivir demonstrating no correlation between remdesivir and side effects. (Ko et al., 2020)

Remdesivir and COVID-19

Remdesivir should be applied as early as possible, because its mechanism is to inhibit viral reproduction. In vitro studies in Vero E6 cells confirmed the antiviral activity of remdesivir against SARS- CoV-2. The EC50- value was relatively low at 0,77 µM and the EC90 at 1.76 µM. (Amirian & Levy, 2020) In a rhesus macaque model remdesivir administration significantly reduced viral load and pulmonary infiltrates. (Singh et al., 2020)

On the 1st of May, 2020 the FDA gave the Emergency Use Authorization for the administration of remdesivir in COVID-19 patients with severe symptoms, with SpO2 ≤ 94 % requiring mechanical ventilation or ECMO. (Singh et al., 2020)

A patient in Washington was treated with remdesivir and showed improvement in clinical symptoms regarding pneumonia, oxygen saturation and viral loads. Nevertheless this were only the observations in one patient and therefore no conclusion, whether viral loads decreased as a result of treatment with remdesivir or the natural duration of COVID-19, can be drawn. (Yu chen Cao et al., 2020)

In a cohort study, the data of 53 patients from Europe, Japan, United States and Canada was analyzed. After 18 days 68% of the patients demonstrated improvement regarding oxygen support including many patients who required mechanical ventilation. 47 patients were released from hospital at the 18-day follow-up and 7 patients died. The greatest limitation of this study beside the lack of randomization and its uncontrolled nature, is that viral load was not measured to confirm evaluate suppression by remdesivir. (Grein et al., 2020)

Another study treated 35 patients with remdesivir, whereas treatment was aborted in 13 patients after five doses because of adverse effects (n=8), discharge (n=1) or death (n=4). On the 10th day of treatment four patients (22,2%) improved and four (22,2%) died, while the remaining patients showed no shift in their clinical status. At day 28 after treatment 38,9% of participants improved and 44,4% died, while the other patients received mechanical ventilation. Still, after an average of 12 days after receiving remdesivir all patients tested negative for SARS- CoV-2. This study did not include a control group, making it difficult to draw conclusions. (Grein et al., 2020)

The adaptive COVID-19 trial by the National Institute of Health demonstrates a decrease in recovery time set by side to the results of the comparison group. Patients receiving remdesivir presented an average recovery time of 11 days set by side to 15 days in the placebo group. Furthermore, patients treated with remdesivir showed a mortality rate of 8% compared to 11,6 % in the control group. (Yang, 1996) Mortality was lower but not significant ($p= 0.059$) compared to significant time to recovery ($p<0.001$). (Jorgensen et al., 2020)

A randomized, controlled and double- blind study by Wang et al. including 236 patients (185 patients were administered remdesivir) observed no significant improvement in clinical signs, viral load or mortality. Another randomized and controlled trial by Beigel et al. recruited 1059 patients and observed a recovery time of 11 days in patients who were treated with remdesivir as to the placebo group with a recovery time of 15 days. (Singh et al., 2020)

A comparative analysis of a phase 3 trial including 312 patients, demonstrated the recovery of 74.4% of participants treated with remdesivir compared to 59% of the patients receiving standard care only. The death rate was 7.6% in the remdesivir cohort as to 12.5% in the supportive care group. (*Gilead*, 2020).

The open- label and randomized phase 3 trial (SIMPLE-Severe trial) compared remdesivir administration for 5 days to 10 days in 397 COVID-19 patients with severe symptoms. Interestingly, the 5-day-remdesivir group demonstrated better results in clinical improvement, discharge from the hospital and recovery. Remdesivir demonstrated more benefit when administered within 10 days from onset of symptoms. (Singh et al., 2020)

Adverse effects

The most frequent adverse effects for remdesivir included diarrhea, hypotension, hepatotoxicity, increased levels of transaminase and renal impairment. In seriously ill patients multiple organ- dysfunction syndrome, acute kidney injury and septic shock occurred. (Grein et al., 2020)

Ivermectin

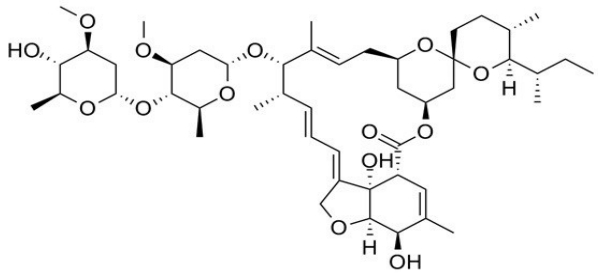

Figure 13 Chemical structure of Ivermectin
Source: https://www.researchgate.net/figure/Chemical-structure-of-the-macrocylic-highly-effective-antifouling-compound-ivermectin_fig2_269398772
Permission: Creative Commons CC0 1.0 Universal Public Domain Dedication

Mechanism of action

Ivermectin is an anti- parasitic drug approved by the FDA that binds to glutamate- gated chloride ion channels which leads to hyperpolarization and death of parasites. Furthermore, it is a GABA- agonist causing disruption of neurotransmission. (Chaccour et al., 2020)
The antiviral effect of Ivermectin is based on its ability to inhibit IMPα/β1, which many RNA viruses, including SARS- CoV, depend on for infection. (Caly et al., 2020)
The binding of Impα/β1 by ivermectin prevents its binding to viral proteins. Thereby viral proteins are prevented from nucleus entry. Furthermore, ivermectin demonstrated suppression of replication by suppressing the nuclear import of a DNA polymerase subunit in pseudorabies virus and bovine herpesvirus 1. (Sharun et al., 2020)

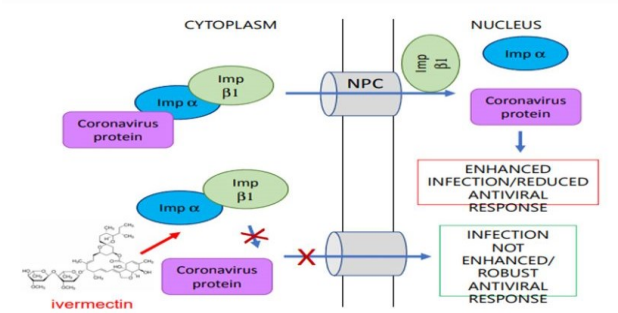

Figure 14 Ivermectin mechanism of action
Source: http://www.sci-news.com/medicine/ivermectin-replication-sars-cov-2-coronavirus-cell-cultures-08300.html
Permission: CC-BC-NC-NC license

Existing studies
Ivermectin has shown antiviral impact against various RNA viruses like Influenza, Dengue Virus, West Nile Virus and Venezuelan Equine Encephalitis Virus in vivo and in vitro by blockage of the importin α/ß 1 heterodimer mediated nuclear transport. This mechanism leads to inhibition of the translocation of viral proteins and therefore disruption of replication. (Rizzo, 2020)

Ivermectin and COVID-19
A single dose of Ivermectin 2 hours after infection achieved ~5000-fold reduction of SARS-CoV- 2 RNA in Vero- hSLAM cells. Resulting into abolishing the total viral material after 48 hours. The IC50 was determined at ~2, 5 µM. (Caly et al., 2020)

An observational study treated critically ill SARS-CoV-2 patients with ivermectin and linked it to a lower mortality rate. However, a clinical trial that is randomized is essential for valid results. (Sharun et al., 2020)

Suppression of excessive inflammatory response

Chloroquine and Hydroxychloroquine

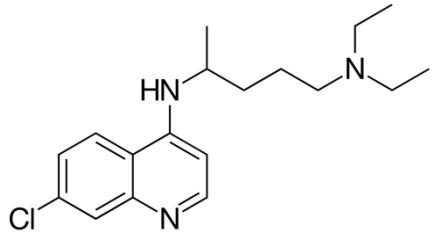

Figure 16 Chemical structure of Chloroquine
Source: https://en.wikipedia.org/wiki/Chloroquine
Permission: Creative Commons CC0 1.0 Universal Public Domain Dedication

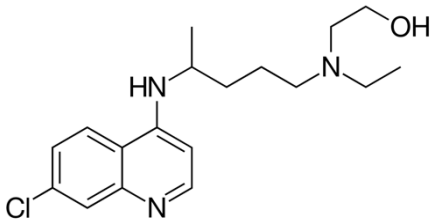

Figure 15 Chemical structure of Hydroxychloroquine
Source: https://en.wikipedia.org/wiki/Hydroxychloroquine
Permission: Creative Commons CC0 1.0 Universal Public Domain Dedication

Mode of action
Hydroxychloroquine and chloroquine present similar structure and mode of action by operating as immunomodulators and weak bases. They are able to raise the pH of endosomes and lysosomes, which play an essential role in early replication, membrane fusion and distribution of viral particles. Furthermore, chloroquine has the potential to hinder SARS-CoV- 2 entry by modifying the glycosylation patterns of the spike protein and ACE2 receptor avoiding the attachment process. (Liu et al., 2020)
The immunomodulatory effect of chloroquine is based on its ability to inhibit T- receptors, B-receptors, toll-like receptors and production of inflammatory cytokines like TNF-alpha, IL-1 and IL-6, which are increased in the duration of viral infections. (Sinha & Balayla, 2020)
Both drugs are used to treat malaria, lupus erythematosus and arthritis, because of their anti-inflammatory effect. (Sharma, 2020)
Hydroxychloroquine and chloroquine were used for treatment of malaria with dosages up 20 2g. Both have relatively long half- lives from 20 to 60 days. Hydroxychloroquine needs up to four hours to reach maximum plasma concentration while chloroquine requires half an hour. (Pastick et al., 2020)

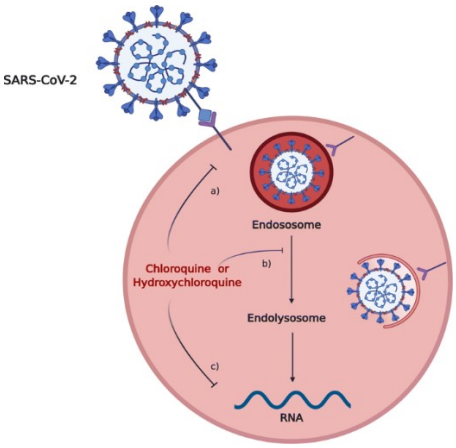

Figure 17 Chloroquine and Hydroxychloroquine mechanism of action
Source: https://ccforum.biomedcentral.com/articles/10.1186/s13054-020-02932-4
Permission: Creative Commons Attribution 4.0 International License

"(a) the drugs interfere with the terminal glycosylation of cellular receptor ACE-2, thus hampering virus-receptor binding; (b) the drugs increase the pH of acidic cellular organelles, hindering endocytosis at intermediate stages with negative effects on virion transport and potentially altering post-translational modification of newly synthesized viral proteins; and (c) the drugs may contrast the process of virion assembly and viral protein synthesis"
(https://ccforum.biomedcentral.com/articles/10.1186/s13054-020-02932-4)

Existing studies with other viruses

Due to chloroquine's ability to block pH- dependent replication steps, it was tested on various viruses e.g. Zika virus, Influenza virus, SARS- CoV, Ebola virus, Chikungunya virus and HIV. (Rebeaud & Zores, 2020)
Two in vitro studies proved the efficacy of chloroquine to inhibit SARS- CoV directly after viral intake and up to 5 hours after viral intake in Vero E6 cells. Furthermore, they demonstrated chloroquine`s ability to disable terminal ACE2 receptor glycosylation and in result reducing the affinity of viral attachment to the receptor. Chloroquine also showed a prophylactic potential considering that the cells administered with chloroquine were preserved from the virus. (Sinha & Balayla, 2020)
Chloroquine was able to inhibit the replication of SARS- CoV at 10 µM concentration in in vitro studies. The ED_{50} was stated at approximately 4.4 µM. A study by Biot et al. showed that chloroquine was more efficient regarding viral replication inhibition in vitro in comparison to hydroxychloroquine. (Pastick et al., 2020)
Chloroquine inhibited replication of Ebola and chikungunya virus in vitro but worsened the infection and did not improve mortality in vivo. Similar with dengue and influenza virus, where chloroquine showed efficacy in vitro, but failed in randomized studies. Additionally in vitro studies for Epstein- Barr virus demonstrated elevated viral replication when chloroquine was used. (Ferner & Aronson, 2020)

Chloroquine and Hydroxychloroquine in COVID- 19

Chloroquine's and hydroxychloroquine's anti- SARS- CoV- 2 mechanism of action is not entirely understood. It is believed that chloroquine prevents SARS- CoV-2 from binding to the ACE-2 receptor by hindering terminal glycosylation. Hydroxychloroquine can also avoid binding of SARS- CoV-2 to gangliosides, which might constrain SARS-CoV-2 attachment to the ACE-2 receptor. Furthermore, chloroquine and hydroxychloroquine can also effect exocytosis, endocytosis and protein propagation and there viral replication and infection by increasing the pH in lysosomes and endosomes. (Pastick et al., 2020)

Furthermore, hydroxychloroquine can block the toll-like-receptor mediated pathway, the activation of T-cells, complement-dependent antibody reactions and cytokine storm. Therefore hydroxychloroquine might be an important anti-inflammatory in SARS- CoV-2. (Mégarbane & Scherrmann, 2020)
On the grounds of pharmacokinetic modeling studies on hydroxychloroquine, presently the suggested initial dosage is defined at 400 mg two times a day 200 mg two times a day for maintenance. (Pastick et al., 2020)
Both drugs were proven to inhibit viral replication of SARS- CoV- 2 in vitro. The EC50 of hydroxychloroquine was lower than chloroquine at 0.72 μM compared to 5.47 μM, indicating a superior antiviral activity. (Yao et al., 2020) Furthermore, hydroxychloroquine was more potent with an EC_{50} of 5.85 μM at 48 hours compared to 18.01 μM with chloroquine. (Pastick et al., 2020)
Gao et al's study demonstrated improvement of over 100 patients regarding negative virus conversion, pneumonia and duration of COVID- 19 when treated with chloroquine phosphate compared to the control group. But it should be noted that results of this study were collected from different hospitals, making it difficult to draw a conclusion. Furthermore, they did not present any clinical information of the patients. (Touret & de Lamballerie, 2020)
In a non- randomized, open- label and controlled trial 20 patients received hydroxychloroquine. 57 % of the patients that were administered hydroxychloroquine, showed negative SARS- CoV- 2 test results after six days in comparison to 12,5 % in the control group. All participants receiving azithromycin and hydroxychloroquine showed viral clearance six days after treatment, indicating that this combination could be more efficient in eliminating the virus. Limitations of this study include the small size and the non- randomized nature. (Gautret et al., 2020)
Another study by Raoult et al. also presented the antiviral activity of treatment with hydroxychloroquine and azithromycin in 80 patients. Treatment contributed to fast decrease of viral load resulting into negative virus results in 93% of the participants after 8 days. (Gao & Hu, 2020)
Gautret et al. demonstrated in an unblinded, open- label trial including 80 patients, the absence of virus in 83% of the patients treated for seven days with hydroxychloroquine and azithromycin. One patient died and three still needed intensive care. However this study did not offer a control group for comparison. (Pastick et al., 2020)
A double- blinded study on 62 patients by Chen et al. showed clinical recovery and radiographic improvement. However selection bias was present in this study, excluding all critical cases of COVID-19 from the study. (Chowdhury et al., 2020)
Chen et al also published a trial of 900 patients demonstrated no convincing difference in outcomes between patients who were administered hydroxychloroquine and patients in the control group. It is worth mentioning that few patients receiving standard care, as well as patients receiving hydroxychloroquine, received arbidol. Moreover most patients who presented severe COVD-19 were excluded from the trial. (Chowdhury et al., 2020)
A study by Tang et al included 150 patients and presented similar results to the study by Chen et al. No difference in viral loads nor in in time of improvement were found in patients treated with hydroxychloroquine. Hydroxychloroquine was able to reduce CRP significantly and therefore was associated with a potential to control inflammation and disease progression. A deficiency in this trial is that patients in both groups were treated with other antiviral medication, making it difficult to attribute effects to hydroxychloroquine. (Chowdhury et al., 2020)
A retrospective trial analyzed treating 1061 patients with confirmed COVID-19 with azithromycin and hydroxychloroquine in France showed that 91.7 % of the patients had favorable clinical results and 97.6% did not experience any adverse effects. A prolonged QT-

interval between 60 and 500 ms occurred in nine patients, but no rhythmic cardiac events or death happened as a result. Furthermore, viral shedding persistence was only at 4.4% after medication for ten days. This shows a drastic decrease since viral shedding can last between 20 to 38 days normally. However, the majority of patients presented mild symptoms and only 0.99 % needed intensive care. This makes it difficult to apply the results on critically ill patients. (Million et al., 2020)

In a multicentered, retrospective study in 25 New York hospitals, 1438 participants either received azithromycin (211 participants), hydroxychloroquine combined with azithromycin (735 participants), hydroxychloroquine (271 participants), or neither (221 participantss). No difference in mortality was demonstrated between all four groups. Furthermore, cardiac arrests were more common in those who were administered a combination therapy of azithromycin and hydroxychloroquine compared to patients who were not prescribed these treatments. (Rosenberg et al., 2020)

A retrospective study in China included 550 severe ill COVID-19 patients and treated 48 of them with low doses of hydroxychloroquine. The fatality rate was at 18.8 % compared to 47.4 % in the non- treatment group. Hydroxychloroquine was also associated with a longer survival rate and significantly decreased IL-6 levels. (B. Yu et al., 2020)

On the other hand, a trial by Borba and colleagues showed high mortality rates in patients treated with chloroquine due to ventricular tachycardia and QT- prolongation. However the credibility of this study is very low, because all patients were also treated with azithromycin and oseltamivir, which increase the risk of QT- prolongation. (Fihn et al., 2020)

Molina et al. also reported that 80% of 11 patients still demonstrated positive SARS- CoV- 2 tests after a six day treatment with hydroxychloroquine and azithromycin. Of only 11 patients, one died, one presented prolonged QT interval and two needed intensive care. 10 out of 11 patients still tested positive for SARS- CoV-2 after treatment. (Pastick et al., 2020; Tselios & Skendros, 2020)

Results of a retrospective analysis found no decreased death rate in patients receiving hydroxychloroquine. However the retrospective setting of this analysis lead to administering hydroxychloroquine to patients who were critically ill at time of administration leading to higher fatality in the treatment cohort. (Magagnoli et al., 2020)

A study in China treated 75 participants with hydroxychloroquine and compared the treatment results to 75 patients in a comparison group. Although the hydroxychloroquine dosage was relatively high (1200 mg once a day for the course of three days followed by 800 mg once a day for two weeks), no difference regarding viral titers were found amidst the groups receiving different dosage. (Tselios & Skendros, 2020)

Furthermore, a French study administered hydroxychloroquine to 84 patients and included 97 patients in the comparison group and did not notice significant survival benefit hydroxychloroquine treatment. 2.8 % of the patients dies in the hydroxychloroquine compared to 4.6% in the comparison group. Overall 20.2% in the treatment group needed ICU admission or died compared to 22.1 % in the comparison group. (Tselios & Skendros, 2020)

Similar outcome was demonstrated in a retrospective trial in the US including 368 patients. The parallel administration of azithromycin with hydroxychloroquine was not correlated to a reduced fatality risk or mechanical ventilation. (Tselios & Skendros, 2020)

In the US, a retrospective study including 807 participants, treated 198 participants with hydroxychloroquine, 214 participants with hydroxychloroquine and azithromycin and the patients left were designated for the control group. The death rate was highest in those who were administered hydroxychloroquine only. No disparities in the rates of mechanical ventilation were demonstrated between all groups. (Magagnoli et al., 2020)

Due to the paradoxical results of chloroquine and hydroxychloroquine studies, high caution is needed before both drugs are used widely. (Sharma, 2020)

Adverse effects and safety

The most common side effects of chloroquine and hydroxychloroquine are gastrointestinal and dermatological symptoms. Side effects with minor occurrence include neuromyopathy, retinopathy, torsade de pointes and QT prolongation. The risk of adverse reactions is increased for patients that suffer from hepatic or renal dysfunction. (Sinha & Balayla, 2020)
Chloroquine and hydroxychloroquine are metabolized by kidney and liver. Severe ill patients often have changes regarding kidney and liver function, leading to increased adverse effects. (Gevers et al., 2020)
In a study on chloroquine nausea and abdominal pains occurred in 24% and diarrhea in 17% of the patients. Hydroxychloroquine lead to gastrointestinal symptoms in 50% of the patients. Irreversible retinopathy is a result of long- term (> 5 years) and high dosage (> 5mg/kg) use of chloroquine and hydroxychloroquine. (Pastick et al., 2020)
QT prolongation also presented in COVID-19 patients who were prescribed chloroquine. In a retrospective and observational study 23% of 95 patients presented QT- prolongation greater than 500 ms. (van den Broek et al., 2020)
Hydroxychloroquine is mostly used with azithromycin that also has the potential to prolong the QT interval leading to a higher risk of cardiovascular mortality and heart failure, because of the additive risk. (Mégarbane & Scherrmann, 2020)

Conclusion

One of the advantages of chloroquine and hydroxychloroquine is that they offer a settled safety profile since they have been administered for decades especially for malaria treatment and prophylaxis. Furthermore, the cost of both drugs would be inconsequential. (Colson et al., 2020)
The aftermath of the broad usage would be shortage for patients who depend on chloroquine for treatment of chronic inflammatory diseases. Medical institutions already announced a warning regarding the possible shortage of chloroquine and hydroxychloroquine. (Moiseev et al., 2020)
Furthermore, adverse effects are more common in patients with preexisting conditions, those are the same individuals that are at higher risk for worse course of COVID-19. (Alanagreh et al., 2020)
On May 26, 2020 the WHO halted chloroquine and hydroxychloroquine trials for COVID-19 treatment due to safety concerns. (https://www.theguardian.com/world/2020/may/25/who-world-health-organization-hydroxychloroquine-trial-trump-coronavirus-safety-fears)
Furthermore, *The Lancet* published a paper demonstrating that hydroxychloroquine increased mortality in COVID-19 patients. On 5 June 2020 results of the Recovery trial, the largest trial for hydroxychloroquine including 1543 patients, showed that 25.7% of the patients who were prescribed hydroxychloroquine died after 28 days compared to 23.5% of the patients receiving only standard care. In addition, the hoped-for prophylactic effect of hydroxychloroquine has been disproved in the largest post exposure prophylaxis study. 12 % of the individuals receiving hydroxychloroquine were tested positive after being in contact with a COVID-19 patient, compared to 14 % in the placebo group, a statistically not significant difference. These results were supported by another large post exposure prophylaxis trial including 2300 patients and presented no superior prophylactic effect of hydroxychloroquine compared to placebo. (Kupferschmidt, 2020)

Tocilizumab

Mode of action

Interleukin 6 is a monoclonal, humanized and recombinant antibody of the IgG1 class. (Guaraldi et al., 2020) It binds to its membrane bound receptor and this complex binds to glycoprotein 120 leading to activation of the JAK- STAT pathway or MAPK/NF-kB pathway. This leads to activation of inflammatory effects in the immune system. IL-6 also binds to its soluble form of the receptor inducing pro-inflammatory effects. (Saha et al., 2020)
Interleukin 6 (IL-6) is a cytokine essential for immune and inflammatory responses, leading to C-reactive protein (CRP) production in the liver. Il-6 is associated with osteoporosis, insulin resistance and cardiovascular disease. Tocilizumab is a monoclonal antibody that targets membrane- bound and soluble interleukin 6 receptors, inhibiting their interaction with IL-6. Furthermore, the communication of IL-6 with the glycoprotein 130 complex is prevented leading to blockage of the JAK-STAT pathway. Tocilizumab has been widely prescribed for autoimmune and inflammatory diseases e.g. rheumatoid arthritis, giant cell arthritis, systemic and polyarticular juvenile idiopathic arthritis and cytokine release syndrome. (González-Gay et al., 2020) Tocilizumab has an established safety profile due to its use for rheumatoid arthritis therapy. (Fu et al., 2020)

Tocilizumab and COVID-19

Tocilizumab, a monoclonal antibody, targets the Interleukin-6 receptor and therefore decreases the risk of increased cytokine storms, which occur in severe COVID- 19 patients. IL- 6 seems to be the most involved in elevated cytokine storms in COVID-19 patients. (Luo et al., 2020)
SARS- CoV-2 activates dendritic cells, macrophages and monocytes leading to release of IL-6 and various inflammatory cytokines. (Chakraborty et al., 2020)
Interleukin 6 was found to be highly elevated in inflammatory storms in critically ill COVID-19 patients, presumably resulting in defective oxygen diffusion, pulmonary fibrosis and ultimately to organ failure. Therefore tocilizumab, as a IL-6 receptor antagonist, might be advantageous with cytokine release syndrome. (X. Xu et al., 2020)

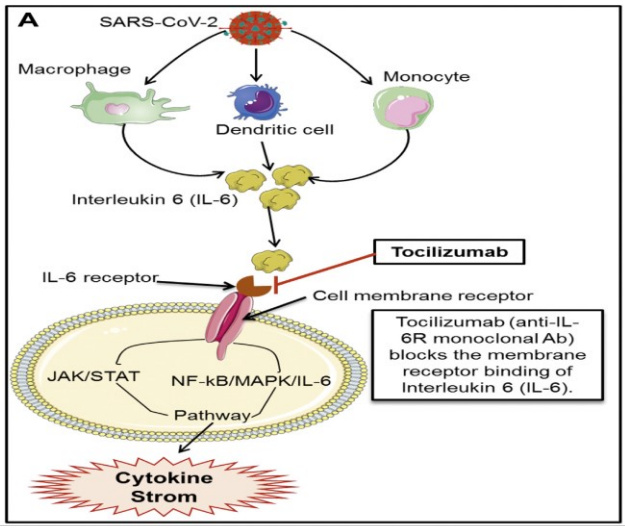

Figure 18: Tocilizumab mechanism of action with SARS- CoV-2
Source: (Saha et al., 2020)
Permission: Licensed Content from Elsevier, permission through Copyright Clearance Center's Rightslink ® service, License Number: 4873750531805

IL-6 seems to affect the pathogenesis of COVID-19, as higher levels are correlated with higher death rate, lung injury and severe sepsis. A meta- analysis included 9 studies of COVID-19 patients and elevated IL-6 levels were associated to higher mortality and severity of COVID-19. (Levi, 2020)
In a study that included 15 patients diagnosed with COVID-19, tocilizumab lead to reduction of IL-6 and CRP levels. Furthermore, patients reached a stable condition. (Luo et al., 2020)
Another study in China observed 21 severe COVID-19 patients after treatment with tocilizumab. Beside of decreased CRP, lymphocytes and IL-6 levels, clinical symptoms like improved and neither oxygen support nor hospitalization were required after an average of two weeks. (X. Xu et al., 2020)

A retrospective, controlled study in Nord France- Comté Hospital treated 20 patients with tocilizumab and compared them to 25 patients with standard treatment (hydroxychloroquine, oxygen, lopinavir/ritonavir and antibiotics). Death, ICU admission and mechanical ventilation was more common in the standard care group, suggesting that tocilizumab might reduce these endpoints. (Klopfenstein et al., 2020)
A retrospective study in Qatar treated 25 patients with tocilizumab one day after ICU admission. After seven days, patients who needed invasive ventilation declined from 84% to 60%. Radiological improvement appeared in 44 % of the patients after 7 days and in 68 % after 14 days of treatment. Nine patients no longer needed intensive care, thirteen remained in the ICU and three patients died. The mortality rate was at 12% although the most patients were critically ill. The most remarkable change due to the immunomodulatory effect of tocilizumab was observed with the rapid decrease of temperature and CRP levels. However no control group was included and the retrospective nature limits the study. (Alattar et al., 2020)
A pilot prospective open, multi center, single- arm study treated 63 patients with tocilizumab and was correlated to higher survival rates. Tocilizumab was administered intravenously in in 34 patients and subcutaneously in 29 patients. They observed improvement in laboratory parameters e.g. ferritin, CRP, D-dimer and in the relation of PaO_2 to FiO_2. After tocilizumab administration fast improvement in fever and respiratory parameters were noted. No difference in mortality were noted regarding the route of application. (Sciascia et al., 2020)
A study in Italy treated 21 patients with tocilizumab and compared them to 91 patients receiving standard care. The effect of tocilizumab regarding mortality and ICU admission was not significant. Because of tocilizumab's effect on the IL-6 receptor, CRP decreased significantly. Moreover PLT, which is associated with exacerbation of COVID-19, did not increase. Furthermore, INR, which is linked to severe cases, decreased noticeably in patients treated with tocilizumab. Limitations of this study include the small cohort and that steroid therapy was administered in both groups. (Colaneri et al., 2020)
In a retrospective and observational study 62 COVID-19 patients were administered tocilizumab and showed lower mortality rates than patients with no inhibition of the IL-6 receptor. Furthermore, participants who were prescribed tocilizumab improved regarding the requirement of mechanical ventilation and oxygen therapy compared to the control group, whose condition declined and still relied on mechanical ventilation. (Capra et al., 2020)
Capra et al. treated 62 out of 85 patients with tocilizumab. A considerably lower mortality rate of 3.2% compared to 47.8% in the non-treated patients was observed. (Levi, 2020)
Morena et al. administered tocilizumab to 51 patients and observed improvement in fever, CRP- levels and lymphopenia. Clinical signs improved in 67% and worsened in 33% of the patients. The death rate was 27%. However, side effects including elevated hepatic enzymes (in 29% of the participants), bacterial and fungal infections (in 27%) and thrombocytopenia (in 14% of the patients.) Limitations of this study include the lack of randomization and a comparison group. Furthermore, all patients received remdesivir, lopinavir/ritonavir or hydroxychloroquine. (Levi, 2020; Morena et al., 2020)

A retrospective study treated 21 critically ill patients with tocilizumab and observed improvement in health condition. Besides improvement of fever within one day, chest tightness and lung function bettered. Oxygen saturation improved, two patients did not require mechanical ventilation and altogether 15 patients lowered oxygen intake five days after treatment with tocilizumab. Moreover, lymphocyte levels lowered in 85 % in patients within 5 days and CRP and IL-6 levels normalized. All patients have been released from the hospital, including severely ill patients. (X. Xu et al., 2020)

A retrospective study included 65 patients and treated 32 patients with tocilizumab while the remaining patients received standard care. At day 18, 33 % of the patients in the control group died compared to 16 % in the tocilizumab group. 63 % of the participants in the tocilizumab-group were discharged compared to 49 participants in the comparison group. (Campochiaro et al., 2020)
A case-controlled study treated 96 severely ill patients with tocilizumab and compared them to a control group including 97 patients with severe COVID-19. When patients who required intubation were precluded, the death rate was significantly decreased in those receiving tocilizumab. However, when intubated patients were considered, no significant variation in the mortality rates was demonstrated. The results suggest that tocilizumab did not lower mortality in intubated patients but was associated with lower fatality in non-intubated patients. (Rojas-Marte et al., 2020)
A retrospective study, including 544 COVID-19 patients with severe symptoms, administered tocilizumab to 179 patients while the rest received standard care. The results demonstrated that death and ICU admissions were less frequent in patients who received tocilizumab. 25% of those treated with tocilizumab died or were relocated to ICU in comparison to 72% of those receiving standard care (p=0.002). (Guaraldi et al., 2020)

Adverse effects

ALT increased, but no hepatic damage was noticed. (Colaneri et al., 2020) Infections were more common in participants receiving tocilizumab, compared the group receiving standard care in the trial by Guaraldi et al.

Dexamethasone

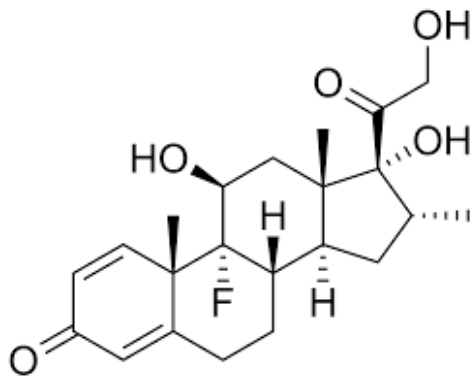

Figure 19 Chemical structure of Dexamethasone
https://de.wikipedia.org/wiki/Datei:Dexamethasone_structure.svg
Permission: Creative Commons CC0 1.0 Universal Public Domain Dedication

Mechanism of action

Dexamethasone, a corticosteroid, is employed for bacterial infections, myeloma and is indicated for gastrointestinal, dermatologic, ophthalmic, rheumatic, edematous, allergic, collagen and neoplastic conditions. Dexamethasone inhibits inflammatory effects by binding to the glucocorticoid receptor. High doses achieve an immunosuppressive effect, while lower dosage is anti-inflammatory. (Source: drugbank.ca/drugs/DB01234)

Dexamethasone and COVID-19

The RECOVERY trial is a controlled, open-label and randomized trial including 6425 COVID-19 patients. 2100 patients received 6 mg of dexamethasone daily for ten days and were compared to 4321 patients who received standard care. (Horby et al., 2020)

Table 6 Outcomes of Dexamethasone RECOVERY trial

	Mortality rate in dexamethasone group	Mortality in standard care group
Patients not requiring respiratory intervention	16%	13%
Patients requiring oxygen	20%	25%
Patients requiring ventilation	27%	41%

Source: (Horby et al., 2020)

There were no significant outcome disparities amidst both groups in participants not relying respiratory intervention. Mortality in participants relying on oxygen reduced by one fifth in those treated with dexamethasone (p=0.0021). A 35% relative risk reduction of mortality was demonstrated in patients requiring ventilation (p=0.86). Based on these findings, 8 patients requiring ventilation or 20 patients relying on oxygen, are required to avoid on death. These results advocate that dexamethasone only has an effect in severely ill patients, as a result of the elevated cytokine storm present. (Medicine, n.d.)

Interferons

Mechanism of action

Type 1 interferons are divided into α, ß, ε, ω and κ subtypes. IFN-1 are produced early during viral infections and bind to the interferon- alpha/beta receptor (IFNAR) inducing the phosphorylation of STAT1 and thereby activating interferon-stimulated genes. This activation plays a task in disruption of viral replication and adaptive immunity. Because of this immunomodulatory effects of IFN-1 they are used for treatment of diseases like MS. (Sallard et al., 2020)

Interferons and other viruses

IFNα and β were tested for SARS-CoV-1 and MERS-CoV inhibiting both viruses in vitro and in some animal models but failed to be efficient and show improvement in humans. However, it was demonstrated that IFNß1 was the foremost potent subtype in inhibiting both coronaviruses. (Sallard et al., 2020) Type 1 interferons improved respiratory function, lung abnormalities and oxygen saturation. (C. Yu et al., 2020)

Interferons and COVID-19

In vitro studies demonstrated that IFN α and ß were able to inhibit replication of SARS-CoV-2 even at low concentrations of fifty IU/ml. With higher concentration viral titers were reduced by increasing logs of magnitude as seen in Figure 20. (Mantlo et al., 2020)

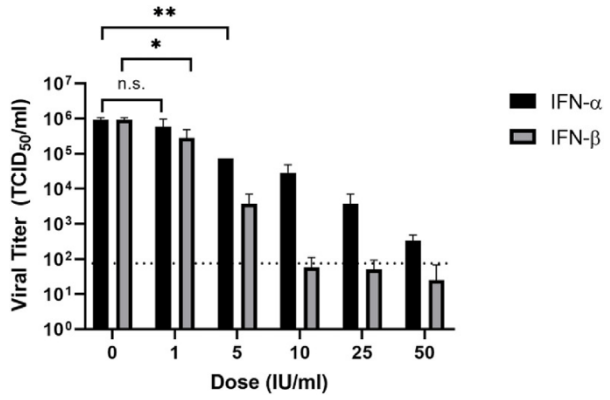

Figure 20 Interferon effect in vitro
Source: (Mantlo et al., 2020)
Permission: Licensed Content from Elsevier, permission through Copyright Clearance Center's Rightslink ® service, License Number: 4878800034401

An open-label, randomized phase II trial included 127 patients and compared the combination medication with lopinavir/ritonavir, interferon beta-1b and ribavirin to lopinavir and ritonavir. Patients within the interferon group demonstrated a major difference in viral shedding duration compared to the LPV/r group. (Shalhoub, 2020)

An exploratory study demonstrated that IFNα2b reduced the viral shedding duration of SARS-CoV-2. Furthermore, IFN-α2b reduced IL-6 and CRP levels and was related to improvement of ARDS. (Q. Zhou et al., 2020)

Overview and evaluation of treatments

Evaluation of Lopinavir- Ritonavir studies for COVID-19

Table 7 Lopinavir- Ritonavir evaluation

Author, date and country	Patient group	Study type	Outcomes	Key results	Study weaknesses
Cao et al., 2020, Wuhan, China	199 COVID-19 patients with low oxygen saturations and radiological disparities.	Randomized controlled trial, off label trial	28- day mortality, time to clinical improvement and medical condition after seven days.	No significant disparities in time to recovery (HR 1.31, 95% CI 0.95 to 1.8).	Not blinded. Improvement in treatment group was only demonstrated after separation of deceased patients.
Ye et al, 2020, Rui'an, China	47 COVID-19 patients Age: 5 to 68 years old.	Retrospective cohort study	Time to reduction of fever. Blood test results: CRP, PLT, WCC	4.8±1.94 days versus 7.3±1.53 days in comparison group, p=0.0364. No significant disparities in time to reduction of fever (p>0.05).	Results not applicable to death rate or hospital stay duration. 42 patients in treatment group and only 5 patients served as control. Retrospective and underpowered study. Claim that lopinavir/ritonavir 'could achieve better efficacy' with no evidence. Outcomes only based on disease not on patients.
Yuan et al, 2020, Shenzhen, China	94 patients COVID-19 patients. Age: 1 to 78 years old. 67 patients treated with lopinavir/ritonavir	Retrospective cohort study, single center	Hospital stay duration	No significant difference amidst the varying antiviral combinations. Actual results not stated but presented as a bar graph.	Only discharged patients were considered. Observational study without control. Combination treatments in both groups.
Zhou et al, 2020, China	191 COVID-19 patients	Retrospective cohort study, multicenter	To assess risk factors/ prognostic markers.	No significant difference regarding survival rates in treatment group (p=0.89).	Descriptive study, no direct correlation to lopinavir/ritonavir as a treatment and outcomes.

					Confounding variables not tested for steroid usage at the same time. Standard care participants received varying treatments.
Deng et al, 2020, China	33 adult COVID-19 patients not requiring mechanical ventilation.	Retrospective cohort study	Negative conversion rate of coronavirus. Assessment of pneumonia by CT.	16 patients treated with Lopinavir/ritonavir + arbidol while 17 patients were prescribed lopinavir/ritonavir only. Better outcomes in combination group (69% improved) compared to monotherapy group (29% improved). ($p<0.05$)	No control group, only comparing LPV/r to combination therapy. Outcomes not comparable regarding fatality and length of hospitalization. Conflicting factors and circumstantial steroid use in some patients. Small cohort bound to power errors. Demonstrated no benefit to treatment with lopinavir/ritonavir, since no control group was involved.

Source: (Dolan, Ingham, Baombe, 2020)

"Clinical bottom line: There is no current evidence to support the use of lopinavir-ritonavir in COVID-19 to improve clinical outcomes." (Dolan, Ingham, Baombe, 2020)

Evaluation of hydroxychloroquine studies for COVID-19

Table 8 Hydroxychloroquine evaluation

Author, date, country	Patient group	Study type	Outcomes measured	Results found	Study weaknesses
Mahevas et al, 2020, France	Adult COVID-19 patients from four hospitals with pneumonia and requiring mechanical ventilation. 181 patients: 84 patients were administered HCQ and 97 patients served as control.	Multicenter, observational collection of data	ICU transfer within 7 days and death rate. Secondary outcome: incidence of ARDS.	After 21 days: 89% survival rate in HCQ group compared to 91% in control group. 81% did not require oxygen anymore in HCQ group compared to 76% of the patients in control group. 9.5% of the patients developed long QTs and therefore discontinued treatment with HCQ.	Short period, treatment not assigned randomly. Few patients in HCQ group also received antibiotics.
Wei Tang et al, 2020, China	150 COVID-19 patients. 75 received HCQ and standard care and 75 were assigned to standard care only. Most patients presented moderate to mild symptoms.	Multicenter, randomized, open label clinical trial	Negative viral conversion after 28 days. Adverse events.	The difference in time to negative viral conversion between treatment and control group was 4.1% (95% CI 10.3 to 18.5).	Underpowered. Included no critically ill patients. 60% of the patients received accompanying medication before the study. HCQ was administered in the late course of the disease.
Mingxing et al, 2020, China	22 COVID-19 patients. Intervention treatment in 10 patients was HCQ and 12 patients received lopinavir/ritonavir and served as control.	Single- center, randomized and open label clinical trial	Negative conversion at 14 days. CT scan lung improvement. 14-day release and side effects.	Improvement regarding pulmonary function (CT imaging) was double as high in chloroquine group compared to lopinavir/ritonavir. Duration of hospitalization was lower in chloroquine group.	Not blinded. Small cohort
Borba et al, 2020, Brazil	81 COVID-19 patients with were either administered low dose or high dose of CQ.	Phase 2 randomized controlled trial	Mortality and prolonged QTc	Higher mortality (17% compared to 13.5% in low dosage group) and higher	Double blinded. The trial was terminated because of safety concerns and all patients who received high

				incidence of prolonged QT interval in high dosage group.	doses of HCQ switched to the low dose group.
Gautret et al, 2020, France	80 COVID-19 patients with mild symptoms HCQ in combination with azithromycin	Single- center, interventional, single- arm study	Requirement of oxygen therapy or ICU admission. Negative PCR and duration of hospitalization.	All patients, except for two, improved. 83% showed negative nasopharyngeal swabs at day 7. Mean of hospital stay was 5 days.	No control group to interpret improvement. Negative nasopharyngeal swabs are not conclusive enough.
Gautret et al, 2020, France	42 patients were included. 26 patients received HCQ and 10 patients received standard care.	Two- center, interventional, non-randomized trial	Negative nasopharyngeal swab and PCR test.	After 6 days of treatment, 70% in the HCQ group tested negative compared to 12.5% in control group.	Standard care was not defined. Decreasing viral titers may be influenced by technique and disease development rather than recovery. 1/2 of HCQ patients were relocated to ICU and were therefore not considered d in the follow-up. Two other patients were excluded because of adverse effects and high mortality risk. 6/26 of the patients in HCQ group were administered azithromycin.
Katheron et al, 2020, Canada	Intention-to-treat reanalysis of Gautret et al. study. Also included patients that were lost in follow-up, adverse effects, ICU transfer and one death compared to the original study.	Non-randomized and interventional trial	Negative nasopharyngeal swab and PCR test.	No significant disparities were found between HCQ group and control group regarding viral clearance.	Only reanalysis of Gautret et al.'s trial.
Huang et al, 2020, China	197 COVID-19 patients from 12 hospitals, received either low dosage (500 mg daily) or high dosage (two	Multicenter, observational and prospective	Time to negative viral RNA. Duration of hospitalization,	Duration of fever, and time to negative seroconversion shorter in HCQ group.	Outcome was not patient-centered. No severly ill patients were included.

	administration of 500 mg daily). 176 patients served as control group.	study	duration of fever. Adverse effects.		
Horby and Landray, 2020, UK	Ongoing prospective RCT, enrolling adult patients with confirmed COVID-19. 10 infections in 175 hospitals in the UK. 1542 patients recruited to HCQ treatment. 3132 patients were assigned to standard care.	Multicenter prospective RCT	28- day mortality. Hospital stay duration.	No significant disparities regarding fatality. 25.7% vs 23.5% with p=0.10. HR 1.11 (95% CI 0.98 to 1.26). No evidence of benefit (no further detail available).	Interim analysis. Full trial still ongoing. Results not fully published for critical appraisal yet.

Source: (Dolen, Ingham, Baombe, 2020)

"Clinical bottom line: Hydroxychloroquine has not been proven to be an effective treatment for COVID-19." (Dolen, Ingham, Baombe, 2020)

Evaluation of tocilizumab studies for COVID-19

Table 9: Tocilizumab evaluation

Author, date, country	Patient group	Study type	Outcomes measured	Results found	Study weaknesses
Xu et al, 2020	21 patients with critical and severe symptoms of COVID-19. All patients had fever and abnormal chest on CT.	Retrospective, observational study.	Body temperature, clinical symptoms, oxygen saturation, CRP and IL-6 levels and white blood cell count.	CT opacities, body temperature, oxygen saturation and clinical symptoms improved shortly after tocilizumab administration. CRP levels returned to normal. IL-6 levels elevated before decreasing.	Small cohort, single observational study.
Luo et al, 2020, China	15 patients with confirmed COVID-19	Retrospective, single-arm study	IL-6 and CRP levels before and after treatment were measured.	Tocilizumab prevented cytokine storms; acute phase reactant levels, IL-6 and CRP levels decreased. Except in four	Small cohort, retrospective, not controlled and short treatment duration.

				critically ill patients IL-6 levels, a persistent increase of IL-6 was demonstrated.	
Sciascia et al, 2020, Italy	63 patients	Pilot retrospective open, single-arm, multicenter study	Respiratory and laboratory parameters were observed.	Improvement in ferritin levels, CRP levels, D-dimer levels and PaO2/FiO2 ratio improved.	Not controlled and retrospective study. Heterogeneous tocilizumab administration routes.
Toniati et al, 2020, Italy	100 patients with confirmed COVID-19, ARDS and pneumonia requiring ventilatory support.	Prospective, single-center study	Improvement in acute respiratory failure assessed by Brescia COVID Respiratory Severity Score.	Within 12 to 72 hours CRP, fibrinogen and ferritin levels decreased. Lymphocyte count increased. D-Dimers level remained high and IL-6 levels increased.	Uncontrolled and not randomized.
Campochiaro et al, 2020, Italy	65 patients with severe COVID-19 pneumonia. 32 patients received tocilizumab.	Retrospective, single-center cohort study.	Clinical status assessed using six-category ordinal scale.	No statistically significant difference was demonstrated between the groups.	Retrospective design and small cohort.
Rojas- Marte et al, 2020	193 patients with severe COVID-19, 96 received tocilizumab.	Retrospective, case-control study	Primary endpoint: Overall mortality rate. Secondary endpoint: Mortality rate in intubated patients; mortality rate in non-intubated patients.	No statistically significance in lower mortality between both groups. When intubated patients were not considered, tocilizumab was correlated to lower mortality.	Retrospective, groups were not homogenic. Only one dose of tocilizumab was administered.
Guaraldi et al, 2020, Italy	544 patients with severe COVID-19. 16% needed mechanical ventilation. 179 patients received tocilizumab.	Retrospective, observational cohort study	Death or invasive mechanical ventilation.	Death and ICU admission were higher in standard care group compared to tocilizumab group. (72% vs 25%, p=0.002)	Not randomized and retrospective. Patients receiving standard care were older and more patients had cancer.

Source: (Campochiaro et al., 2020; Guaraldi et al., 2020; Luo et al., 2020; Rojas-Marte et al., 2020; Sciascia et al., 2020; Toniati et al., 2020; X. Xu et al., 2020)

“The current preliminary evidence of use of tocilizumab in COVID-19 patients is promising.” (Madenidou & Bukhari, 2020)

Evaluation of remdesivir studies for COVID-19

Table 10 Remdesivir evaluation

Author, date, country	Patient group	Study type	Outcomes measured	Results found	Study weaknesses
Wang et al, 2020, China	236 COVID-19 patients. ≤ 12 days onset of symptoms+ pneumonia and PF ratio B 300 mmHg or SpO2 ≤ 94%	Remdesivir treatment compared to placebo administration for 10 days.	Clinical improvement time, 28-day mortality, deterioration time and reduction of viral loads were assessed.	No significant difference was demonstrated in primary or secondary outcome for remdesivir. Remdesivir demonstrated a mean of 21 days and placebo group demonstrated a mean of 23 days. Study terminated early because of outbreak containment.	Insufficient power to detect differences in clinical outcomes, absence of data on infectious virus recovery, late initiation of treatment. (Y. Wang et al., 2020)
Beigel et al, 2020, US, Spain, UK, Denmark, Singapore, Germany, Greece, Japan, Korea.	1059 COVID-19 patients. Pneumonia, SpO2 ≤ 94% and oxygen requirement.	Remdesivir set side by side to treatment with placebo (ten days).	Time to recovery.	Remdesvir mean of recovery time was 11 days compared to mean of 15 days in placebo group. (95% CI 1.12-1.55; P < 0.001). No significantly lower mortality in remdesivir group (only numerically lower 7.1% compared to 11.9%).	Study results were unblinded before the trial ended because of the strong results of remdesivir, so that others can benefit from remdesivir. (Beigel et al., 2020)
Goldman et al, 2020, US, Taiwan, Italy, Spain, South Korea, Germany, Singapore and Hong Kong.	237 COVID-19 patients. Oxygen support, radiographic infiltrates + ambient SpO2 ≤ 94%, multiorgan failure and MV/ECMO excluded	Remdesivir 5 days compared to 10 days administration.	Clinical status after 14 days (7-point scale) Difference was not significant between both groups. (P = 0.14)	10-day group included patients that were more critically ill than in 5-day group. (P = 0.02); Taking this into consideration the outcomes were similar in both groups.	Open-label design and lack of a randomized placebo control group. (Goldman et al., 2020)

Source: (Davis et al., 2020)

"Results have been mixed for remdesivir in studies of COVID-19, but it is the first effective therapy for COVID-19 regarding shortening time to recovery. Remdesivir is generally well tolerated with comparable rated of adverse events to placebo." (Davis et al., 2020)

Convalescent plasma and antibody treatment

Convalescent plasma

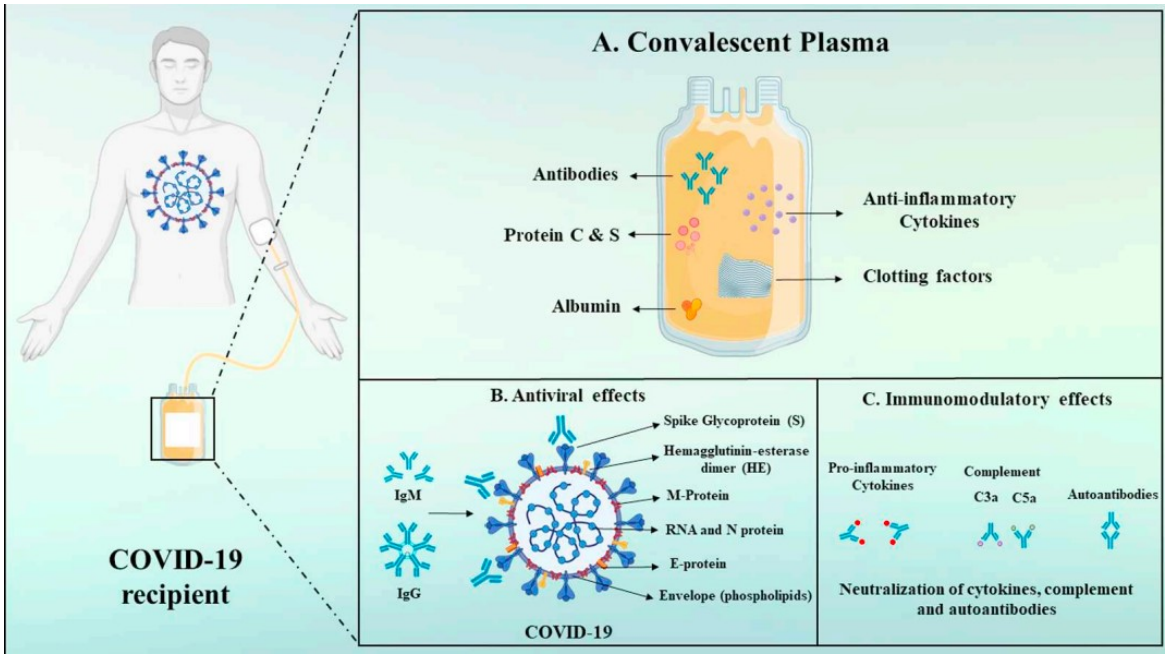

Figure 21 Convalescent Plasma effects
Source: (A. Pandey et al., 2020)
Permission: Licensed Content from Elsevier, permission through Copyright Clearance Center's Rightslink ® service, License Number: 4873760109732

Mechanism of action

Convalescent plasma is a tool for achieving immediate, short- term protection by transferring antibodies against the pathogen of interest to the blood of a patient. The plasma is obtained from individuals after infection resolution and antibody production. Passive therapy with antibodies from convalescent plasma might prevent infection or restrain illness severity in patients with recent pathogen exposure by operating against the pathogen and inhibiting its interaction with target receptors. Even though passive antibody therapy seems to be mostly effective in boosting immunity when used prophylactically or in early stages, it can also improve manifesting symptoms. (Alzoughool & Alanagreh, 2020; Bloch et al., 2020)
This is achievable due to the various mechanisms and effects of convalescent plasma. The antibodies can neutralize a pathogen by binding it, stimulate the complement cascade, phagocytosis and cellular cytotoxicity. (Bloch et al., 2020)
Neutralizing antibodies, which are also found in convalescent plasma, are essential for viral clearance and protection from viruses. IN SARS and MERS neutralizing antibodies were able to bind the spike protein and receptor binding domain leading to entry inhibition. (Rojas et al., 2020)

Previous experience with convalescent plasma

Already during the Spanish flu in 1918, convalescent plasma was linked to reduced mortality. (Casadevall et al., 2020) There are several studies on a variety of diseases (e.g. mumps, polio, influenza, hepatitis, H1N1) presenting promising results for convalescent plasma as post-exposure prophylaxis or treatment. Convalescent plasma was used in two other coronavirus-epidemics: SARS and MERS. In studies, convalescent plasma administration was correlated to better outcomes, reduced mortality, shorter hospitalization, and decreased viral loads.

Improved clinical signs occurred notably in patients receiving convalescent plasma earlier. (Bloch et al., 2020; Zeng et al., 2020)
A research by Hung et al. demonstrated viral load reduction within 5 days in 10 patients. Furthermore, mortality rate and cytokine response were significantly reduced. (Pawar et al., 2020)
A study on convalescent plasma in SARS that included 80 patients, presented that participants who received convalescent plasma earlier were more prone to improve compared to those who were transfused convalescent plasma later. (Barone et al., 2019)

Potential risks and adverse effects

Antibody-dependent enhancement (ADE) is a potential risk of treatment with convalescent plasma. In this case, antibodies attach to the surface of viruses without neutralizing them, instead they lead to improved viral entry and replication. (Bloch et al., 2020)
Furthermore, there is the risk of hyperimmune attacks and infections, like syphilis, hepatitis B and C, that could be transmitted by transfusion of plasma. (Zhao & He, 2020)
No significant adverse effects, beside fever, acute lung injury and anaphylactic reactions, for treatment with convalescent plasma were reported in a systematic review from 2015. (Tiberghien et al., 2020)
No side effects were presented in the mentioned studies. Adverse effects can be fever, nausea, and skin rashes. (Pawar et al., 2020)

Workflow

There are many steps to consider when collecting and distributing convalescent plasma. First and foremost, donor eligibility should be confirmed by nucleic acid tests and antibody testing. Criteria for donor suitability include affirmation of recovery from previous SARS- CoV- 2 infection and absence of infections that could be transmitted through transfusion (e.g. syphilis, HBV, HIV, HCV). Conditions for plasma collection consist of using approved equipment, trained supervisors and being performed at a qualified establishment. Post-donation plasma should be treated appropriately by freezing at -20°C. Before the last step of transfusion, it is vital to guarantee ABO compatibility amid recipient and donor. (Epstein & Burnouf, 2020)
The donor should be symptom-free for a minimum of 28 days prior to donating or 14 days after testing negative for COVID-19. After confirmation that there is no longer any risk of infection, neutralizing antibody titers have to be identified. The FDA endorses titers of 1:160 at least. (Sahu et al., 2020)
The suggested way to collect plasma is through apheresis, which centrifuges the donor's blood repeatedly until 400 to 800 ml of plasma are selectively obtained. (Rojas et al., 2020)

Efficacy of convalescent plasma in COVID-19

Currently convalescent plasma is used for severely ill COVID-19 patients suffering septic shock, organ failure, dyspnea radiological worsening or low oxygen saturation. Furthermore, the FDA proposed to use convalescent plasma prophylactically for high risk populations. (Sahu et al., 2020)
A study in China included 175 recovered COVID-19 patients and demonstrated a stable peak of neutralizing antibodies 10 days after infection. (Pawar et al., 2020)
During apheresis of convalescent plasma not only neutralizing antibodies, but also immunoglobulin G, immunoglobulin M, anti- inflammatory cytokines and natural antibodies are collected. This may lead to immunomodulation of cytokine storms and severe inflammatory response in COVID-19. Antibody titers in COVID-19 vary between 1800 and 16200. Neutralizing antibody titers range between 80 and 480. (Rojas et al., 2020)

A pilot study in China included 10 patients who presented severe COVID-19 receiving convalescent plasma showing neutralizing antibody titers with a dilution of 1:640. No severe side effects occurred, and all participants presented clinical improvement (e.g. high body temperature, difficulties breathing, pulmonary lesions, cough and viral titers) within three days of convalescent plasma administration. Improvement occurred faster, when convalescent plasma was administered before 14 d poi (post- onset of illness). Furthermore, they observed decreased CRP levels and an improvement of oxygen saturation. Another uncontrolled study in China included five patients with severe COVID-19, presented similar results after immune plasma as a medication. Nevertheless, both studies are limited by the small size and the shortcomings of their study design. Neither of the studies compared results to a control group. (Barone et al., 2019; Bloch et al., 2020; Sahu et al., 2020)

The study that included 5 patients by Shen and colleagues, demonstrated that convalescent plasma did not benefit a patient with high (≥ 1:640) neutral antibody titer before transfusion. This patient was intubated until the study was finished. (Barone et al., 2019)
Two patients in Korea with ARDS due to SARS- CoV- 2 infection were administered convalescent plasma. Viral loads immediately started reducing after an increasing inclination before transfusion of convalescent plasma. Both patients were administered convalescent plasma later in the course of the disease (22 days after showing symptoms), therefore it is not possible to attribute the reduction of viral loads to the impact of convalescent plasma, because this decreasing trend at the final stage is typical for the natural development of COVID-19. Furthermore, patients were treated with other antiviral medications, which could have influenced the effect of convalescent plasma. (Ahn et al., 2020)
Zhang and colleagues conducted a retrospective study of 4 patients with severe COVID-19. Patients received convalescent plasma between 11 to 18 days after admission. All patients recovered amongst them a pregnant woman. (Franchini, 2020)
In a retrospective study in China 6 patients obtained convalescent plasma and viral clearance was observed in all of them leading to longer survival duration. The study reasoned this by stating that convalescent plasma is able to inhibit viral shedding. Furthermore, they recommend passive immunization early on because they did not observe reduction of death rate in severely ill patients. (Zeng et al., 2020)
Another study treated three patients with convalescent plasma. Symptoms included fever, respiratory distress, nausea, dry cough and oxygen saturation ≤ 93% and respiratory frequency ≥ 30/min. Moreover IL-6 and CRP- levels were significantly increased and lymphocyte levels were decreased. After administration of convalescent plasma, the PaO_2/FiO_2 improved in all patients within 24 hours. CRP and IL-6 levels also decreased to normal range within one day. All patients did not need high- flow oxygen five days after receiving convalescent plasma. Criteria for discharge were met ten days after convalescent plasma administration including negative nucleic acid tests, normal temperature and absence of respiratory symptoms. (L. Zhang et al., 2020)
The first randomized convalescent plasma trial in Chine included 103 patients of whom 52 patients received convalescent plasma, and 51 patients served as a control. The recovery time at 28 days was faster by 2.15 days in relation to the comparison group. Clinical improvement at 28-day follow-up was demonstrated in 51.9 % of participants who were administered convalescent plasma compared with 43.1% in the non-treatment group. However severely ill patients demonstrated no change in recovery compared to the group receiving no treatment. Especially in patients who relied on mechanical ventilation showed no improvement. Mortality rate was lower by 8.3 % in patients who received convalescent plasma and adverse effects such as chills and rash occurred only in 2 patients. (Casadevall et al., 2020)

Adverse effects

No adverse effects were observed.

Convalescent plasma it contraindicated when patients have a complete deficiency in IgA. Passive immunization can decrease the immune response in patients leading to higher vulnerability to reinfection. Furthermore, caution is needed because of the possibility of transfusion associated circulatory overload (TACO). (Patrizia et al., 2020)

Conclusion

In the current situation of a pandemic convalescent plasma would be an advantageous treatment option, because numerous donations would be easy to achieve and it would be ready to use immediately. (Alzoughool & Alanagreh, 2020)

It is necessary to take into consideration that convalescent plasma might be more efficient when received earlier in the course of the disease. In patients at an advanced stage of COVID-19 with critical symptoms, convalescent plasma does not appear to reverse clinical signs. (Zeng et al., 2020)

The optimal time of administration after onset of symptoms is 7 days, but convalescent plasma seems to be effective up to two weeks. (Patrizia et al., 2020)

Antibody treatment

Mechanism of action

Monoclonal antibodies bind to specific targets in the body, mimicking, blocking and causing changes. Antibodies that target the epitope region of viruses can inhibit virus proliferation and increase severity of the disease. (Jahanshahlu & Rezaei, 2020)

Antibody treatment and COVID-19

Table 11 Overview clinical trials for antibody treatment in COVID-19

Candidate	Sponsor	Trial phase	Institution
Ultomiris (ravulizumab-cwvz), complement inhibitor		Phase III	Alexion Pharmaceuticals
Eculizumab (soliris), complement inhibitor		Phase II	Assistance Publique-Hopital Paris
MEDI3506, a monoclonal antibody. Target: interleukin 33	UK government	Phase II	AstraZeneca, ACCORD trial
Infliximab (remsima), anti-TNF antibody		Phase I	Celltrion
CER-002, monoclonal antibody (anti-light)		Phase I	Cerecor
Ieronlimab (PRO140), CCR5 antagonist		Phase II	CytoDyn
LY3127804, anti-Angiopoietin 2 antibody		Phase II	Eli Lilly
LY-CoV555 Antibody derived from patients who recovered from SARS-CoV-2	Canada Government	Phase I	AbCellera and Eli Lilly
Otilimab, anti-granulocyte macrophase colony stimulating factor		Phase II	GSK

Lenzilumab, anti-granulocyte- macrophage stimulating factor		Phase III	Humanigen Inc
TJM2 (TJ003234), anti-granulocyte- macrophage colony stimulating factor		Phase I/II	I-Mab Biopharma
IFX-1 An anti-C5a antibody		Phase II	InflaRx N-V.
JS016 antibody		Phase I	Junshi Biosciences/ Eli Lilly
Ilaris (canakinumab), interleukin- 1 beta blocker		Phase III	Novartis
Antibody blocking PD-1, thymosin		Phase I	Chinese research sponsors
Avastin (Bevacizumab), inhibitor of VEGF		Phase II/III	Numerous trials with Chinese research sponsors; Roche
Tocilizumab (actemra). IL-6 receptor antagonist	Biomedical Advanced Development and Research Authority	Phase II	Roche; REMAP-CAP; RECOVERY
Antibody combination REGN-COV-2 targeting the spike protein	Biomedical Advanced Development and Research Authority	Phase I/II	Regeneron
Gimsilumab, monoclonal antibody, anti-granulocyte-macrophage colony stimulating factor		Phase II	Roivant Sciences
Sarilumab (kevzara), IL-6 receptor antagonist	Biomedical Advanced Development and Research Authority	Phase II	Sanofi/ Regeneron; Feinstein Institutes; REMAP-CAP trial
Emapalumab (gamifant), anti-interferon gamma antibody		Phase III	Swedish Biovitrum
Meplazumab, anti- CD147 antibody		Phase II/III	Tang-Du Hospital
TY027, a monoclonal antibody		Phase I	SingHealth/ Tychan
Nivolumab (opdivo) antibody blocking PD-1		Phase II	Hong Kong University

Source: Milken Institute, Covid-19 Tracker-
https://airtable.com/shrSAi6t5WFwqo3GM/tblEzPQS5fnc0FHYR/viwJJuMA1ioIgAcPs?blocks=bipZFzhJ7wHPv7x9z&bip=full

SARS- CoV-2 mediates cell entry via binding of the spike to the ACE2 receptor, similar to SARS-CoV and MERS-CoV. Sine many antibodies targeting the receptor binding domain of MERS- CoV and SARS- CoV were identified, screening of convalescent patients for neutralizing antibodies is essential. (Wu et al., 2020)

The S protein includes the S1 and S2 domain. The RBD in the S1 unit interacts with high affinity with the ACE2 receptor. (G. Zhou & Zhao, 2020) Since the receptor binding domain is critical for entry into host cells, it is an important target to neutralize by antibodies. (X. Chen et al., 2020) SARS- CoV2's spike protein shares 77.5% similarity with the spike of

SARS-CoV. (C. Wang et al., 2020) Furthermore, the receptor binding domain of SARS-CoV-2 binds to the ACE2 receptor with higher affinity than SARS-CoV. (Venkat Kumar et al., 2020)
47DII and S309 obtained from SARS- CoV survivors, are human monoclonal antibodies that exhibited cross neutralization between SARS- CoV and SARS- CoV-2. (Venkat Kumar et al., 2020) Current outcomes of convalescent plasma treatment in COVID-19 patients indicate that neutralizing antibodies from recovered patients could inhibit SARS-CoV-2 infection. (Shi et al., 2020) A study examined the sera of 26 patients recovered from COVID-19. While all patients generated antibodies targeting RBD and S1, only 3 patients showed antibodies inhibiting binding of the RBD of SARS-CoV-2 to hACE2. (X. Chen et al., 2020)A study selected specific memory B cells from convalescent plasma by using a recombinant RBD protein of SARS-CoV-2. In HEK293T cells they identified two MAbs, called CA1 and CB6, being able to inhibit the binding of the soluble RBD to hACE2 receptor. Both MAbs were able to block pseudovirus transduction into HEK293T, Calu-3, Vero E6 and Huh7 cells. CA1 presented higher efficacy than CB6 in in neutralizing SARS-CoV-2 in all cell lines. Before in vivo testing, the Fc side of CB6 was introduced to LALA mutation to reduce the possibility of acute lung infection mediated by the Fc portion. CB6 reduced viral titers in rhesus macaque infection model instantly after administration. Furthermore, CB6-mAb was demonstrated to protect monkeys from SARS- CoV-2 infection when administered prophylactically. Compared to control animals, monkeys treated with CB6, after infection or prophylactically, showed no lung damages, intact alveolar, decreased edema, less infiltration and less fibrosis. (Shi et al., 2020)

B38 and H4 are monoclonal antibodies that were obtained from convalescent plasma of COVID-19 patients and exhibited neutralizing effects against SARS-CoV-2. Both antibodies competed for RBD binding with ACE2. Furthermore, both antibodies were able to bind RBD at the same time, indicating that the antibodies bind to different epitopes of the RBD. In transgenic mice, B38 and H4 reduced viral RNA by 32.8% and 26%. Furthermore, no pneumonia, edema or infiltration in alveolar spaces were observed compared to the control group. (Wu et al., 2020)

Eli Lilly and AbCellera designed a LY-CoV555, an antibody with the spike protein of SARS-CoV-2 as an aim, entered phase I trials. It was obtained from a convalescent COVID-19 patient and inhibits virus attachment and cell entry by neutralizing SARS-CoV-2. (Mullard, 2020)

High-throughput single-cell sequencing of convalescent patients' B cells identified various neutralizing antibodies confirmed by their effect in transgenic mice. One of those antibodies, BD-368-2, is included in clinical trials. (Yunlong Cao et al., 2020)

SARS and MERS/ other disease
Palivizumab, used to protect children from respiratory syncytial virus, is the first Mab approved by the FDA. Studies for SARS-CoV and MERS-CoV demonstrated neutralizing activity of many antibodies with the receptor binding domain (RBD) as a target. The use of neutralizing MAbs with Ebola virus achieved reduced mortality. (Shi et al., 2020)

Recombinant human monoclonal antibodies are also used for heart disease, arthritis, cancer and osteoporosis. (Sempowski et al., 2020)

Neutralizing antibodies such as monoclonal antibodies, single domain antibodies, functional antigen-binding fragment and single- chain variable region fragment were developed for

SARS-CoV and MERS-CoV. Targets include the RBD in particular the S1 and S2 region and inhibits the binding to the ACE2 receptor, thereby blocking cell entry and membrane fusion. (Jiang et al., 2020)Neutralizing antibodies were able to block MERS and SARS-CoV-1 infection in mice. (Sempowski et al., 2020)

Conclusion

Neutralizing antibodies could potentially be used not only as a treatment but also prophylactically. (Jiang et al., 2020) If an effective neutralizing antibody is identified, it can be produced using monoclonal antibody producing B cells. The target of antibodies is the RBD, which is profoundly conserved and therefore unlikely to mutate. (Cohen, 2020) Furthermore, isolating antibodies from recovered COVID-19 patients and manufacturing them would be the fastest way to develop a treatment. (Sempowski et al., 2020)

Vaccine development

Vaccine development commonly lasts for decades. But modern computational biology, manufacturing technologies, gene synthesis, antigen-based design and protein engineering might help to develop vaccines faster. Antiviral vaccines can be divided into two categories. The first category presents gene- based vaccines, for example: nucleic acid vaccines, recombinant vectors and live viruses. The second category are protein- based vaccines like viral proteins, viral particles or whole- inactivated viruses. (Graham, 2020)

Understanding the time frames

Vaccine development can take decades. To prove the protective function and safety in the preclinical phase, the vaccine has to be tested in animal models for months. After that samples of cGMP quality vaccines are produced for clinical trials. Clinical trials are divided in phase I, phase II and phase III trials with growing cohorts on every phase to assess efficacy and safety. Furthermore, time for production, distribution and administration has to be taken in to amount especially in a situation of a pandemic. Manufacturing capacities will be outpaced when the goal is to vaccinate the global population will be exceeded. In conclusion, a vaccine for SARS- CoV- 2 will take 12-18 months, even if abbreviations of the mentioned steps occur. (Amanat & Krammer, 2020)

In phase I the vaccine is tested for safety and immunogenicity in healthy volunteers for the first time. In Phase II the focus shifts to the immunogenicity and is tested in a larger cohort. Phase III trials describe the statistical power of the vaccine in stimulating an immune response in a large population.

Nucleic acid and recombinant vector vaccines are ideal for fast production, because they can be adapted to manufacturing technologies easily. (Graham, 2020)

One potential risk is antibody- dependent enhancement (ADE) that leads to infection enhancement by increasing virus- antibody complexes binding efficiency and therefore viral entry. ADE was demonstrated especially in flaviviruses for example dengue virus. It was also demonstrated in vitro for SARS- CoV- 1. Another possible risk is vaccine- associated enhanced respiratory disease (VAERD). This occurred in tests with respiratory syncytial virus and measles whole inactivated- virus vaccines. The reason behind this phenomenon are incorrect antigens resulting into immune complex degradation, allergic inflammation and complement activation. Therefore, it is important to guarantee the safety for a future SARS-CoV- 2 vaccine to minimize those potential risks. (Graham, 2020)

Vaccine development and other viruses

It is challenging to develop vaccines for respiratory viruses. Approved vaccines are only available against influenza. Furthermore, current vaccines show a limited effect with seasonal

influenza. Influenza and coronaviruses tend to rapid mutation because of the low constancy of RNA polymerase. (Giurgea et al., 2020)
Three vaccines have been tested in phase I trials for SARS- CoV and MERS CoV. Even though recipients developed neutralizing antibodies, antibody levels started declining after 30 weeks and returned to the initial stage after 60 weeks. This was also observed in patients that presented undetectable levels of neutralizing antibodies after 6 months of recovering from MERS- CoV. Therefore it is still unknown if long- term protection will be possible with a vaccine for COVID-19. (Lv et al., 2020)

COVID-19

Even though prior coronavirus vaccines had not reached beyond phase 1, studies and utilization of strategies on SARS- CoV and MERS- CoV are making the current rapid vaccine development for SARS- CoV-2 possible. (Diamond & Pierson, 2020)
From studies on both viruses, the spike protein was rapidly defined as a target for vaccines to neutralize the virus. (Amanat & Krammer, 2020)
The spike glycoprotein interacts with ACE2 and thereby mediates cell entry. Given that the spike protein is surface-exposed it became the focus for vaccine design. (Salvatori et al., 2020)
Most vaccines that are currently under development are neutralizing antibodies targeting the spike protein and the receptor binding domain of SARS- CoV-2. Even though neutral antibodies have been effective in other viral vaccines, some patients did not develop neutralizing antibodies after recovering from COVID-19. Furthermore, neutral antibody responses in SARS and MERS were observed to last for a short period of time. (Burton & Walker, 2020)

Advantages and disadvantages of vaccine platforms

Table 12 Advantages and disadvantages of vaccine platforms

Platform	Target	Existing vaccines	Advantages	Disadvantages
RNA vaccines	S protein	No	No infectious virus, vaccines are immunogenic, fast production	Safety concerns regarding reactogenicity due to reports
DNA vaccines	S protein	No	No infectious virus used, low costs of production, scale up is achieved easily, previously tested for SARS-CoV-1 and fast production achievable.	Vaccine requires specific administration devices to achieve high immunogenicity
Recombinant protein vaccines	S protein	Yeast expression (HBV, HPV) and Baculovirus (influenza, HPV)	Infectious virus not used, in combination with adjuvants immunogenicity can be increased.	Production capacity limited for global distribution. Confirmation of integrity of antigen and/or epitope is needed. High enough proceeds are needed.
Viral vector-based vaccines	S protein	VSV (ervebo)	No infectious virus, promising preclinical and clinical data for various emerging viruses such as MERS-CoV.	Vector immunity can affect the efficacy of the vaccine. Effect is vector dependent.

Live attenuated vaccines	Whole virion	Yes	Many licensed vaccines for humans, infrastructure is ready to use.	Since coronaviruses have a large genome, creating clones that are infectious for the attenuated vaccine can be time consuming. Extensive safety testing will be required.
Inactivated vaccines	Whole virion	Yes	Since licensed vaccines for humans are available, existing infrastructure is ready to use. Furthermore, adjuvants can achieve higher immunogenicity. Tested for SARS-CoV-1.	Infectious virus has to be handled in large amount. Confirmation of the integrity of antigen and/or epitope is needed.

Source: (Amanat & Krammer, 2020)

Vaccine clinical trials

Table 13 Overview clinical trials for COVID-19 vaccine

Candidate	Sponsor	Phase	Institution
Bacillus Calmette Guerin (BCG) live-attenuated vaccine	General Hospital in Massachusetts (Faustman Lab), Medical Center; Melbourne University and Children's research Institute of Murdoch; University of Radboud	Phase II/III	Radboud University; University of Melbourne, General Hospital at Massachusetts (Faustman Lab), Children's Research Institute in Murdoch.
AZD1222	Oxford University	Phase II/III	Jenner Institute,University of Oxford
mRNA-1273	Moderna	Phase II	Kaiser Permanente Health Institute, Washington
BNT162	Pfizer, BioNTech	Phase I/II	Various sites in Europe
Inactivated vaccine	Sinopharm, China; Biological Products Institute	Phase I/II	Henan Provincial Center for Disease Control and Prevention
BBIBP-CorV	China National Pharmaceutical Group (Sinopharm), Biological Products Institute, Beijing	Phase I/II	Henan Provincial Center for Disease Control and Prevention
Ad5-nCoV	CanSino Biologics	Phase I	Tongji Hospital; China
INO-4800	Inovio Pharmaceuticals	Phase I	University of Pennsylvania and Center for Pharmaceutical Research,
CoronaVac	Sinovac	Phase I/II	Sinovac Research and Development
mRNA-based vaccine	CureVac	Phase I	CureVac
bacTRL-spike	Symvivo	Pre-clinical	Symvivo Corporation

PittCoVacc	University of Pittsburgh	Pre-clinical	University of Pittsburgh
Measles vector vaccine	University of Pittsburgh's Center for Vaccine Research	Pre-clinical	Themis Biosciences; University of Pittsburgh; Pasteur Institute
NVX-CoV2373	Novavax	Pre-clinical	Novavax
Ii-Key peptide COVID-19 vaccine	Generex Biotechnology	Pre-clinical	Generex
Recombinant vaccine	Vaxart	Pre-clinical	Vaxart
Self-amplifying RNA vaccine	Imperial College London	Pre-clinical	Imperial College London
Plant-based COVID-19 vaccine	Medicago	Pre-clinical	Medicago
DNA-based vaccine	Takis Biotech	Pre-clinical	Takis Biotech
Ad26.COV2-S	Johnson & Johnson	Pre-clinical	Johnson & Johnson
AdCOVID	Altimmune	Pre-clinical	University of Alabama at Birmingham
T-COVIDTM	Altimmune	Pre-clinical	
Protein subunit vaccine	University of Saskatchewan Vaccine , Infectious Disease Organization-International Vaccine Centre	Pre-clinical	University of Saskatchewan Vaccine, Infectious Disease Organization-International Vaccine Centre
LUNAR-COV19	Arcturus Therapeutics and Duke-NUS Medical School	Pre-clinical	Duke-NUS Medical School, Singapore
Recombinant vesicular stomatitis virus (rVSV) vaccine	Merck; IAVI	Pre-clinical	
Adenovirus-based vaccine	ImmunityBio; NantKwest	Pre-clinical	
Molecular clamp vaccine	The University of Queensland	Pre-clinical	
AAVCOVID	Massachusetts Eye and Ear; Massachusetts General Hospital; University of Pennsylvania	Pre-clinical	

Source: https://www.raps.org/news-and-articles/news-articles/2020/3/covid-19-vaccine-tracker

Currently 140 vaccines are under development including: DNA-based, inactivated virus, live-attenuated virus, non- replicating viral vector, protein subunit, replicating viral vector, RNA-based and virus- like particle vaccines. (Source: https://milkeninsitute.org/covid-19-tracker)
Many companies like CureVac, Moderna, Inovio and Pfizer are developing vaccines that are nucleic acid based. Advantages include fast production based on the viral sequence and therefore fast access to the clinic. However experience is limited because no DNA- or mRNA- based vaccines are licensed yet. (Corey et al., 2020)
The mRNA molecules by Moderna express SARS-CoV-2-S that are enveloped with lipid nanoparticles so that entry into host cells is simplified. The spike protein is expressed and induces antibody response after entering host cells. The DNA vaccine, INO-4800 expresses SARS- CoV-2 inside an identical DNA vector. (Sharpe et al. 2020)

Sanofi and Novavax are using the well-known recombinant protein technology. Even though manufacturing time would be longer compared to nucleic acid-based vaccines, experience is well established with protein vaccines. Protein vaccines are licensed for varicella zoster, hepatitis B, influenza and human papillomavirus. However it is worth mentioning, that protein vaccines depend on potent adjuvants. (Corey et al., 2020)
CanSino Biologicsare developing the adenovirus vaccine, Ad5-nCoV, while Sinovac is working on an inactivated vaccine against SARS- CoV-2. (Sharpe et al., 2020)
An adenovirus vaccine is in phase II and four vaccines including plasmid DNA, inactivated virus and lipid nanoparticle encapsulated mRNA are in phase I. Currently at preclinical stage are protein subunit vaccines and live attenuated virus vaccines. (Lv, Wu, and Mok 2020)
Furthermore, nonspecific vaccines for SARS-CoV-2, such as the BCG vaccine, are tested. BCG is known as a tuberculosis vaccine and as treatment for bladder- carcinoma. Currently there is one phase IV trial and two phase III trials evaluating the protective effect of the BCG vaccine from SARS-CoV-2. (Checcucci et al. 2020)

Current results of vaccine candidates
The synthetic DNA-based vaccine, INO-4800, targets spike protein of SARS-CoV-2. Cell lines transfected with INO-4800 expressed spike protein at protein levels. In vivo studies of immunogenicity demonstrated levels of spike protein reactive IgG and RBD binding antibodies in INO-4800 immunized mouse and guinea pigs with an average ND50 titer above 320. Antibodies were also found in lung washes of the immunized animals. These antibodies were revealed to neutralize SARS-CoV-2 by inhibiting the attachment to the ACE2 receptor by SARS-CoV-2's spike protein. Seven days after vaccine administration, T cell response were induced against SARS-CoV-2 in the immunized animals. (Smith et al., 2020)

The first open-label, non- randomized phase 1 trial in Wuhan, China tested the Ad5 vectored vaccine candidate for COVID-19 in 108 individuals, who did not experience a SARS-CoV-2 infection. 36 patients received a low dose, 36 patients received a middle dose and the remaining 36 patients received a high dose of the vaccine. Immunogenicity was achieved in all dose groups leading to peaking T- cell responses after 14 days and peaking antibody levels after 28 days of vaccination. A four- fold increase if RBD- binding antibodies was achieved after one administration of the vaccine in 94-100% of the participants and in 50-75 % of the cohort a four-fold gain of live virus. $CD8^+$ T cells and $CD4^+$ T cells activation was demonstrated in all participants but waned of in recipients with pre-existing anti- Ad5 immunity. Adverse effects were most common in the high and middle dose group and included pain, fever, fatigue and headache. No severe adverse effects occurred within 28 days and adverse effects did not last longer than 48 h. (F.-C. Zhu et al., 2020)
BBIBP-CorV, an inactivated vaccine for SARS-CoV-2, protected rats, guinea pigs, micynomolgus monkeys, mice, rabbits and rhesus macaques from SARS-CoV-2 infection by inducing high neutralizing antibody levels. Protection was achieved by two doses of 2 µg and no adverse effects such as immunological exacerbation or antibody-dependent infection enhancement were observed. (H. Wang et al., 2020)

Data from a study on Pfizer and BioNTech's mRNA vaccine candidate was released. 12 patients received 10 µg of the vaccine two times with a 21-day interval, another 12 patients received two 30 µg doses with a 21-day interval and 12 patients were administered a single dose of 100 µg. A group receiving placebo and a group receiving convalescent plasma served as comparison. No serious adverse effects were reported, expect for individuals who received a 100 µg- dose. They reported headache, fever, soreness and fatigue. RBD- binding antibodies were present 21 says after the first administration and increased by 8 to 50 times after the second administration, depending on the dosage. 28 days post the first administration,

neutralizing antibodies were 1.8 to 2.8 times greater than in convalescent patients. (Lowe D. (2020, July). Pfizer and BioNTech's First Vaccine Candidate, *In the Pipeline*).

ChAdOx1 nCoV-19 is an adenovirus-vectored chimpanzee vaccine, which expresses the SARS-CoV-2 spike protein. An ongoing phase 1/2 randomized, single-blinded and controlled trial tested the vaccine as a single intramuscular injection in 534 healthy adults with no prior infection with SARS-CoV-2. Another 534 patients served as control group and received meningococcal conjugate vaccine (MenACWY). 10 patients were assigned to receive another dose of ChAdOx1 nCoV-19. No serious side effects were presented for CHAdOx1 nCoV-19. T- cell responses specific for the spike protein elevated on day 14 and peaked at day 28. After one dose of the vaccine 91% of the participants showed neutralizing antibody response and 100% had neutralizing activity after a second dose. (Folegatti et al., 2020)

„ChAdOx1 nCoV-19 showed an acceptable safety profile, and homologous boosting increased antibody responses. These results, together with the induction of both humoral and cellular immune responses, support large-scale evaluation of this candidate vaccine in an ongoing phase 3 programme.“ (Folegatti et al., 2020)

Conclusion

Coronaviruses do not always lead to long- lasting immunity. Furthermore, vaccination in elderly patients seems to be less effective. Nevertheless vaccination of the younger population would still protect high- risk- groups indirectly. (Amanat & Krammer, 2020)

Clinical trials

China registered the most studies, followed by Italy and the USA. Most studies are conducted by non-governmental organizations, universities or hospitals. The majority of studies have the efficacy of a treatment as a purpose. Chloroquine and hydroxychloroquine are the drugs that are studied the most as seen in Figure 20.

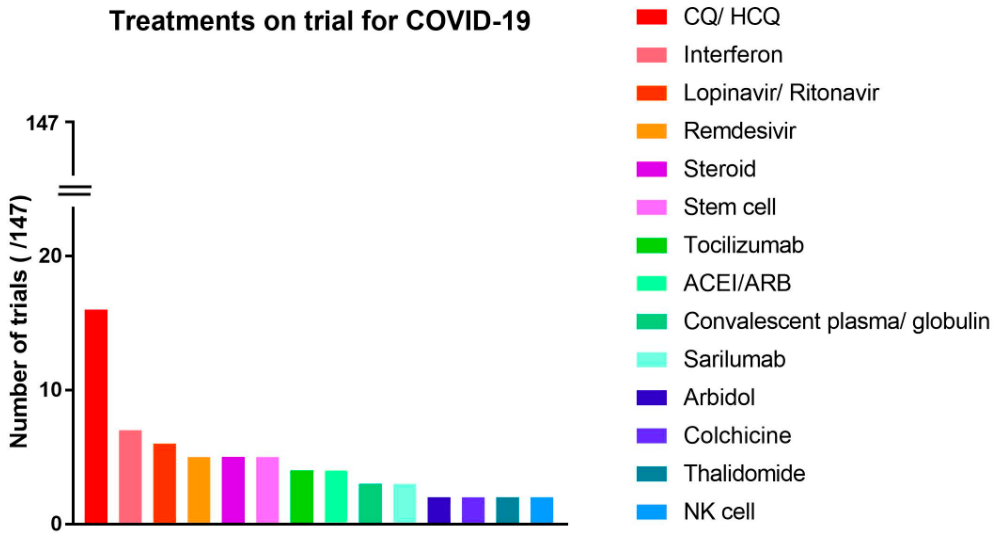

Figure 22 Distribution of COVID-19 treatments
(Lee et al., 2020)
Permission: CC BY 4.0 license

3.1. Overview ongoing clinical trials

Table 14 Overview clinical trials for COVID-19

Therapy	Phase	Administration route	Category and goal	Sponsor	ClinicalTrials.gov identifier
Chloroquine	II&III, IV, II	Oral	Antimalarial, for mild or asymptomatic COVID-19 patients	Oxford University Wroclaw Medical University, Poland Clinical Research Unit, Vietnam	NCT04331600, NCT04333628, NCT04328493
Hydroxychloroquine	III, III, II, II, II	Oral	Antimalarial, prevention of severe COVID-19	Germany, University of Calgary, California, Rambam Health Care Campus, Dr. Michael Hill, Canada, Baylor University Medical Center	NCT04340544, NCT04329611, NCT04333225, NCT04335084, NCT0432363, NCT04329923,
Remdesivir	III	i.v	Antiviral, treating COVID-19	Gilead Sciences	NCT04292730, NCT04292899
Azithromycin	III	Oral	Antibiotic, prevention of COVD-19 development	University of California	NCT04332107
Atovaquone/Azithromycin		Oral	Anti-Malarial/Anti-infective Combination for treating COVID-19	US, HonorHealth Research Institute	NCT04339426
Lopinavir/ritonavir	II	Oral	Antiretroviral, treating COVID-19	Sunnybrook Health Sciences	NCT04330690
Hydroxychloroquine versus Lopinavir/Ritonavir	II	Oral	COVID-19 with mild symptoms	Korea Medical Center	NCT04307693
1. Lopinavir/ritonavir 2. Hydroxychloroquine 3. Baricitinib,	II	1, 2, & 3 Oral, 4. Subcutan injection	Severe to moderate COVID-19	Canada, Lisa Barrett	NCT04321993

4. Sariluma					
Remdesivir, interferon β-1A, Lopinavir/ ritonavir and hydroxychloroquine.	II	I.V, oral, subcutan and oral respectively	COVID-19 treatment	France, National Institute of Medical and Health Research	NCT04315948
Oseltamivir, Hydroxychloroquine, Azithromycin	III	Oral	COVID-19 treatment	Pakistan, Shehnoor Azhar	NCT04338698
Hydroxychloroquine and Nitazoxanide	II, III	Oral	Evaluation of safety and effectiveness in COVID-19	Egypt, University of Tanta	NCT04361318
Azithromycin versus Hydroxychloroquine	II, III	Oral	COVID-19 treatment	Intermountain Medical Center and Health Care, Inc., United States	NCT04334382, NCT04329832
1.Lopinavir/ritonavir 2. Ribavirin and 3. Interferon beta-1b	II	1 & 2 oral, 3 subcutan	COVID-19 treatment	University of Hong Kong	NCT04276688
Clevudine	II	Oral	Antiviral, evaluation of safety and effectiveness in COVID-19	Bukwang Pharmaceutical, Korea	NCT04347915
Arbidol	IV	Oral	Antiviral, treating pneumonia in COVID-19	Jieming QU, Ruijin Hospital, China	NCT04260594
Isotretinoin	III	Oral	Retinoid, evaluation of the safety and effectiveness in COVID-19	Egypt, University of Tanta	NCT04361422
Nitazoxanide and Ivermectin	II, III	Oral	Evaluation of safety and efficacy in COVID-19	Egypt, University of Tanta	NCT04360356
Recombinant human Interferon α1β	I	Nebulization	COVID-19 treatment	Tongji Hospital, China	NCT04293887
1. Bromhexine hydrochloride 2. Arbidol hydrochloride and	N/A	1 & 2 oral, 3 spray	COVID-19 pneumonia treatment	China, Second Affiliated Hospital of Wenzhou Medical University	NCT04273763

3. Recombinant Human-Interferon α2b					
Deferoxamine	I, II	Intravenous	Iron chelator, severity reduction of COVID-19 clinical signs	Iran, Kermanshah University of Medical Sciences	NCT04333550
Dexamethasone	IV	I.V.	Steroid, COVID-19 ARDS treatment	Spain, Dr. Negrin University Hospital	NCT04325061
Piclidenoson	II	Oral	A3 adenosine receptor agonist, COVID-19 treatment	Israel, Can-Fite BioPharma	NCT04333472
Favipiravir	III	Oral	Antiviral, evaluation of safety and effectiveness in patients with COVID-19	Italy, Giuliano Rizzardini	NCT04336904
Huaier Granule	II, III	Oral	Adjuvant treatment in COVID-19	China, Tongji Hospital	NCT04291053
Tranexamic acid	II	Oral	Antifibrinolytics, study effect in COVID-19	US, The University of Alabama	NCT04338126
BLD-2660	II	Oral	Small molecule with antiviral effect, treating COVID-19	US, Blade Therapeutics	NCT04334460
Sildenafil citrate	III	Oral	Phosphodiesterase inhibitor, treating COVID-19	China, Tongji Hospital	NCT04304313
Losartan	I	Oral	Angiotensin receptor blocker, COVID-19 respiratory failure treatment	US, University of Kansas	NCT04335123
Telmisartan	II	Oral	Angiotensin receptor blocker, evaluation of the effectiveness in COVID-19	Argentina, Laboratorio Elea Phoenix	NCT04355936
Atorvastatin	II	Oral	Statin, assessment of the effectiveness in reducing the deterioration in COVID-19 patients	Mount Auburn Hospital	NCT04380402
Prazosin	II	Oral	Alpha-blockers, evaluation of the safety and efficacy in preventing cytokine storm	US, Johns Hopkins University	NCT04365257
Chlorpromazine	III	Oral	Antipsychotics, COVID-19 treatment	France, Centre Hospitalier St Anne	NCT04366739

Lenalidomide	IV	Oral	Antiangiogenic agent, COVID-19 (mild to moderate)	Spain, Getafe University Hospital	NCT04361643
Pluripotent stem cell-FT516	I		To identify MTD for treatment of COVID-19	Masonic Cancer Center, University of Minnesota	NCT04363346
Allogeneic Mesenchymal Stromal Cells	II	I.V.	Evaluation of safety and effectiveness in COVID-19 patients with pneumonia	Spain, Cell Therapy Network	NCT04361942
Human Mesenchymal Stem Cells	I, II	I.V.	Treatment of pneumonia in COVID-19	China, Puren Hospital	NCT04339660
Convalescent plasma	II	I.V.	Evaluation of safety and effectiveness	US, Hackensack Meridian Health, Sweden, Medical College of Wisconsin	NCT04343755, NCT04354831, NCT04390178
Convalescent plasma	III	I.V	Assessment of efficacy	US and Mexico, National Institute of Medical Sciences and Nutrition Salvador Zubiran France, Central Directorate of the Army Health Service	NCT04388410, NCT04372979
Hyperimmune plasma with standard care	II, III	I.V.	Assessment of safety and effectiveness in COVID-19 patients	Italy, University of Catanzaro	NCT04385043
bac-TRL-Spike	I	Oral	COVID-19 prevention	Canada, Symvivo Corporation	NCT04334980
IFX-1 combined with supportive care	II, III	I.V.	C5a antibody, pneumonia treatment	Netherlands, InflaRx GmbH	NCT04333420
Acalabrutinib combined with supportive care	II	Oral	Bruton's tyrosine kinase inhibitor, Assessment of safety, pharmacokinetics and efficacy	US, AstraZeneca	NCT04346199, NCT04380688
Baricitinib	II, III	I.V.	Janus Kinase inhibitor, COVID-19 treatment	US, University of Colorado	NCT04340232

Tocilizumab	II	I.V.	Immunosuppressive, pneumonia in COVID-19	Switzerland, University Hospital Inselspital Naples, National Cancer Institute	NCT04335071, NCT04317092
Canakinumab	III	I.V.	Monoclonal antibody: Anti-human-IL-1β Assessment of safety and effectiveness in COVID-19 cytokine release syndrome	US, Novartis Pharmaceuticals	NCT04362813
Ruxolitinib	II	-	Kinase inhibitor, hyper inflammation in COVID-19	Germany, Dr. Andreas Hochhaus	NCT04338958
Ruxolitinib	III	Intracutaneous	COVID-19 health care workers	Australia, Children Research Institute Netherlands, UMC Utrecht	NCT04327206, NCT04328441

Source : (A. Pandey et al., 2020)

3.2. Completed clinical trials

Table 15 Completed clinical trials

Intervention	Characteristics	Population	Locations	NCT Number	Results
DAS181	Study Type: Interventional Phase: N/A Study Design: •Primary Purpose: Treatment •Allocation: N/A •Masking: Open label •Intervention Model: Single Group Assignment Outcome Measures: •Death •No requirement of ventilation •Improved clinical signs •Viral titers	Enrollment: 4 Age: 18 to 70 Years Sex: All	China, Renmin Hospital of Wuhan University	NCT04324489	No data publicly available

	•Discharge				
Hyperimmune plasma	Study Type: Interventional Phase: Not Applicable Study Design: •Allocation: not applicable •Intervention Model: Single Group •Masking: Open Label •Purpose: Treatment Outcome Measures: •death •viral load •time to CPAP weaning •time to extubation •immune response •length of stay in ICU	Enrollment: 49 Age: ≥ 18 years Sex: All	Italy, Catherine Klersy Italy, Ospedale Asst Carlo Poma Mantova	NCT04321421	No data publicly available
Hydroxychloroquine Drug: Lopinavir / Ritonavir Drug: Interferon Beta-1A Drug: Interferon Beta-1B	Study Type: Interventional Phase: Phase II Study Design: •Allocation: Randomized •Intervention Model: Parallel Assignment •Masking: Open label •Purpose: Treatment Outcome Measures: •Length of hospitalization •Mortality •Improvement of SpO2 •New incidence of mechanical ventilation •Time to clinical improvement	Enrollment: 60 Age: ≥ 18 years Sex: All	Shahid Beheshti University of Medical Sciences and Health Services, Iran, Tehran, Loghman Hakim Hospital	NCT04343768	No data publicly available
Tocilizumab	Study Type: Interventional Phase: Phase 2 Study Design: •Allocation: Non- Randomized •Intervention Model: Single	Enrollment: 32 Age: ≥ 18 years Sex: All	US, University of Chicago Medicine	NCT04331795	No data publicly available

	Group Assignment •Masking: Open Label •Purpose: Treatment Outcome Measures: •Rate and duration of inotrope utilization/ vasopressor •Biochemical response •Survival to release from the hospital •Mechanical ventilation rate (non-elective) •Clinical response •Time to requirement of ventilation •Survival •COVID-19 pneumonia progression •Mechanical ventilation duration •and three others				
Methylprednisolone therapy	Study Type: Interventional Phase: •Phase II and III Study Design: •Allocation: Randomized •Intervention Model: Parallel Assignment •Masking: None (Open Label) •Primary Purpose: Treatment Outcome Measures: •All-cause mortality •PaO2/FiO2 disparities amidst groups •Mechanical ventilation •Score of lower Murray lung injury •Clearance of SARS-CoV-2 •Assessment score of Organ Failure	Enrollment: 80 Age: ≥ 18 years Sex: All	China, Medical ICU, Medical College Hospital, Peking Union	NCT04244591	No data publicly available
Favipravir	Study Type: Interventional Phase: Phase 3 Study Design: •Allocation: Randomized	Enrollment: 100 Age: 18 to 80 years Sex: All	Egypt, Faculty of Medicine Ain Shams, Clinical Research Center,	NCT04349241	No data publicly available

	•Intervention Model: Parallel Assignment •Masking: None (Open Label) •Primary Purpose: Treatment Outcome Measures: •Clinical improvement •Viral clearance •Radiological Improvement		University Research Institute		
Methylprednisolone	Study Type: Interventional Phase: Not Applicable Study Design: •Allocation: Randomized •Intervention Model: Single Group Assignment •Masking: None (Open Label) •Primary Purpose: Treatment Outcome Measures: •duration of SAR-CoV-2 clearance in 14 days •30-day mortality •treatment failure incidence at 14 days •rate of ICU admissions at 30 days	Enrollment: 86 Age: ≥ 18 years Sex: All	Various hospitals in China	NCT04273321	No data publicly available
Danoprevir +Ritonavir	Study Type: Interventional Phase: Phase 4 Study Design: •Allocation: N/A •Intervention Model: Single Group Assignment •Masking: None (Open Label) •Primary Purpose: Treatment Outcome Measures: Rates of: •Absence of fever •Composite side effects •Absence of dyspnea •Serious adverse effects •Absence of cough	Enrollment: 10 Age: 18 to 75 Years Sex: All	China, Hubei, Huoshenshan Hostipal	NCT04345276	No data publicly available

	•Ventilation support •Relying on oxygen therapy •Undetectable SARS-CoV-2 •ICU admission •Recovery time				
Ganovo + ritonavir+/- nebulization of interferon	Study Type: Interventional Phase: Phase 4 Study Design: •Allocation: N/A •Intervention Model: Single Group Assignment •Masking: None (Open Label) •Primary Purpose: Treatment Outcome Measures: Rates of: •Recovery time •Absence of cough •Absence of oxygen requirement •Mechanical ventilation •Dyspnea •Undetectable SARS-CoV-2 •Fever •ICU admission •Serious side effects •Composite side effects	Enrollment: 11 Age: 18 to 75 years Sex: All	China, the Ninth Hospital of Nanchang	NCT04291729	No data publicly available
Hydroxychloroquine	Study Type: Interventional Phase: Phase III Study Design: •Allocation: Randomized •Intervention Model: Parallel Assignment •Masking: Open Label •Primary Purpose: Treatment Outcome Measures: •Mortality rate •Severe illness •Side effects •Viral clearance rate of lower respiratory tract secretions, sputum and throat swabs at the 5^{th} day	Enrollment: 30 Age: ≥ 18 years Sex: All	•China, Shanghai Public Health Clinical Center •China, Shanghai Public Health Clinical Center	NCT04261517	No data publicly available

	•Viral clearance rate of sputum, lower respiratory tract secretions and throat swabs at the 7th day				
Ivermectin	Study Type: Interventional Phase: Phase I Design: •Allocation: Randomized •Intervention Model: Parallel Assignment •Masking: Double blinded •Primary Purpose: Treatment Outcome Measures: •Number of cured patients •Mean time to cure of the COVID-19 patients	Enrollment: 100 Age: ≥ 18 years Sex: All	Iraq, General Directorate of Medical City	NCT04343092	No data publicly available
•Favipiravir •Kaletra •Lopinavir/Ritonavir •Hydroxychloroquine	Study Type: Interventional Phase: Not Applicable Study Design: •Allocation: Non- Randomized •Intervention Model: Parallel Assignment •Masking: None (Open Label) •Primary Purpose: Treatment Outcome Measures: •Oxygen saturation •hospitalization duration •Fatality •Response to treatment •Blood cell count •Oxygen therapy •Dyspnea	Enrollment: 40 Age: Between 16 and 100 years Sex: All	Iran, Mohammad Sadegh Bagheri Baghdasht	NCT04376814	No data publicly available
Baricitinib	Study Type: Interventional Phase: •Phase II/ III Study Design: •Allocation: Non- Randomized •Intervention Model: Crossover Assignment •Masking: None (Open Label) •Primary Purpose: Treatment	Enrollment: 12 Age: 18 to 85 Years Sex: All	Italy, Fabrizio Cantini	NCT04358614	No data publicly available

	Outcome Measures: •Discharge rate •Assessment of baricitinib safety combined with antivirals (lopinavir-ritonavir) in terms of incidence of side effects. •Evaluation of the baricitinib's impact on clinical, respiratory and laboratory parameters. •ICU admission rate				
Convalescent plasma	Study Type: Interventional Phase: Phase 1 Study Design: •Allocation: N/A •Intervention Model: Single Group Assignment •Masking: None (Open Label) •Primary Purpose: Health Services Research Outcome Measures: •Chest X-ray •Plaque reduction neutralization test •International Normalized Ratio •C-Reactive Protein •Oxygenation Index •D-dimer •Serious side effects	Enrollment: 10 Age: ≥ 18 years Sex: All	Indonesia, Gatot Soebroto central army presidential hospital	NCT04407208	No data publicly available
Convalescent plasma	Study Type: Interventional Phase: Phase 2 Study Design: •Allocation: Randomized •Intervention Model: Parallel Assignment •Masking: None (Open Label) •Primary Purpose: Treatment Outcome Measures: •Dialysis free days •Fatality	Enrollment: 29 Age: ≥ 18 years Sex: All	•India, Maulana Azad medical College, •India, Institute of Liver and Biliary Sciences	NCT04346446	No data publicly available

	•PaO2/FiO2 ratio improvement •Mechanical ventilation •Hospitalization duration •Improvement of SOFA score •Length of ICU stay •Requirements of vasopressor				
Convalescent plasma	Study Type: Interventional Phase: Not Applicable Study Design: •Allocation: Randomized •Intervention Model: Parallel Assignment •Masking: None (Open Label) •Primary Purpose: Treatment Outcome Measures: •Death versus survival in patients receiving convalescent plasma •Length of hospitalization	Enrollment: 49 Age: ≥ 18 years Sex: All	•Akarkh Healt hdirectorate, Baghdad, Iraq	NCT04441424	No data publicly available
•Hydroxychloroquine + azithromycin •Hydroxychloroquine	Study Type: Interventional Phase: Phase III Study Design: •Allocation: Randomized •Intervention Model: Parallel Assignment •Masking: None (Open Label) •Primary Purpose: Treatment Outcome Measures: •Mortality •Length of mechanical ventilation requirement •Secondary infections •Effect of SARS-CoV-2 on quality of life, morbimortality, mental health and daily activities •Clinical status assessment •Proportion of days without mechanical ventilation •Length of hospitalization •Assessment of the role of leucocyte phenotype on the effect of therapies	Enrollment: 440 Age: ≥ 18 years Sex: All	> 50 hospitals in Brazil	NCT04321278	No data publicly available

Convalescent plasma	Study Type: Interventional Phase: Not Applicable Study Design: •Allocation: Randomized •Intervention Model: Crossover Assignment •Masking: Double blinded •Primary Purpose: Treatment Outcome Measures: •Plasma ferritin level •Lymphocyte count •D-Dimer level •C-Reactive protein level •Plasma procalcitonin level •Plasma fibrinogen level •Fractional Inspired Oxygen Level •Partial Oxygen Saturation level •Arterial Oxygen level	Enrollment: 60 Age: 18 Years to 90 Years (Adult, Older Adult) Sex: All	Turkey, Istanbul Training and Research Hospital	NCT04442958	No data publicly available
•Lopinavir/ ritonavir •Ribavirin •Interferon Beta-1B	Study Type: Interventional Phase: Phase 2 Study Design: •Allocation: Randomized •Intervention Model: Parallel Assignment •Masking: None (Open Label) •Primary Purpose: Treatment Outcome Measures: •Side effects •Time until saliva, all clinical specimens and NPS are negative •Mortality •Time to clinical recovery •Immune reaction •Hospitalization	Enrollment: 127 Age: ≥ 18 years Sex: All	Hong Kong Queen Mary Hospital and University of Hong Kong	NCT04276688	No data publicly available
Hydroxychloroquine	Study Type: Interventional Phase: Phase 3 Study Design: •Allocation: Randomized	Enrollment: 1309 Age: ≥ 18 years Sex: All	•University of Minnesota •University of Manitoba •University of Alberta,	NCT04308668	No data publicly available

	•Intervention Model: Parallel Assignment •Masking: Quadruple blinded •Purpose: Treatment Outcome Measures: •Disease severity in the course of 14 days •Death rate •Severity of symptoms at 5 days and 14 days •COVID-19 rates in asymptomatic patients •Rate of hospitalization •Detection of SARS-CoV-2 rates •AllCause incidence withdrawal or discontinuation of medication •COVID-19 severity on ordinal scale in patients with symptoms at 14 days		•Research Institute of the McGill University Heath Centre		

Source: clinicaltrials.gov

Conclusion

This diploma thesis aims to identify current treatment approaches for COVID-19 by summarizing and providing an overview of the ongoing and completed trials and studies. Treatment candidates include lopinavir/ritonavir, remdesivir, ivermectin, chloroquine/hydroxychloroquine, tocilizumab, interferons, dexamethasone, convalescent plasma and antibody treatment.
By current evidence it can be concluded that, tocilizumab, dexamethasone and convalescent plasma have presented promising results regarding improvement of clinical signs, especially in critically ill COVID-19 patients. However, no current evidence supports the use of chloroquine/hydroxychloroquine or lopinavir/ritonavir for COVID-19. Opinions differ for the use of remdesivir for COVID-19 therapy, however it is proven that remdesivir shortens the recovery time.
Many SARS-CoV-2 vaccines are already in clinical trials. The Ad5-CoV vaccine was proven to be safe and is currently in phase II. The mRNA-1273 vaccine was able to develop neutralizing antibodies in individuals. The most encouraging results are seen with the ChAdOx1 nCoV-19 vaccine, that achieved neutralizing antibody results in 100% of the included individuals in a phase I/II trial.
Even though it was a challenge to collect, read and summarizes the sheer amount of information available on COVID-19 treatment and vaccine candidates, this thesis includes most of the current studies and trials and evaluates them.
Further research is needed to correctly evaluate current treatments, since few studies meet the criteria of being randomized, placebo-controlled, with a large cohort and double-blinded. Along with the results of the ongoing and completed clinical trials, this would be important to identify the best available treatment for COVID-19.

References

Ahn, J. Y., Sohn, Y., Lee, S. H., Cho, Y., Hyun, J. H., Baek, Y. J., Jeong, S. J., Kim, J. H., Ku, N. S., Yeom, J. S., Roh, J., Ahn, M. Y., Chin, B. S., Kim, Y. S., Lee, H., Yong, D., Kim, H. O., Kim, S., & Choi, J. Y. (2020). Use of convalescent plasma therapy in two covid-19 patients with acute respiratory distress syndrome in Korea. *Journal of Korean Medical Science*. https://doi.org/10.3346/JKMS.2020.35.E149

Alanagreh, L., Alzoughool, F., & Atoum, M. (2020). Risk of using hydroxychloroquine as a treatment of COVID-19. *The International Journal of Risk & Safety in Medicine*, *1*, 1–6. https://doi.org/10.3233/JRS-200024

Alattar, R., Ibrahim, T. B. H., Shaar, S. H., Abdalla, S., Shukri, K., Daghfal, J. N., Khatib, M. Y., Aboukamar, M., Abukhattab, M., Alsoub, H. A., Almaslamani, M. A., & Omrani, A. S. (2020). Tocilizumab for the Treatment of Severe COVID-19. *Journal of Medical Virology*, *April*. https://doi.org/10.1002/jmv.25964

Alzoughool, F., & Alanagreh, L. (2020). Coronavirus drugs: Using plasma from recovered patients as a treatment for COVID-19. In *International Journal of Risk & Safety in Medicine*. https://doi.org/10.3233/JRS-201017

Amanat, F., & Krammer, F. (2020). SARS-CoV-2 Vaccines: Status Report. In *Immunity*. https://doi.org/10.1016/j.immuni.2020.03.007

Amirian, E. S., & Levy, J. K. (2020). Current knowledge about the antivirals remdesivir (GS-5734) and GS-441524 as therapeutic options for coronaviruses. In *One Health*. https://doi.org/10.1016/j.onehlt.2020.100128

Bai, Y., Yao, L., Wei, T., Tian, F., Jin, D. Y., Chen, L., & Wang, M. (2020). Presumed Asymptomatic Carrier Transmission of COVID-19. In *JAMA - Journal of the American Medical Association*. https://doi.org/10.1001/jama.2020.2565

Barone, P., Desimone, R. A., & Medicine, T. (2019). *CONVALESCENT PLASMA TO TREAT CORONAVIRUS DISEASE 2019 (COVID-19): CONSIDERATIONS FOR CLINICAL TRIAL DESIGN Paul Barone, Robert A. DeSimone Department of Pathology and Laboratory Medicine, Weill Cornell Medicine, New York, NY*. *2019*.

Beigel, J. H., Tomashek, K. M., Dodd, L. E., Mehta, A. K., Zingman, B. S., Kalil, A. C., Hohmann, E., Chu, H. Y., Luetkemeyer, A., Kline, S., Lopez de Castilla, D., Finberg, R. W., Dierberg, K., Tapson, V., Hsieh, L., Patterson, T. F., Paredes, R., Sweeney, D. A., Short, W. R., … Lane, H. C. (2020). Remdesivir for the Treatment of Covid-19 — Preliminary Report. *New England Journal of Medicine*. https://doi.org/10.1056/nejmoa2007764

Bloch, E. M., Shoham, S., Casadevall, A., Sachais, B. S., Shaz, B., Winters, J. L., van Buskirk, C., Grossman, B. J., Joyner, M., Henderson, J. P., Pekosz, A., Lau, B., Wesolowski, A., Katz, L., Shan, H., Auwaerter, P. G., Thomas, D., Sullivan, D. J., Paneth, N., … Tobian, A. A. R. (2020). Deployment of convalescent plasma for the prevention and treatment of COVID-19. *Journal of Clinical Investigation*. https://doi.org/10.1172/jci138745

Burton, D. R., & Walker, L. M. (2020). *Forum Rational Vaccine Design in the Time of COVID-19 Forum*. 695–698.

Caly, L., Druce, J. D., Catton, M. G., Jans, D. A., & Wagstaff, K. M. (2020). The FDA-approved drug ivermectin inhibits the replication of SARS-CoV-2 in vitro. *Antiviral Research*. https://doi.org/10.1016/j.antiviral.2020.104787

Campochiaro, C., Della-Torre, E., Cavalli, G., De Luca, G., Ripa, M., Boffini, N., Tomelleri, A., Baldissera, E., Rovere-Querini, P., Ruggeri, A., Monti, G., De Cobelli, F., Zangrillo, A., Tresoldi, M., Castagna, A., Dagna, L., & TOCI-RAF Study Group. (2020). Efficacy and safety of tocilizumab in severe COVID-19 patients: a single-centre retrospective cohort study. *European Journal of Internal Medicine*, *76*(May), 43–49. https://doi.org/10.1016/j.ejim.2020.05.021

Cao, B., Wang, Y., Wen, D., Liu, W., Wang, J., Fan, G., Ruan, L., Song, B., Cai, Y., Wei, M., Li, X., Xia, J., Chen, N., Xiang, J., Yu, T., Bai, T., Xie, X., Zhang, L., Li, C., … Wang, C. (2020). A Trial of Lopinavir-Ritonavir in Adults Hospitalized with Severe Covid-19. *The New England Journal of Medicine*. https://doi.org/10.1056/NEJMoa2001282

Cao, Yu chen, Deng, Q. xin, & Dai, S. xue. (2020). Remdesivir for severe acute respiratory syndrome coronavirus 2 causing COVID-19: An evaluation of the evidence. In *Travel Medicine and Infectious Disease*. https://doi.org/10.1016/j.tmaid.2020.101647

Cao, Yunlong, Su, B., Guo, X., Sun, W., Deng, Y., Bao, L., Zhu, Q., Zhang, X., Zheng, Y., Geng, C., Chai, X., He, R., Li, X., Lv, Q., Zhu, H., Deng, W., Xu, Y., Wang, Y., Qiao, L., … Xie, X. S. (2020). Potent Neutralizing Antibodies against SARS-CoV-2 Identified by High-Throughput Single-Cell Sequencing of Convalescent Patients' B Cells. *Cell*. https://doi.org/10.1016/j.cell.2020.05.025

Capra, R., De Rossi, N., Mattioli, F., Romanelli, G., Scarpazza, C., Sormani, M. P., & Cossi, S. (2020). Impact of low dose tocilizumab on mortality rate in patients with COVID-19 related pneumonia. *European Journal of Internal Medicine*, *April*. https://doi.org/10.1016/j.ejim.2020.05.009

Casadevall, A., Joyner, M. J., & Pirofski, L.-A. (2020). A Randomized Trial of Convalescent Plasma for COVID-19-Potentially Hopeful Signals. *Jama*, 3–5. https://doi.org/10.1001/jama.2020.10218

Cattaneo, D., Corbellino, M., Clementi, E., Galli, M., Riva, A., & Gervasoni, C. (2020). Does lopinavir really inhibit SARS-CoV-2? *Pharmacological Research*, *158*(April), 104898. https://doi.org/10.1016/j.phrs.2020.104898

Chaccour, C., Hammann, F., Ramón-García, S., & Rabinovich, N. R. (2020). Ivermectin and Novel Coronavirus Disease (COVID-19): Keeping Rigor in Times of Urgency. *The American Journal of Tropical Medicine and Hygiene*. https://doi.org/10.4269/ajtmh.20-0271

Chakraborty, C., Sharma, A. R., Bhattacharya, M., Sharma, G., Lee, S.-S., & Agoramoorthy, G. (2020). COVID-19: Consider IL6 receptor antagonist for the therapy of cytokine storm syndrome in SARS-CoV-2 infected patients. *Journal of Medical Virology*, 0–2. https://doi.org/10.1002/jmv.26078

Chen, N., Zhou, M., Dong, X., Qu, J., Gong, F., Han, Y., Qiu, Y., Wang, J., Liu, Y., Wei, Y., Xia, J., Yu, T., Zhang, X., & Zhang, L. (2020). Epidemiological and clinical characteristics of 99 cases of 2019 novel coronavirus pneumonia in Wuhan, China: a descriptive study. *The Lancet*. https://doi.org/10.1016/S0140-6736(20)30211-7

Chen, X., Li, R., Pan, Z., Qian, C., Yang, Y., You, R., Zhao, J., Liu, P., Gao, L., Li, Z., Huang, Q., Xu, L., Tang, J., Tian, Q., Yao, W., Hu, L., Yan, X., Zhou, X., Wu, Y., … Ye, L. (2020). Human monoclonal antibodies block the binding of SARS-CoV-2 spike protein to angiotensin converting enzyme 2 receptor. In *Cellular and Molecular Immunology*. https://doi.org/10.1038/s41423-020-0426-7

Chowdhury, M. S., Rathod, J., & Gernsheimer, J. (2020). A Rapid Systematic Review of Clinical Trials Utilizing Chloroquine and Hydroxychloroquine as a Treatment for COVID-19. *Academic Emergency Medicine : Official Journal of the Society for Academic Emergency Medicine*. https://doi.org/10.1111/acem.14005

Cohen, J. (2020). The race is on for antibodies that stop the new coronavirus. *Science*. https://doi.org/10.1126/science.abc6444

Colaneri, M., Bogliolo, L., Valsecchi, P., Sacchi, P., Zuccaro, V., Brandolino, F., Montecucco, C., Mojoli, F., Giusti, E. M., Bruno, R., & The Covid Irccs San Matteo Pavia Task Force. (2020). Tocilizumab for Treatment of Severe COVID-19 Patients: Preliminary Results from SMAtteo COvid19 REgistry (SMACORE). *Microorganisms*, *8*(5). https://doi.org/10.3390/microorganisms8050695

Colson, P., Rolain, J. M., & Raoult, D. (2020). Chloroquine for the 2019 novel coronavirus

SARS-CoV-2. In *International Journal of Antimicrobial Agents*. https://doi.org/10.1016/j.ijantimicag.2020.105923

Corey, L., Mascola, J. R., Fauci, A. S., & Collins, F. S. (2020). A strategic approach to COVID-19 vaccine R&D. *Science (New York, N.Y.)*, *368*(6494), 948–950. https://doi.org/10.1126/science.abc5312

Davis, M. R., McCreary, E. K., & Pogue, J. M. (2020). That Escalated Quickly: Remdesivir's Place in Therapy for COVID-19. *Infectious Diseases and Therapy*. https://doi.org/10.1007/s40121-020-00318-1

De Buck, E., & Van de Velde, S. (2010). Towards evidence based emergency medicine: best BETs from the Manchester Royal Infirmary. BET 1. Optimal body position in oral poisoning cases. *Emergency Medicine Journal : EMJ*, *27*(12), 952–953. https://doi.org/10.1136/emj.2010.104919

Deng, L., Li, C., Zeng, Q., Liu, X., Li, X., Zhang, H., Hong, Z., & Xia, J. (2020). Arbidol combined with LPV/r versus LPV/r alone against Corona Virus Disease 2019: A retrospective cohort study. In *Journal of Infection*. https://doi.org/10.1016/j.jinf.2020.03.002

Diamond, M. S., & Pierson, T. C. (2020). The Challenges of Vaccine Development against a New Virus during a Pandemic. *Cell Host and Microbe*, *27*(5), 699–703. https://doi.org/10.1016/j.chom.2020.04.021

Doggrell, S. A. (2020). Does lopinavir measure up in the treatment of Covid-19? *Expert Opinion on Investigational Drugs*, *0*(0). https://doi.org/10.1080/13543784.2020.1777277

Eastman, R. T., Roth, J. S., Brimacombe, K. R., Simeonov, A., Shen, M., Patnaik, S., & Hall, M. D. (2020). Remdesivir: A Review of Its Discovery and Development Leading to Emergency Use Authorization for Treatment of COVID-19. *ACS Central Science*. https://doi.org/10.1021/acscentsci.0c00489

Epstein, J., & Burnouf, T. (2020). Points to consider in the preparation and transfusion of COVID-19 convalescent plasma. *Vox Sanguinis*. https://doi.org/10.1111/vox.12939

Ferner, R. E., & Aronson, J. K. (2020). Chloroquine and hydroxychloroquine in covid-19. In *The BMJ*. https://doi.org/10.1136/bmj.m1432

Fihn, S. D., Perencevich, E., & Bradley, S. M. (2020). Caution Needed on the Use of Chloroquine and Hydroxychloroquine for Coronavirus Disease 2019. *JAMA Network Open*. https://doi.org/10.1001/jamanetworkopen.2020.9035

Folegatti, P. M., Ewer, K. J., Aley, P. K., Angus, B., Becker, S., Belij-Rammerstorfer, S., Bellamy, D., Bibi, S., Bittaye, M., Clutterbuck, E. A., Dold, C., Faust, S. N., Finn, A., Flaxman, A. L., Hallis, B., Heath, P., Jenkin, D., Lazarus, R., Makinson, R., … Yau, Y. (2020). Safety and immunogenicity of the ChAdOx1 nCoV-19 vaccine against SARS-CoV-2: a preliminary report of a phase 1/2, single-blind, randomised controlled trial. *The Lancet*. https://doi.org/10.1016/S0140-6736(20)31604-4

Franchini, M. (2020). Why should we use convalescent plasma for COVID-19? *European Journal of Internal Medicine*. https://doi.org/10.1016/j.ejim.2020.05.019

Fu, B., Xu, X., & Wei, H. (2020). Why tocilizumab could be an effective treatment for severe COVID-19? In *Journal of Translational Medicine*. https://doi.org/10.1186/s12967-020-02339-3

Galanti, M., & Shaman, J. (2020). Direct observation of repeated infections with endemic coronaviruses. *MedRxiv*, 2020.04.27.20082032. https://doi.org/10.1101/2020.04.27.20082032

Gao, J., & Hu, S. (2020). Update on use of chloroquine/hydroxychloroquine to treat coronavirus disease 2019 (COVID-19). *Bioscience Trends*, 1–3. https://doi.org/10.5582/bst.2020.03072

Gautret, P., Lagier, J.-C., Parola, P., Hoang, V. T., Meddeb, L., Mailhe, M., Doudier, B., Courjon, J., Giordanengo, V., Vieira, V. E., Dupont, H. T., Honoré, S., Colson, P.,

Chabrière, E., La Scola, B., Rolain, J.-M., Brouqui, P., & Raoult, D. (2020). Hydroxychloroquine and azithromycin as a treatment of COVID-19: results of an open-label non-randomized clinical trial. *International Journal of Antimicrobial Agents*. https://doi.org/10.1016/j.ijantimicag.2020.105949

Gevers, S., Kwa, M. S. G., Wijnans, E., & van Nieuwkoop, C. (2020). Safety considerations of chloroquine and hydroxychloroquine in treatment of COVID-19. *Clinical Microbiology and Infection*. https://doi.org/10.1016/j.cmi.2020.05.006

Gilead Presents Additional Data on Investigational Antiviral Remdesivir for the Treatment of COVID-19. (n.d.).

Giurgea, L. T., Han, A., & Memoli, M. J. (2020). Universal coronavirus vaccines: the time to start is now. *Npj Vaccines*, *5*(1), 3–5. https://doi.org/10.1038/s41541-020-0198-1

Goldman, J. D., Lye, D. C. B., Hui, D. S., Marks, K. M., Bruno, R., Montejano, R., Spinner, C. D., Galli, M., Ahn, M.-Y., Nahass, R. G., Chen, Y.-S., SenGupta, D., Hyland, R. H., Osinusi, A. O., Cao, H., Blair, C., Wei, X., Gaggar, A., Brainard, D. M., … Subramanian, A. (2020). Remdesivir for 5 or 10 Days in Patients with Severe Covid-19. *New England Journal of Medicine*. https://doi.org/10.1056/nejmoa2015301

González-Gay, M. A., Mayo, J., Castañeda, S., Cifrián, J. M., & Hernández-Rodríguez, J. (2020). Tocilizumab: From the Rheumatology Practice to the Fight Against COVID-19, a virus infection with multiple faces. *Expert Opinion on Biological Therapy*. https://doi.org/10.1080/14712598.2020.1770222

Graham, B. S. (2020). Rapid COVID-19 vaccine development. *Science (New York, N.Y.)*. https://doi.org/10.1126/science.abb8923

Grein, J., Ohmagari, N., Shin, D., Diaz, G., Asperges, E., Castagna, A., Feldt, T., Green, G., Green, M. L., Lescure, F.-X., Nicastri, E., Oda, R., Yo, K., Quiros-Roldan, E., Studemeister, A., Redinski, J., Ahmed, S., Bernett, J., Chelliah, D., … Flanigan, T. (2020). Compassionate Use of Remdesivir for Patients with Severe Covid-19. *New England Journal of Medicine*. https://doi.org/10.1056/nejmoa2007016

Griffin, S. (2020). Covid-19: Lopinavir-ritonavir does not benefit hospitalised patients, UK trial finds. *BMJ*, *370*, m2650. https://doi.org/10.1136/bmj.m2650

Guan, W., Ni, Z., Hu, Y., Liang, W., Ou, C., He, J., Liu, L., Shan, H., Lei, C., Hui, D. S., Du, B., Li, L., Zeng, G., Yuen, K.-Y., Chen, R., Tang, C., Wang, T., Chen, P., Xiang, J., … Zhong, N. (2020). Clinical characteristics of 2019 novel coronavirus infection in China. *New England Journal of Medicine*. https://doi.org/10.1101/2020.02.06.20020974

Guaraldi, G., Meschiari, M., Cozzi-Lepri, A., Milic, J., Tonelli, R., Menozzi, M., Franceschini, E., Cuomo, G., Orlando, G., Borghi, V., Santoro, A., Di Gaetano, M., Puzzolante, C., Carli, F., Bedini, A., Corradi, L., Fantini, R., Castaniere, I., Tabbì, L., … Mussini, C. (2020). Tocilizumab in patients with severe COVID-19: a retrospective cohort study. *The Lancet Rheumatology*. https://doi.org/10.1016/s2665-9913(20)30173-9

Hamed, M. A. (2020). An overview on COVID-19: reality and expectation. *Bulletin of the National Research Centre*. https://doi.org/10.1186/s42269-020-00341-9

Hoffmann, M., Kleine-Weber, H., Schroeder, S., Krüger, N., Herrler, T., Erichsen, S., Schiergens, T. S., Herrler, G., Wu, N. H., Nitsche, A., Müller, M. A., Drosten, C., & Pöhlmann, S. (2020). SARS-CoV-2 Cell Entry Depends on ACE2 and TMPRSS2 and Is Blocked by a Clinically Proven Protease Inhibitor. *Cell*. https://doi.org/10.1016/j.cell.2020.02.052

Horby, P., Lim, W. S., Emberson, J., Mafham, M., Bell, J., Linsell, L., Staplin, N., Brightling, C., Ustianowski, A., Elmahi, E., Prudon, B., Green, C., Felton, T., Chadwick, D., Rege, K., Fegan, C., Chappell, L. C., Faust, S. N., Jaki, T., … Group, R. C. (2020). Effect of Dexamethasone in Hospitalized Patients with COVID-19: Preliminary Report. *MedRxiv*, 2020.06.22.20137273. https://doi.org/10.1101/2020.06.22.20137273

Hraiech, S., Bourenne, J., Kuteifan, K., Helms, J., Carvelli, J., Gainnier, M., Meziani, F., &

Papazian, L. (2020). Lack of viral clearance by the combination of hydroxychloroquine and azithromycin or lopinavir and ritonavir in SARS-CoV-2-related acute respiratory distress syndrome. *Annals of Intensive Care*, *10*(1), 4–6. https://doi.org/10.1186/s13613-020-00678-4

Huang, D., Yu, H., Wang, T., Yang, H., Yao, R., & Liang, Z. (2020). Efficacy and safety of umifenovir for coronavirus disease 2019 (COVID-19): A systematic review and meta-analysis. *Journal of Medical Virology*, *n/a*(n/a). https://doi.org/10.1002/jmv.26256

Jahanshahlu, L., & Rezaei, N. (2020). Monoclonal Antibody as a Potential Anti-COVID-19. *Biomedicine & Pharmacotherapy*, *129*(May), 110337. https://doi.org/10.1016/j.biopha.2020.110337

Jaume, M., Yip, M. S., Cheung, C. Y., Leung, H. L., Li, P. H., Kien, F., Dutry, I., Callendret, B., Escriou, N., Altmeyer, R., Nal, B., Daeron, M., Bruzzone, R., & Peiris, J. S. M. (2011). Anti-Severe Acute Respiratory Syndrome Coronavirus Spike Antibodies Trigger Infection of Human Immune Cells via a pH- and Cysteine Protease-Independent Fc R Pathway. *Journal of Virology*, *85*(20), 10582–10597. https://doi.org/10.1128/jvi.00671-11

Jiang, S., Hillyer, C., & Du, L. (2020). Neutralizing Antibodies against SARS-CoV-2 and Other Human Coronaviruses. In *Trends in Immunology*. https://doi.org/10.1016/j.it.2020.03.007

Jorgensen, S. C., Kebriaei, R., & Dresser, L. D. (2020). Remdesivir: Review of pharmacology, pre-clinical data and emerging clinical experience for COVID-19. *Pharmacotherapy*, 0–3. https://doi.org/10.1002/phar.2429

Kang, C. K., Seong, M.-W., Choi, S.-J., Kim, T. S., Choe, P. G., Song, S. H., Kim, N.-J., Park, W. B., & Oh, M.-D. (2020). In vitro activity of lopinavir/ritonavir and hydroxychloroquine against severe acute respiratory syndrome coronavirus 2 at concentrations achievable by usual doses. *The Korean Journal of Internal Medicine*. https://doi.org/10.3904/kjim.2020.157

Kang, S., Peng, W., Zhu, Y., Lu, S., Zhou, M., Lin, W., Wu, W., Huang, S., Jiang, L., Luo, X., & Deng, M. (2020). Recent progress in understanding 2019 novel coronavirus (SARS-CoV-2) associated with human respiratory disease: detection, mechanisms and treatment. *International Journal of Antimicrobial Agents*. https://doi.org/10.1016/j.ijantimicag.2020.105950

Klopfenstein, T., Zayet, S., Lohse, A., Balblanc, J.-C., Badie, J., Royer, P.-Y., Toko, L., Mezher, C., Kadiane-Oussou, N. J., Bossert, M., Bozgan, A.-M., Charpentier, A., Roux, M.-F., Contreras, R., Mazurier, I., Dussert, P., Gendrin, V., & Conrozier, T. (2020). Tocilizumab therapy reduced intensive care unit admissions and/or mortality in COVID-19 patients. *Medecine et Maladies Infectieuses*, 1–4. https://doi.org/10.1016/j.medmal.2020.05.001

Ko, W. C., Rolain, J. M., Lee, N. Y., Chen, P. L., Huang, C. T., Lee, P. I., & Hsueh, P. R. (2020). Arguments in favour of remdesivir for treating SARS-CoV-2 infections. In *International Journal of Antimicrobial Agents*. https://doi.org/10.1016/j.ijantimicag.2020.105933

Korber, B., Fischer, W. M., Gnanakaran, S., Yoon, H., Theiler, J., Abfalterer, W., Hengartner, N., Giorgi, E. E., Bhattacharya, T., Foley, B., Hastie, K. M., & Parker, D. G. (2020). Tracking changes in SARS-CoV-2 Spike: evidence that D614G increases infectivity of the COVID-19 virus. *Cell*. https://doi.org/10.1016/j.cell.2020.06.043

Kupferschmidt, K. (2020). Big studies dim hopes for hydroxychloroquine. *Science (New York, N.Y.)*, *368*(6496), 1166–1167. https://doi.org/10.1126/science.368.6496.1166

Lee, J., Shin, H. W., Lee, J. Y., Kim, J. S., Yang, J. W., Lee, K. H., Kronbichler, A., & Shin, J. Il. (2020). A comprehensive analysis of clinical trials in the COVID-19 pandemic era. *Medicina (Lithuania)*, *56*(6), 1–12. https://doi.org/10.3390/medicina56060315

Levi, M. (2020). Tocilizumab for severe COVID-19: a promising intervention affecting inflammation and coagulation. *European Journal of Internal Medicine*, *May*, 18–19. https://doi.org/10.1016/j.ejim.2020.05.018

Li, H., Yang, L., Liu, F., Ma, X., He, P., Tang, W., Tong, X., & Zuo, J. (2020). Overview of therapeutic drug research for COVID-19 in China. *Acta Pharmacologica Sinica*. https://doi.org/10.1038/s41401-020-0438-y

Liu, J., Cao, R., Xu, M., Wang, X., Zhang, H., Hu, H., Li, Y., Hu, Z., Zhong, W., & Wang, M. (2020). Hydroxychloroquine, a less toxic derivative of chloroquine, is effective in inhibiting SARS-CoV-2 infection in vitro. In *Cell Discovery*. https://doi.org/10.1038/s41421-020-0156-0

Luo, P., Liu, Y., Qiu, L., Liu, X., Liu, D., & Li, J. (2020). Tocilizumab treatment in COVID-19: A single center experience. *Journal of Medical Virology*. https://doi.org/10.1002/jmv.25801

Lv, H., Wu, N. C., & Mok, C. K. P. (2020). COVID-19 vaccines: knowing the unknown. *European Journal of Immunology*, eji.202048663. https://doi.org/10.1002/eji.202048663

Madenidou, A. V., & Bukhari, M. (2020). Real-life experience of tocilizumab use in COVID-19 patients. *Rheumatology (Oxford, England)*. https://doi.org/10.1093/rheumatology/keaa325

Magagnoli, J., Narendran, S., Pereira, F., Cummings, T., Hardin, J. W., Sutton, S. S., & Ambati, J. (2020). Outcomes of hydroxychloroquine usage in United States veterans hospitalized with Covid-19. *MedRxiv*. https://doi.org/10.1101/2020.04.16.20065920

Mantlo, E., Bukreyeva, N., Maruyama, J., Paessler, S., & Huang, C. (2020). Antiviral activities of type I interferons to SARS-CoV-2 infection. *Antiviral Research*, *179*(April), 104811. https://doi.org/10.1016/j.antiviral.2020.104811

Medicine, S. T. (n.d.). *Dexamethasone for Coronavirus Infection*. *32*.

Mégarbane, B., & Scherrmann, J.-M. (2020). Hydroxychloroquine and Azithromycin to Treat Patients With COVID-19: Both Friends and Foes? *Journal of Clinical Pharmacology*, *April*. https://doi.org/10.1002/jcph.1646

Million, M., Lagier, J.-C., Gautret, P., Colson, P., Fournier, P.-E., Amrane, S., Hocquart, M., Mailhe, M., Esteves-Vieira, V., Doudier, B., Aubry, C., Correard, F., Giraud-Gatineau, A., Roussel, Y., Berenger, C., Cassir, N., Seng, P., Zandotti, C., Dhiver, C., … Raoult, D. (2020). Full-length title: Early treatment of COVID-19 patients with hydroxychloroquine and azithromycin: A retrospective analysis of 1061 cases in Marseille, France. *Travel Medicine and Infectious Disease*, *April*, 101738. https://doi.org/10.1016/j.tmaid.2020.101738

Moiseev, S., Avdeev, S., Brovko, M., Novikov, P., & Fomin, V. (2020). Is there a future for hydroxychloroquine/chloroquine in prevention of SARS-CoV-2 infection (COVID-19)? In *Annals of the Rheumatic Diseases*. https://doi.org/10.1136/annrheumdis-2020-217570

Moreira, A. (2020). Kawasaki disease linked to COVID-19 in children. *Nature Reviews Immunology*, *20*(7), 407. https://doi.org/10.1038/s41577-020-0350-1

Morena, V., Milazzo, L., Oreni, L., Bestetti, G., Fossali, T., Bassoli, C., Torre, A., Cossu, M. V., Minari, C., Ballone, E., Perotti, A., Mileto, D., Niero, F., Merli, S., Foschi, A., Vimercati, S., Rizzardini, G., Sollima, S., Bradanini, L., … Corbellino, M. (2020). Off-label use of tocilizumab for the treatment of SARS-CoV-2 pneumonia in Milan, Italy. *European Journal of Internal Medicine*, *April*, 1–7. https://doi.org/10.1016/j.ejim.2020.05.011

Mullard, A. (2020). First antibody against COVID-19 spike protein enters phase I. *Nature Reviews Drug Discovery*. https://doi.org/10.1038/d41573-020-00108-x

New York City Health. (2020). Daily Data Summary Daily Data Summary. *NYCHEalth*, *2019*, 15233.

Nile, S. H., Nile, A., Qiu, J., Li, L., Jia, X., & Kai, G. (2020). COVID-19: Pathogenesis,

cytokine storm and therapeutic potential of interferons. In *Cytokine and Growth Factor Reviews*. https://doi.org/10.1016/j.cytogfr.2020.05.002

Nittari, G., Pallotta, G., Amenta, F., & Tayebati, S. K. (2020). Current pharmacological treatments for SARS-COV-2: A narrative review. *European Journal of Pharmacology*, *June*, 173328. https://doi.org/10.1016/j.ejphar.2020.173328

Omer, S. B., Malani, P., & Del Rio, C. (2020). The COVID-19 Pandemic in the US: A Clinical Update. In *JAMA - Journal of the American Medical Association*. https://doi.org/10.1001/jama.2020.5788

Pandey, A., Nikam, A. N., Shreya, A. B., Mutalik, S. P., Gopalan, D., Kulkarni, S., Padya, B. S., Fernandes, G., Mutalik, S., & Prassl, R. (2020a). Potential therapeutic targets for combating SARS-CoV-2: Drug repurposing, clinical trials and recent advancements. In *Life Sciences*. https://doi.org/10.1016/j.lfs.2020.117883

Pandey, A., Nikam, A. N., Shreya, A. B., Mutalik, S. P., Gopalan, D., Kulkarni, S., Padya, B. S., Fernandes, G., Mutalik, S., & Prassl, R. (2020b). Potential therapeutic targets for combating SARS-CoV-2: Drug repurposing, clinical trials and recent advancements. *Life Sciences*. https://doi.org/10.1016/j.lfs.2020.117883

Pandey, S., Yadav, B., Pandey, A., Tripathi, T., Khawary, M., Kant, S., & Tripathi, D. (2020). Lessons from SARS-CoV-2 Pandemic: Evolution, Disease Dynamics and Future. *Biology*, *9*, 141. https://doi.org/10.3390/biology9060141

Pastick, K. A., Okafor, E. C., Wang, F., Lofgren, S. M., Skipper, C. P., Nicol, M. R., Pullen, M. F., Rajasingham, R., McDonald, E. G., Lee, T. C., Schwartz, I. S., Kelly, L. E., Lother, S. A., Mitjà, O., Letang, E., Abassi, M., & Boulware, D. R. (2020). Review: Hydroxychloroquine and Chloroquine for Treatment of SARS-CoV-2 (COVID-19). *Open Forum Infectious Diseases*, *2*, 1–9. https://doi.org/10.1093/ofid/ofaa130

Patrizia, A., Pierluigi, B., de Angelis Vincenzo, Giustina, D. S., Luca, M., & Angelo, O. (2020). Position paper on the preparation of immune plasma to be used in the treatment of patients with COVID-19. *Transfusion and Apheresis Science*. https://doi.org/https://doi.org/10.1016/j.transci.2020.102817

Pawar, A. Y., Hiray, A. P., Sonawane, D. D., Bhambar, R. S., Derle, D. V., & Ahire, Y. S. (2020). Convalescent plasma: A possible treatment protocol for COVID- 19 patients suffering from diabetes or underlying liver diseases. *Diabetes and Metabolic Syndrome: Clinical Research and Reviews*, *14*(4), 665–669. https://doi.org/10.1016/j.dsx.2020.05.023

Pfizer and BioNTech's First Vaccine Candidate _ In the Pipeline. (n.d.).

Prather, K. A., Wang, C. C., & Schooley, R. T. (2020). Reducing transmission of SARS-CoV-2. *Science*. https://doi.org/10.1126/science.abc6197

Rebeaud, M. E., & Zores, F. (2020). SARS-CoV-2 and the Use of Chloroquine as an Antiviral Treatment. *Frontiers in Medicine*, *7*(April), 1–5. https://doi.org/10.3389/fmed.2020.00184

Rizzo, E. (2020). Ivermectin, antiviral properties and COVID-19: a possible new mechanism of action. *Naunyn-Schmiedeberg's Archives of Pharmacology*, 19–22. https://doi.org/10.1007/s00210-020-01902-5

Rojas-Marte, G. R., Khalid, M., Mukhtar, O., Hashmi, A. T., Waheed, M. A., Ehrlich, S., Aslam, A., Siddiqui, S., Agarwal, C., Malyshev, Y., Henriquez-Felipe, C., Sharma, D., Sharma, S., Chukwuka, N., Rodriguez, D. C., Alliu, S., Le, J., & Shani, J. (2020). Outcomes in Patients with Severe COVID-19 Disease Treated with Tocilizumab - A Case- Controlled Study. *QJM : Monthly Journal of the Association of Physicians*, *June*, 1–5. https://doi.org/10.1093/qjmed/hcaa206

Rojas, M., Rodríguez, Y., Monsalve, D. M., Acosta-Ampudia, Y., Camacho, B., Gallo, J. E., Rojas-Villarraga, A., Ramírez-Santana, C., Díaz-Coronado, J. C., Manrique, R., Mantilla, R. D., Shoenfeld, Y., & Anaya, J. M. (2020). Convalescent plasma in Covid-

19: Possible mechanisms of action. *Autoimmunity Reviews*, 102554. https://doi.org/10.1016/j.autrev.2020.102554

Rosenberg, E. S., Dufort, E. M., Udo, T., Wilberschied, L. A., Kumar, J., Tesoriero, J., Weinberg, P., Kirkwood, J., Muse, A., DeHovitz, J., Blog, D. S., Hutton, B., Holtgrave, D. R., & Zucker, H. A. (2020). Association of Treatment With Hydroxychloroquine or Azithromycin With In-Hospital Mortality in Patients With COVID-19 in New York State. *Jama*, *2019*. https://doi.org/10.1001/jama.2020.8630

Saha, A., Sharma, A. R., Bhattacharya, M., Sharma, G., Lee, S.-S., & Chakraborty, C. (2020a). Tocilizumab: A Therapeutic Option for the Treatment of Cytokine Storm Syndrome in COVID-19. *Archives of Medical Research*, 9–11. https://doi.org/10.1016/j.arcmed.2020.05.009

Saha, A., Sharma, A. R., Bhattacharya, M., Sharma, G., Lee, S. S., & Chakraborty, C. (2020b). Tocilizumab: A Therapeutic Option for the Treatment of Cytokine Storm Syndrome in COVID-19. *Archives of Medical Research*. https://doi.org/10.1016/j.arcmed.2020.05.009

Sahu, K. K., Jindal, V., Siddiqui, A. D., Cerny, J., & Gerber, J. M. (2020). Convalescent Plasma Therapy: A Passive Therapy for An Aggressive COVID-19. *Journal of Medical Virology*, 0–2. https://doi.org/10.1002/jmv.26047

Sallard, E., Lescure, F. X., Yazdanpanah, Y., Mentre, F., & Peiffer-Smadja, N. (2020). Type 1 interferons as a potential treatment against COVID-19. *Antiviral Research*, *178*(March). https://doi.org/10.1016/j.antiviral.2020.104791

Salvatori, G., Luberto, L., Maffei, M., Aurisicchio, L., Roscilli, G., Palombo, F., & Marra, E. (2020). SARS-CoV-2 SPIKE PROTEIN: an optimal immunological target for vaccines. In *Journal of translational medicine*. https://doi.org/10.1186/s12967-020-02392-y

Sarvepalli, D. (2020). Coronavirus Disease 2019: A Comprehensive Review of Etiology, Pathogenesis, Diagnosis, and Ongoing Clinical Trials. *Cureus*. https://doi.org/10.7759/cureus.8076

Schoergenhofer, C., Jilma, B., Stimpfl, T., Karolyi, M., & Zoufaly, A. (2020). Pharmacokinetics of Lopinavir and Ritonavir in Patients Hospitalized With Coronavirus Disease 2019 (COVID-19). *Annals of Internal Medicine*, *2019*(May), 2019–2020. https://doi.org/10.7326/m20-1550

Sciascia, S., Aprà, F., Baffa, A., Baldovino, S., Boaro, D., Boero, R., Bonora, S., Calcagno, A., Cecchi, I., Cinnirella, G., Converso, M., Cozzi, M., Crosasso, P., De Iaco, F., Di Perri, G., Eandi, M., Fenoglio, R., Giusti, M., Imperiale, D., … Rossi, D. (2020). Pilot prospective open, single-arm multicentre study on off-label use of tocilizumab in patients with severe COVID-19. *Clinical and Experimental Rheumatology*, 1–4. http://www.ncbi.nlm.nih.gov/pubmed/32359035

Sempowski, G. D., Saunders, K. O., Acharya, P., Wiehe, K. J., & Haynes, B. F. (2020). Pandemic Preparedness: Developing Vaccines and Therapeutic Antibodies For COVID-19. *Cell*, S0092-8674(20)30674-7. https://doi.org/10.1016/j.cell.2020.05.041

Shalhoub, S. (2020). Interferon beta-1b for COVID-19. *The Lancet*, *395*(10238), 1670–1671. https://doi.org/10.1016/S0140-6736(20)31101-6

Shang, J., Wan, Y., Luo, C., Ye, G., Geng, Q., Auerbach, A., & Li, F. (2020). Cell entry mechanisms of SARS-CoV-2. *Proceedings of the National Academy of Sciences of the United States of America*. https://doi.org/10.1073/pnas.2003138117

Sharma, A. (2020). Chloroquine paradox may cause more damage than help fight COVID-19. In *Microbes and Infection*. https://doi.org/10.1016/j.micinf.2020.04.004

Sharpe, H. R., Gilbride, C., Allen, E., Belij-Rammerstorfer, S., Bissett, C., Ewer, K., & Lambe, T. (2020). The early landscape of COVID-19 vaccine development in the UK and rest of the world. *Immunology*. https://doi.org/10.1111/imm.13222

Sharun, K., Dhama, K., Patel, S. K., Pathak, M., Tiwari, R., Singh, B. R., Sah, R., Bonilla-

Aldana, D. K., Rodriguez-Morales, A. J., & Leblebicioglu, H. (2020). Ivermectin, a new candidate therapeutic against SARS-CoV-2/COVID-19. *Annals of Clinical Microbiology and Antimicrobials*, *19*(1), 23. https://doi.org/10.1186/s12941-020-00368-w

Shi, R., Shan, C., Duan, X., Chen, Z., Liu, P., Song, J., Song, T., Bi, X., Han, C., Wu, L., Gao, G., Hu, X., Zhang, Y., Tong, Z., Huang, W., Liu, W. J., Wu, G., Zhang, B., Wang, L., … Yan, J. (2020). A human neutralizing antibody targets the receptor binding site of SARS-CoV-2. *Nature*. https://doi.org/10.1038/s41586-020-2381-y

Singh, A. K., Singh, A., Singh, R., & Misra, A. (2020). Remdesivir in COVID-19: A critical review of pharmacology, pre-clinical and clinical studies. *Diabetes and Metabolic Syndrome: Clinical Research and Reviews*, *14*(4), 641–648. https://doi.org/10.1016/j.dsx.2020.05.018

Sinha, N., & Balayla, G. (2020). Hydroxychloroquine and covid-19. In *Postgraduate Medical Journal*. https://doi.org/10.1136/postgradmedj-2020-137785

Smith, T. R. F., Patel, A., Ramos, S., Elwood, D., Zhu, X., Yan, J., Gary, E. N., Walker, S. N., Schultheis, K., Purwar, M., Xu, Z., Walters, J., Bhojnagarwala, P., Yang, M., Chokkalingam, N., Pezzoli, P., Parzych, E., Reuschel, E. L., Doan, A., … Broderick, K. E. (2020). Immunogenicity of a DNA vaccine candidate for COVID-19. *Nature Communications*, *11*(1), 2601. https://doi.org/10.1038/s41467-020-16505-0

Sun, J., He, W. T., Wang, L., Lai, A., Ji, X., Zhai, X., Li, G., Suchard, M. A., Tian, J., Zhou, J., Veit, M., & Su, S. (2020). COVID-19: Epidemiology, Evolution, and Cross-Disciplinary Perspectives. In *Trends in Molecular Medicine*. https://doi.org/10.1016/j.molmed.2020.02.008

Tai, W., He, L., Zhang, X., Pu, J., Voronin, D., Jiang, S., Zhou, Y., & Du, L. (2020). Characterization of the receptor-binding domain (RBD) of 2019 novel coronavirus: implication for development of RBD protein as a viral attachment inhibitor and vaccine. *Cellular and Molecular Immunology*. https://doi.org/10.1038/s41423-020-0400-4

Tiberghien, P., de Lambalerie, X., Morel, P., Gallian, P., Lacombe, K., & Yazdanpanah, Y. (2020). Collecting and evaluating convalescent plasma for COVID-19 treatment: why and how. *Vox Sanguinis*. https://doi.org/10.1111/vox.12926

Toniati, P., Piva, S., Cattalini, M., Garrafa, E., Regola, F., Castelli, F., Franceschini, F., Airò, P., Bazzani, C., Beindorf, E.-A., Berlendis, M., Bezzi, M., Bossini, N., Castellano, M., Cattaneo, S., Cavazzana, I., Contessi, G.-B., Crippa, M., Delbarba, A., … Latronico, N. (2020). Tocilizumab for the treatment of severe COVID-19 pneumonia with hyperinflammatory syndrome and acute respiratory failure: A single center study of 100 patients in Brescia, Italy. *Autoimmunity Reviews*, *19*(7), 102568. https://doi.org/10.1016/j.autrev.2020.102568

Touret, F., & de Lamballerie, X. (2020). Of chloroquine and COVID-19. In *Antiviral Research*. https://doi.org/10.1016/j.antiviral.2020.104762

Tselios, K., & Skendros, P. (2020). Hydroxychloroquine against COVID-19: A critical appraisal of the existing evidence. *European Journal of Rheumatology*, 4–10. https://doi.org/10.5152/eurjrheum.2020.2064

Valk, S. J., Piechotta, V., Chai, K. L., Doree, C., Monsef, I., Wood, E. M., Lamikanra, A., Kimber, C., McQuilten, Z., So-Osman, C., Estcourt, L. J., & Skoetz, N. (2020). Convalescent plasma or hyperimmune immunoglobulin for people with COVID-19: a rapid review. *The Cochrane Database of Systematic Reviews*, *5*, CD013600. https://doi.org/10.1002/14651858.CD013600

van den Broek, M. P. H., Möhlmann, J. E., Abeln, B. G. S., Liebregts, M., van Dijk, V. F., & van de Garde, E. M. W. (2020). Chloroquine-induced QTc prolongation in COVID-19 patients. *Netherlands Heart Journal*. https://doi.org/10.1007/s12471-020-01429-7

Vankadari, N. (2020). Arbidol: A potential antiviral drug for the treatment of SARS-CoV-2 by blocking the trimerization of viral spike glycoprotein ? *International Journal of*

Antimicrobial Agents, 105998. https://doi.org/https://doi.org/10.1016/j.ijantimicag.2020.105998

Venkat Kumar, G., Jeyanthi, V., & Ramakrishnan, S. (2020). A short review on antibody therapy for COVID-19. In *New Microbes and New Infections*. https://doi.org/10.1016/j.nmni.2020.100682

Walls, A. C., Park, Y. J., Tortorici, M. A., Wall, A., McGuire, A. T., & Veesler, D. (2020). Structure, Function, and Antigenicity of the SARS-CoV-2 Spike Glycoprotein. *Cell*. https://doi.org/10.1016/j.cell.2020.02.058

Wang, C., Li, W., Drabek, D., Okba, N. M. A., van Haperen, R., Osterhaus, A. D. M. E., van Kuppeveld, F. J. M., Haagmans, B. L., Grosveld, F., & Bosch, B. J. (2020). A human monoclonal antibody blocking SARS-CoV-2 infection. *Nature Communications*. https://doi.org/10.1038/s41467-020-16256-y

Wang, H., Zhang, Y., Huang, B., Deng, W., Quan, Y., Wang, W., Xu, W., Zhao, Y., Li, N., Zhang, J., Liang, H., Bao, L., Xu, Y., Ding, L., Zhou, W., Gao, H., Liu, J., Niu, P., Zhao, L., … Yang, X. (2020). Development of an Inactivated Vaccine Candidate, BBIBP-CorV, with Potent Protection against SARS-CoV-2. *Cell*. https://doi.org/https://doi.org/10.1016/j.cell.2020.06.008

Wang, X., Cao, R., Zhang, H., Liu, J., Xu, M., Hu, H., Li, Y., Zhao, L., Li, W., Sun, X., Yang, X., Shi, Z., Deng, F., Hu, Z., Zhong, W., & Wang, M. (2020). The anti-influenza virus drug, arbidol is an efficient inhibitor of SARS-CoV-2 in vitro. *Cell Discovery*, *6*(1), 4–8. https://doi.org/10.1038/s41421-020-0169-8

Wang, Y., Zhang, D., Du, G., Du, R., Zhao, J., Jin, Y., Fu, S., Gao, L., Cheng, Z., Lu, Q., Hu, Y., Luo, G., Wang, K., Lu, Y., Li, H., Wang, S., Ruan, S., Yang, C., Mei, C., … Wang, C. (2020). Remdesivir in adults with severe COVID-19: a randomised, double-blind, placebo-controlled, multicentre trial. *The Lancet*, *395*(10236), 1569–1578. https://doi.org/10.1016/S0140-6736(20)31022-9

Wu, Y., Wang, F., Shen, C., Peng, W., Li, D., Zhao, C., Li, Z., Li, S., Bi, Y., Yang, Y., Gong, Y., Xiao, H., Fan, Z., Tan, S., Wu, G., Tan, W., Lu, X., Fan, C., Wang, Q., … Liu, L. (2020). A noncompeting pair of human neutralizing antibodies block COVID-19 virus binding to its receptor ACE2. *Science*. https://doi.org/10.1126/science.abc2241

Xia, S., Liu, M., Wang, C., Xu, W., Lan, Q., Feng, S., Qi, F., Bao, L., Du, L., Liu, S., Qin, C., Sun, F., Shi, Z., Zhu, Y., Jiang, S., & Lu, L. (2020). Inhibition of SARS-CoV-2 (previously 2019-nCoV) infection by a highly potent pan-coronavirus fusion inhibitor targeting its spike protein that harbors a high capacity to mediate membrane fusion. *Cell Research*. https://doi.org/10.1038/s41422-020-0305-x

Xia, S., Yan, L., Xu, W., Agrawal, A. S., Algaissi, A., Tseng, C. T. K., Wang, Q., Du, L., Tan, W., Wilson, I. A., Jiang, S., Yang, B., & Lu, L. (2019). A pan-coronavirus fusion inhibitor targeting the HR1 domain of human coronavirus spike. *Science Advances*. https://doi.org/10.1126/sciadv.aav4580

Xia, S., Zhu, Y., Liu, M., Lan, Q., Xu, W., Wu, Y., Ying, T., Liu, S., Shi, Z., Jiang, S., & Lu, L. (2020). Fusion mechanism of 2019-nCoV and fusion inhibitors targeting HR1 domain in spike protein. In *Cellular and Molecular Immunology*. https://doi.org/10.1038/s41423-020-0374-2

Xu, P., Huang, J., Fan, Z., Huang, W., Qi, M., Lin, X., Song, W., & Yi, li. (2020). Arbidol/IFN-α2b Therapy for Patients With Corona Virus Disease 2019: A Retrospective Multicenter Cohort Study. *Microbes and Infection*. https://doi.org/https://doi.org/10.1016/j.micinf.2020.05.012

Xu, X., Han, M., Li, T., Sun, W., Wang, D., Fu, B., Zhou, Y., Zheng, X., Yang, Y., Li, X., Zhang, X., Pan, A., & Wei, H. (2020). Effective Treatment of Severe COVID-19 Patients with Tocilizumab. *ChinaXiv*.

Xu, Y. (2020). Unveiling the Origin and Transmission of 2019-nCoV. In *Trends in*

Microbiology. https://doi.org/10.1016/j.tim.2020.02.001

Yan, D., Liu, X.-Y., Zhu, Y.-N., Huang, L., Dan, B.-T., Zhang, G.-J., & Gao, Y.-H. (2020). Factors associated with prolonged viral shedding and impact of Lopinavir/Ritonavir treatment in hospitalised non-critically ill patients with SARS-CoV-2 infection. *The European Respiratory Journal*. https://doi.org/10.1183/13993003.00799-2020

Yang, K. (1996). Accepted article. *Journal of Substance Abuse Treatment*, *13*(3), 287–288. https://doi.org/10.1016/s0740-5472(96)90021-5

Yao, X., Ye, F., Zhang, M., Cui, C., Huang, B., Niu, P., Liu, X., Zhao, L., Dong, E., Song, C., Zhan, S., Lu, R., Li, H., Tan, W., & Liu, D. (2020). In Vitro Antiviral Activity and Projection of Optimized Dosing Design of Hydroxychloroquine for the Treatment of Severe Acute Respiratory Syndrome Coronavirus 2 (SARS-CoV-2). *Clinical Infectious Diseases : An Official Publication of the Infectious Diseases Society of America*. https://doi.org/10.1093/cid/ciaa237

Yu, B., Li, C., Chen, P., Zhou, N., Wang, L., Li, J., Jiang, H., & Wang, D.-W. (2020). Low dose of hydroxychloroquine reduces fatality of critically ill patients with COVID-19. *Science China Life Sciences*. https://doi.org/10.1007/s11427-020-1732-2

Yu, C., Kang, L., Chen, J., & Zang, N. (2020). Evaluation of safety, efficacy, tolerability, and treatment-related outcomes of type I interferons for Human coronaviruses (HCoVs) infection in clinical practice: An updated critical systematic review and meta-analysis. *International Immunopharmacology*, *86*(136), 106740. https://doi.org/10.1016/j.intimp.2020.106740

Yueping Li, Z. X. W. L. W. C. C. W. Y. G. X. M. J. W. Y. W. P. P. X. C. W. H. G. X. J. L. L. Z. F. H. F. L. F. Z. X. D. L. L. (2020). Efficacy and safety of lopinavir/ritonavir or arbidol in adult patients with mild/moderate COVID-19: an exploratory randomized controlled trial. *Cell Press*. https://doi.org/10.1016/j.medj.2020.04.001

Zeng, Q.-L., Yu, Z.-J., Gou, J.-J., Li, G.-M., Ma, S.-H., Zhang, G.-F., Xu, J.-H., Lin, W.-B., Cui, G.-L., Zhang, M.-M., Li, C., Wang, Z.-S., Zhang, Z.-H., & Liu, Z.-S. (2020). Effect of Convalescent Plasma Therapy on Viral Shedding and Survival in COVID-19 Patients. *The Journal of Infectious Diseases*. https://doi.org/10.1093/infdis/jiaa228

Zhang, L., Zhai, H., Ma, S., Chen, J., & Gao, Y. (2020). Efficacy of therapeutic plasma exchange in severe COVID-19 patients. *British Journal of Haematology*, *2019*, 0–2. https://doi.org/10.1111/bjh.16890

Zhang, T., Wu, Q., & Zhang, Z. (2020). Probable Pangolin Origin of SARS-CoV-2 Associated with the COVID-19 Outbreak. *Current Biology*. https://doi.org/10.1016/j.cub.2020.03.022

Zhao, Q., & He, Y. (2020). Challenges of Convalescent Plasma Therapy on COVID-19. In *Journal of Clinical Virology*. https://doi.org/10.1016/j.jcv.2020.104358

Zhou, G., & Zhao, Q. (2020). Perspectives on therapeutic neutralizing antibodies against the novel coronavirus sars-cov-2. In *International Journal of Biological Sciences*. https://doi.org/10.7150/ijbs.45123

Zhou, Q., Chen, V., Shannon, C. P., Wei, X. S., Xiang, X., Wang, X., Wang, Z. H., Tebbutt, S. J., Kollmann, T. R., & Fish, E. N. (2020). Interferon-α2b Treatment for COVID-19. *Frontiers in Immunology*, *11*(May), 1–6. https://doi.org/10.3389/fimmu.2020.01061

Zhu, F.-C., Li, Y.-H., Guan, X.-H., Hou, L.-H., Wang, W.-J., Li, J.-X., Wu, S.-P., Wang, B.-S., Wang, Z., Wang, L., Jia, S.-Y., Jiang, H.-D., Wang, L., Jiang, T., Hu, Y., Gou, J.-B., Xu, S.-B., Xu, J.-J., Wang, X.-W., … Chen, W. (2020). Safety, tolerability, and immunogenicity of a recombinant adenovirus type-5 vectored COVID-19 vaccine: a dose-escalation, open-label, non-randomised, first-in-human trial. *The Lancet*, *6736*(20), 1–10. https://doi.org/10.1016/S0140-6736(20)31208-3

Zhu, Z., Lu, Z., Xu, T., Chen, C., Yang, G., Zha, T., Lu, J., & Xue, Y. (2020). *Arbidol monotherapy is superior to lopinavir/ritonavir in treating COVID-19*.

https://doi.org/10.1016/j.jinf.2020.03.060
Zuo, Y., Liu, Y., Zhong, Q., Zhang, K., Xu, Y., & Wang, Z. (2020). Lopinavir/ritonavir and interferon combination therapy may help shorten the duration of viral shedding in patients with COVID-19: a retrospective study in two designated hospitals in Anhui, China. *Journal of Medical Virology*, *218*, 0–1. https://doi.org/10.1002/jmv.26127

https://airtable.com/shrSAi6t5WFwqo3GM/tblEzPQS5fnc0FHYR/viwJJuMA1ioIgAcPs?blocks=bipZFzhJ7wHPv7x9z&bip=full

https://www.raps.org/news-and-articles/news-articles/2020/3/covid-19-vaccine-tracker

https://de.wikipedia.org/wiki/Datei:Arbidol.svg

https://en.wikipedia.org/wiki/Ritonavir

https://en.wikipedia.org/wiki/Lopinavir

https://microbenotes.com/remdesivir/

https://www.researchgate.net/figure/Chemical-structure-of-the-macrocylic-highly-effective-antifouling-compound-ivermectin_fig2_269398772

https://en.wikipedia.org/wiki/Chloroquine

https://en.wikipedia.org/wiki/Hydroxychloroquine

https://ccforum.biomedcentral.com/articles/10.1186/s13054-020-02932-4

https://de.wikipedia.org/wiki/Datei:Dexamethasone_structure.svg

https://airtable.com/shrSAi6t5WFwqo3GM/tblEzPQS5fnc0FHYR/viwJJuMA1ioIgAcPs?blocks=bipZFzhJ7wHPv7x9z&bip=full

https://www.raps.org/news-and-articles/news-articles/2020/3/covid-19-vaccine-tracker

https://covid-19-tracker.milkeninstitute.org