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CLINICAL FINDING'S WITH REFERENCE TO COVID-19

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ABSTRACT –

There's no specific treatment for COVID-19. Antibiotics won't help because they treat bacteria, not viruses. Covid-19 created a worldwide pandemic causing millions of deaths.

Clinical findings help us understand the virus and the disease. The evidence from clinical trials gives us the information about the viral activates, which further help in research of the specific vaccine or effective drug. Clinical finding plays a key role in analysis of the disease pattern all over the world. Research units all across the world gather information based on the clinical trials conducted on specific suspects.

Corona viruses have led to two serious outbreaks:

- Middle East respiratory syndrome (MERS). About 858 people have died from MERS, which first appeared in Saudi Arabia and then in other countries in the Middle East, Africa, Asia, and Europe. In April 2014, the first American was hospitalized for MERS in Indiana, and another case was reported in Florida. Both had just returned from Saudi Arabia. In May 2015, there was an outbreak of MERS in South Korea, which was the largest outbreak outside of the Arabian Peninsula.
- Severe acute respiratory syndrome (SARS). In 2003, 774 people died from an outbreak. As of 2015, there were no further reports of cases of SARS.

INTRODUCTION

CLINICAL FINDING WITH REFERENCE TO COVID-19

COVID-19 affects different people in different ways. Most infected people will develop mild to moderate symptoms. Common symptoms, fever, tiredness, dry cough.

The 2019-nCoV infection caused clusters of severe respiratory illness similar to severe acute respiratory syndrome corona virus.

Corona viruses are enveloped non-segmented positive-sense RNA viruses belonging to the family Coronaviridae and the order Nidovirales.

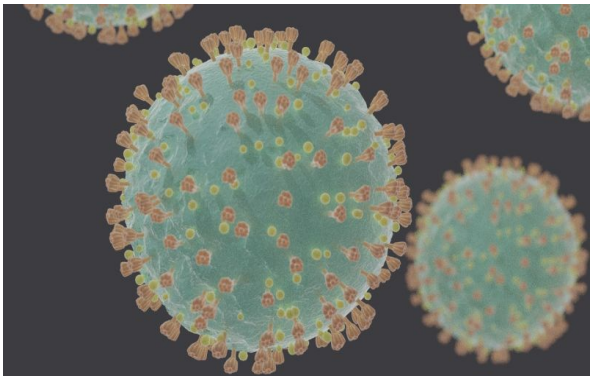
The presence of 2019-nCoV in respiratory specimens was detected by next-generation sequencing or real-time RT-PCR methods. The primers and probe target to envelope gene of CoV were used and the sequences were as follows: forward primer 5'-ACTTCTTTTTCTTGCTTTCGTGGT-3'; reverse primer 5'-GCAGCAGTACGCACACAATC-3'; and the probe 5'CY5-CTAGTTACACTAGCCATCCTTACTGC-3'BHQ1. Conditions for the amplifications were 50°C for 15 min, 95°C for 3 min, followed by 45 cycles of 95°C for 15 s and 60°C for 30 s.

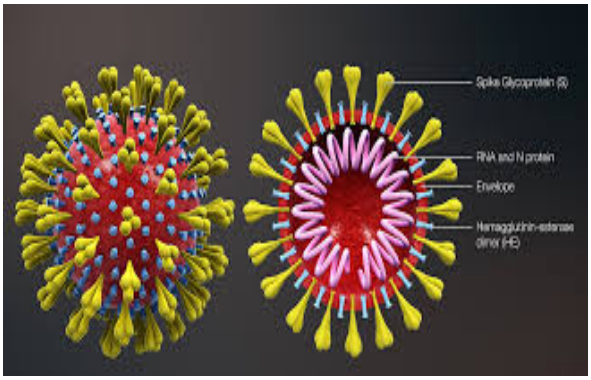
Detection of corona virus in plasma

Each 80 μL plasma sample from the

patients and contacts was added into 240 µL of Trizol LS. Total RNA was extracted by Direct-zol RNA Miniprep kit was 50 µL elution was obtained for each sample. 5 µL RNA was used for real-time RT-PCR, which targeted the *NP* gene using AgPath-ID One-Step RT-PCR Reagent.

The final reaction mix concentration of the primers was 500 nM and probe was 200 nM. Real-time RT-PCR was performed using the following conditions: 50°C for 15 min and 95°C for 3 min, 50 cycles of amplification at 95°C for 10 and 60°C for 45 s.





Virology

The full genome of SARS-CoV-2 was first posted by Chinese health authorities soon after the initial detection, facilitating viral characterization and diagnosis. The CDC analyzed the genome from the first US patient who developed the infection on January 24, 2020, concluding that the sequence is nearly identical to the sequences reported by China. SARS-CoV-2 is a group 2b beta-corona virus that has at least 70% similarity in genetic sequence to SARS-CoV' Like MERS-CoV and SARS-CoV, SARS-CoV-2 originated in bats.

CLINICAL FINGING WITH REFF. TO VIRAL CULTURE

Laboratory finding in patients with covid-19,Leukopenia, leukocytosis, and lymphopenia were common among early cases.
Lactate dehydrogenase and ferritin levels are commonly elevated. It was also reported that, among 200 patients with COVID-19 who were hospitalized, older age, neutrophilia, and elevated lactate dehydrogenase and D-dimer levels increased the risks of ARDS and death.

Clinical Progression

A retrospective, single-center study from Shanghai evaluated clinical progression of COVID-19 in 249 patients. The interval from symptom onset to hospitalization averaged 4 days (range, 2-7 days) among symptomatic patients. The vast majority (94.3%) of patients developed fever. Hospitalization lasted an average of 16 days (range, 12-20 days) before discharge. The estimated median duration of fever in all febrile patients was 10 days after symptom onset.
In 163 patients (65.7%), radiological abnormalities (compared with baseline) occurred on day 7 following symptom onset, 154 (94.5%) of whom improved radiologically by day 14.
The median duration to negative results on RT-PCT using upper respiratory tract samples was 11 days. Viral clearance was more likely to be delayed in ICU patients.
The authors concluded that most cases of COVID-19 are mild. Early viral replication control and host-directed therapy applied at later stages were essential to

improving outcomes

Global efforts toward a vaccine and treatment

Over 70 vaccine candidates or treatment for the coronavirus are in the works, according to World Health Organization. China, where the outbreak began in December, quickly shared the genetic material sequence of the coronavirus allowing research groups to begin studies.

California-based biotech firm Gilead Sciences is currently in a Phase III clinical trial to evaluate the safety and efficacy of its novel antiviral drug Remdesivir, developed originally for Ebola, in adults diagnosed with COVID-19.

Remdesivir, which works by blocking the corona virus's RNA polymerase – one of the key enzymes that this virus needs to replicate its genetic material (RNA) and proliferate in our bodies. Remdesivir works when the enzyme replicating the genetic material for a new generation of viruses accidentally grabs this nucleoside analogue rather than the natural molecule and incorporates it into the growing RNA strand. Doing this essentially blocks the rest of the RNA from being replicated; this in turn prevents the virus from multiplying.

Other vaccines in human trials

In China, the vaccines being developed are either inactivated virus or an adenovirus vector vaccine. The UK vaccine candidate at Oxford University, called Chadox1, is also an adenovirus vector vaccine. In the USA, apart from the aforementioned candidate by Pfizer, one vaccine is being developed by Moderna Inc and is an RNA vaccine while the other one is being worked on Invio Pharmaceuticals is a DNA plasmid-based vaccine.

Biotech experiments with inactivated virus

Recent report indicate that scientists around the world are currently experimenting with eight different types of possible vaccines for SARS-CoV-2 and that researchers are working on at least 90 vaccines right now.

The one that the University of Oxford researchers are trialing is protein-based. It contains an inactivated or weakened virus — in this case, an adenovirus — that acts as a "support" for the SARS-CoV-2 spike protein and should trigger a response from the immune system, "teaching" it to react to that protein.

Another type of vaccine uses inactivated versions of SARS-CoV-2 but has a similar end goal: to "teach" the immune system to identify and fight the virus.

In the preliminary study — the results of which they made available online in preprint form — the scientists tested their inactivated SARS-CoV-2 vaccine, which they call PiCoVacc, in a group of eight rhesus macaque monkeys.

This experiment followed previous tests in mice and rats. When it came to the rhesus macaques, the researchers chose them because, they say, this species can develop COVID-19-like symptoms following infection with SARS-CoV-2.

The researchers report delivering the experimental vaccine intramuscularly to the monkeys three times, in either medium (3 micrograms [mcg] per dose) or high (6 mcg per dose) doses each time.

At 7 days after infection with the virus, the rhesus macaques that had received the high doses of the vaccine showed the best results. None of these animals had a detectable viral load in their pharynx or lungs at this point.

In the race for a successful Coronavirus vaccine, a Clinical

Trial conducted by Oxford has leapt ahead

The New York Times

Most other teams have had to start with small clinical trials of a few hundred participants to demonstrate safety and schedule tests of their new coronavirus vaccine involving more than 6,000 people, hoping to show not only that it is safe but also that it works.

Scientists inoculated six rhesus macaque monkeys with single doses of the Oxford vaccine. The animals were then exposed to heavy quantities of the virus that is causing the pandemic — exposure that had consistently sickened other monkeys in the lab. But more than 28 days later all six were healthy, said Vincent Munster, the researcher who conducted the test.

"The rhesus macaque is pretty much the closest thing we have to humans," noting that scientists were still analyzing the result.

Immunity in monkeys is no guarantee that a vaccine will provide the same degree of protection for humans. A Chinese company that recently started a clinical trial with 144 participants, SinoVac, has also said that its vaccine was effective in rhesus macaques. But with dozens of efforts now underway to find a vaccine, the monkey results are the latest indication that Oxford's accelerated venture is emerging.

More than one vaccine would be needed in any case. Some may work more effectively than others in groups like children or older people, or at different costs and dosages. Having more than one variety of vaccine in production will also help avoid bottlenecks in manufacturing.

Armed with safety data from their human trials of similar vaccines for Ebola, MERS and malaria, though, the scientists at Oxford's institute persuaded British regulators to allow unusually accelerated trials while the epidemic continue.

The institute began a Phase I clinical trial involving 1,100 people. Crucially, it will also begin a combined Phase II and Phase III trial involving another 5,000. Unlike any other vaccine project now underway, that trial is designed to prove effectiveness as well as safety.

A Chinese company, CanSino, has also started clinical trials in China using a technology similar to the Oxford institute's, using a strain of the same respiratory virus that is found in humans, not chimps.

But demonstrating the effectiveness of a vaccine in China may be difficult because COVID-19 infections there have plummeted.

Researchers associated with the Chinese biotechnology company Sinovac Biotech reported having successfully inoculated rhesus macaques with inactivated SARS-CoV-2, protecting them from the new coronavirus, which could affect nonhuman primates as well as humans.

Covid-19 – LA California , A cancer therapy tool

Recent research from the University of California, Los Angeles and the Parker Institute for Cancer Immunotherapy in San Francisco, CA, also suggests that a tool that scientists use in cancer therapy could help researchers who are developing SARS-CoV-2 vaccines.

According to its authors, a computational tool designed to aid in the development of cancer vaccines could also come in handy in figuring out the best approaches to a SARS-CoV-2 vaccine.

This tool, they note, could help researchers understand more about how killer T cells — a type of white blood cell that plays a key role in the immune response — may react to SARS-CoV-2.It could do that by revealing whether or not various vaccines are likely to be effective in a diverse human population.

"T cell vaccines against SARS-CoV-2 are being developed at a rapid pace," "but it is imperative that the proteins or peptides they deliver bind to a large variety of HLA [human leukocyte antigen] haplotypes in the global population.

An individual's HLA haplotype refers to a set of genes that helps their body distinguish its own proteins from those that viruses and bacteria have made.

HLA haplotypes vary among different people, so being able to tell whether or not the proteins in a vaccine bind to a variety of these might be a good indication of whether the vaccine would be able to serve a diverse population.

Covid-19 – Australia , Antiparasitic drug shows promise

Researchers are also investing a lot of effort into trying to come up with a targeted therapy to eliminate SARS-CoV-2 in people who have already contracted the virus. Scientists have been experimenting with both new and old drugs to try to find the most promising avenues.

According to a new study published ahead of print in the journal *Antiviral Research*, ivermectin, an existing antiparasitic drug — a treatment for infestations such as those that head lice cause — shows promise as a treatment.

In laboratory experiments, infected cell cultures with SARS-CoV-2 isolates before exposing them to a dose of 5 micromoles of ivermectin.

This experiment effectively eliminated the virus from the cell cultures in a short amount of time, which led the researchers to conclude that ivermectin may deserve more attention as a potential therapeutic candidate for COVID-19 in the future.

"We found that even a single dose could essentially remove all viral RNA by 48 hours and that even at 24 hours, there was a really significant reduction in it."

– Lead researcher Kylie Wagstaff, PhD

COVID-19 Vaccine: Italy's candidate showed potential in human cells, Pfizer's candidate starts human trials

According to the World Health Organization Draft for COVID-19 vaccine candidates, this vaccine is currently in preclinical phases - but, eight others are in the human trials phase.

Pfizer, an American multinational pharmaceutical company, has started phase 1 and 2 clinical trials on their mRNA vaccine candidate today.

Takis vaccine candidate

They are working on at least four different DNA vaccines for COVID-19. A DNA vaccine contains the genetic code for specific parts of the virus against which our immune system mounts a response.

Out of the four candidates at Takis, one reportedly comprises the gene coding for the spike protein of SARS-COV-2, the causative agent of COVID-19. The spike is what determines the binding of the virus to healthy cells. The other three are DNA sequences corresponding to specific epitomes present on the virus, modified enough that they work properly as a vaccine when introduced into human cells. Epitopes are part of an antigen that is identified by our immune system. An antigen is any foreign substance against which our body makes antibodies

Pfizer's vaccine

Pfizer's reportedly injected the first-ever dose of its mRNA vaccine at the NYU Grossman School of Medicine and University of Maryland School of Medicine.

The pharma giant has about four different RNA vaccine candidates which they are now going to test in a series of human trials. According to the news released on Pfizer's website, they are going to start with 360 healthy people in the age group of 18-55 first and once this testing has shown success, more volunteers will be included in the study. For the trials, more people will soon be enrolled at the University of Rochester Medical Center/Rochester Regional Health and Cincinnati Children's Hospital Medical Center in the USA.

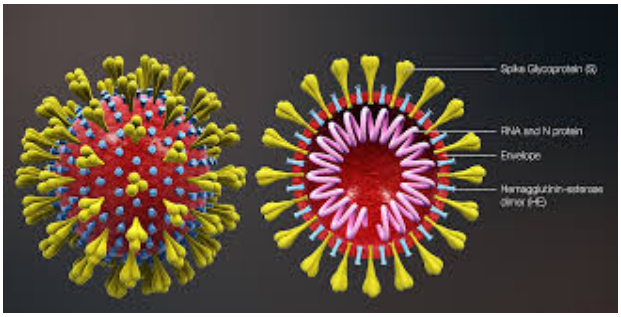
Covid-19: French researcher reports successful drug trial

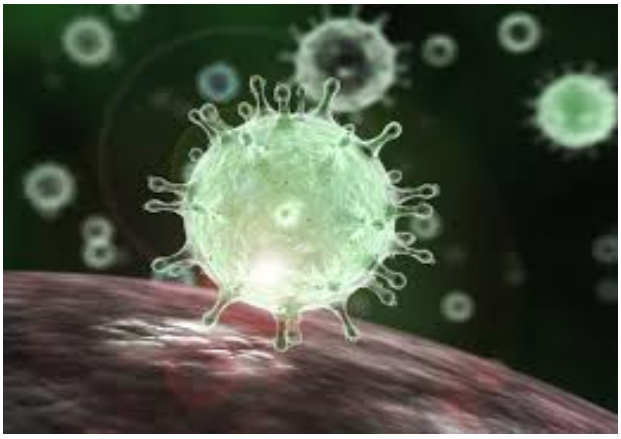
Raoult, an infectious diseases specialist, was tasked by the French government to

research possible treatment for the novel coronavirus.
According to the professor, the first Covid-19 patients he treated with drug chloroquine saw rapid and effective speeding of their healing process, and a sharp decrease in the amount of time they remained contagious.
Chloroquine -- which is normally used to prevent and treat malaria -- was administered via drug Plaquenil.

According to the media report, the treatment was offered to 24 patients, who were among the first to become infected in the southeast of France, and who had voluntarily admitted themselves to hospital for the process.
Patients were given 600mcg per day for 10 days. They were closely monitored, as the drug can interact with other medication, and cause severe side effects in some cases, it added.
"We were able to ascertain that patients who had not received Plaquenil (drug containing hydroxychloroquine) were still contagious after six days, but of those who received Plaquenil, only 25 per cent were still contagious after the given period," he added

Chloroquine phosphate and hydroxychloroquine have previously been used to treat coronavirus patients in China, in ongoing Covid-19 clinical trials.
Kaletra, a US-based antiviral drug used to treat HIV, is another medicine that is being tested in the fight against the deadly virus.





COVID-19 – ISRAEL RESEARCH

Israel develops key Covid antibody that 'attacks and neutralizes' the virus in patient's body

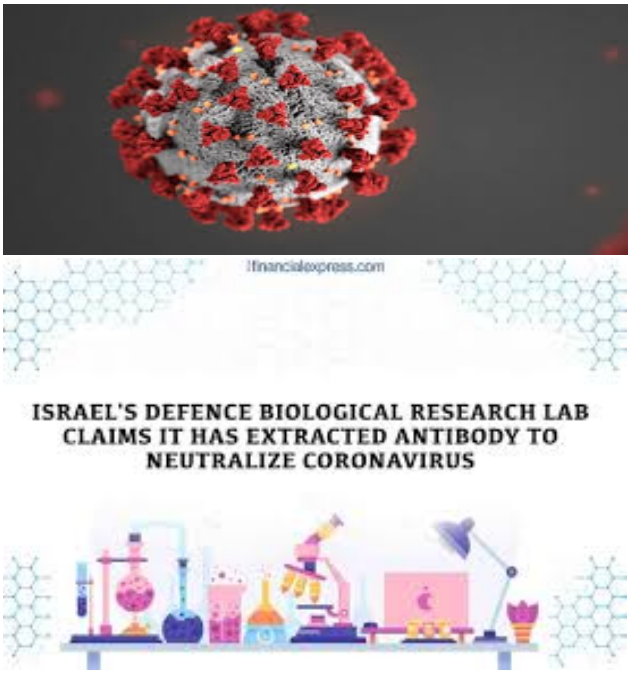
Israel Institute for Biological Research has isolated a monoclonal antibody that can neutralize Covid-19.

In an official statement, Bennet claimed that the "monoclonal neutralizing antibody" developed by the Israel Institute for Biological Research (IIBR) "attacks the virus and neutralizes it" inside the virus carrier's body.

Monoclonal antibodies, as the name suggests, are cloned from a single recovered cell. Thus, they are much easier to create and use, as opposed to

polyclonal antibodies which will have to be derived from multiple cells.

In typical antibody vaccines, neutralization occurs when the laboratory-developed antibodies mimic the body's natural immune response and attacks the virus.



Researcher says the treatment developed for birds could be applicable to humans as the genetic structure of the virus in both humans and birds is very similar

The development process, however, requires a series of tests and experiments that may last many months before the vaccination is deemed effective or safe to use.

COVID-19 – MYCOBACTRIUM w VACCINE

Trials of Mycobacterium w vaccine for coronavirus COVID-19 treatment to begin soon, says PGIMER Chandigarh

The researchers at Postgraduate Institute of Medical Education and Research (PGIMER) in Chandigarh said that the Mycobacterium w (Mw) vaccine is not a vaccine for coronavirus COVID-19 and will be used only as an adjunct

In a recently concluded multi-center trial, it was found that Mw reduces mortality in ICU patients with severe sepsis. Mw can potentially decrease the cytokine storm seen in patients with COVID-19, and may thus be of potential benefit in managing these patients and decreasing mortality. In the pre-study phase, we assessed safety of Mw in four hospitalized patients with COVID-19, and found no short-term adverse effects. The impact of Mw use on long term safety and efficacy will only be known after conclusion of this CSIR-supported clinical trial, which will be initiated soon at all three centers.

Antiviral Favipiravir Developed in Hyderabad to be tried on Covid-19 Patients

Tablets of Avigan (generic name: Favipiravir)

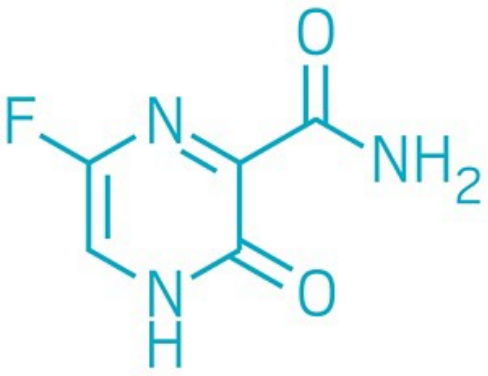
Mande said Favipiravir is used in countries such as China and Japan to treat influenza. Whenever, a virus enters a cell, it tries to create multiple replicas. Favipiravir stops the replication process, he explained.

The CSIR has already tied up with Cadila Pharmaceuticals Ltd to evaluate Mycobacterium W (Mw) for faster recovery of hospitalized COVID-19 patients and minimize the spread of

disease.
Mycobacterium W can reduce mortality of patients suffering from Gram-negative sepsis by 50 per cent. Permission has been granted by the Drug Controller of India to conduct tests on critically ill COVD -19 patients at three major hospitals in the country.

Mycobacterium W helps in boosting TH1 and TH2 cells, which in turn, builds immunity in fighting viruses and in this specific case the novel coronavirus.
"The drug has demonstrated positive outcomes, including a reduction in the duration of COVID-19 and improved lung conditions for the patients,"

Antiviral treatment favipiravir, one of many approved drugs being tested as a possible treatment for COVID-19. Phase III clinical trials are ongoing in Japan, “Avigan tablets are expected to have efficacy against infection with the new coronavirus in view of its characteristic mechanism of action.



Favipiravir

EVIDENCE SUGGESTS THAT THE BCG VACCINE MIGHT WORK AGAINST COVID -19

Dr. Thijs ten Doesschate, UMC Utrecht (BCG-CORONA): Many epidemiological studies have shown that BCG can induce a powerful protection against infectious diseases other than tuberculosis: the so-called nonspecific effects. In addition, there is clinical and experimental evidence that BCG protects against viral infections. BCG vaccination protects against respiratory syncytial virus, human papillomavirus and herpes simplex virus. After BCG vaccination, there is a lower "viral load" of the influenza A virus, leading to less inflammation and lung damage. BCG vaccination leads to fewer virus particles in the blood and a stronger immune response against viruses.

EVIDENCE THAT THE BCG VACCINE

MIGHT NOT WORK AGAINST COVID-19

Dr.Netea: In the setting of low infectious pressure, two recent studies in Denmark and Australia did not show a significant benefit of BCG vaccination in newborn children. There are no data yet on the effect of BCG vaccination on coronaviruses in general or COVID-19 in particular.

PASSIVE ANTIBODY THERAPY

An old method could fight COVID-19

Doctors may be able to use an age-old method called "passive antibody therapy" to treat COVID-19, suggests research featuring in ***The Journal of Clinical Investigation***.

The researchers who authored the paper say, "Deployment of this option requires no research or development," as the method has been around since the 1930s.

The method involves collecting blood from a person who has had the virus and recovered from it. Using the serum — the part that contains infection-fighting antibodies — researchers hope to be able to inject another person, thus either preventing an infection or helping to fight it off.

UK researchers launch trial of blood plasma therapy for Covid-19

Researchers at Guy's and St Thomas' NHS Foundation Trust in the UK have launched a clinical trial to assess blood plasma therapy for Covid-19 treatment.

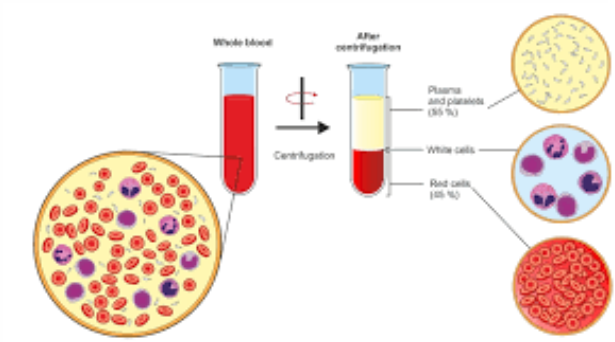
Guy's and St Thomas' is one of the first sites participating in the REMAP-CAP trial, which is assessing various therapies for severely ill patients.

The plasma therapy, called convalescent plasma treatment, requires blood plasma donations from people who have recovered from Covid-19.All the recovered patients produced the required amount of antibodies, because of good immune response and hence the antibodies can be collected from the plasma.

This plasma is administered to Covid-19 patients who could not generate sufficient antibodies against the virus.

"Convalescent plasma is a promising treatment that could help patients whose bodies aren't producing enough antibodies to curb the disease. This trial will help us understand whether the

treatment should be used more widely to treat Covid-19."



Getting the virus may protect against reinfection

A study involving four rhesus macaques found that contracting SARS-CoV-2 — the virus that causes COVID-19 — protected against future reinfections.

The scientists reinfected two of the four monkeys with the virus 28 days after the initial infection.

A total of "96 nasopharyngeal and anal swabs tested negative after the reexposure of SARS-CoV-2," report the researchers. The euthanasia and necropsy of one of the two monkeys confirmed these results.

"Taken together, our results indicated that the primary SARS-CoV-2 infection could protect from subsequent exposures, which have vital implications for vaccine design [and disease prognosis]," conclude the authors of the study.

"I can tell you, if you got [COVID-19] and you got really sick, I am sure that will make an antibody response that will also last."

– Prof. Martin Bachmann

Our immune system could defeat the virus

A new case study, appearing in the journal *Nature Medicine*, documents the case of a COVID-19 patient who recovered from the condition within days.

The patient was a 47-year-old woman who had contracted the virus in Wuhan, China, and the researchers examined her immune response in their effort to understand her recovery.

Prof. Katherine Kedzierska, Head of the Human T cell Laboratory in the Department of Microbiology and Immunology at the Doherty Institute in Melbourne, Australia, and her colleagues found an increase in immunoglobulin G — the most common type of antibody — in the woman's blood samples. Additionally, they found an increase in immunoglobulin M.

The scientists also detected a high number of key immune cells, such as specialized helper T cells, killer T cells, and B cells, 7–9 days after symptom onset.

"This is an incredible step forward in understanding what drives recovery of COVID-19. People can use our methods to understand the immune responses in larger COVID-19 cohorts and also understand what's lacking in those who have fatal outcomes."

– Prof. Katherine.

CONCLUSION –

Many clinical trials are under way to explore treatments used for other conditions that could fight COVID-19 and to develop new ones.

Several studies are focused on an antiviral medication called remdesivir, which was created to fight Ebola. An emergency FDA ruling lets doctors use it for people hospitalized with COVID-19 and in clinical trials. Researchers in the U.S. say remdesivir helped patients in one study recover from the disease 31% faster.

The FDA also issued an emergency use ruling for hydroxychloroquine and chloroquine. These medications are approved to treat malaria and autoimmune conditions like rheumatoid arthritis and lupus. Studies on their use against COVID-19 have had mixed results, and research is ongoing.

Clinical trials are also under way for tocilizumab, another medication used to treat autoimmune conditions. And the FDA is also allowing clinical trials and hospital use of blood plasma from people who've had COVID-19 and recovered to help others build immunity. You'll hear this called convalescent plasma.

University of Oxford, has shown some promising results in a small study with monkeys.

Researchers involved with the ChAdOx1 nCoV-19 trials said the vaccine had shown signs of priming the rhesus macaque monkeys' immune systems to fend off the deadly virus and showed no indications of adverse effects.

OVERVIEW

All the clinical evidences from the university forms a strong base in all criteria of disease understanding and the effect of the specific drug in animal body, which also explains the effect of the drug in human body. Clinical data also helps in measuring the effectiveness of the drug, it gives the information about the dosage which is required by the body in certain time duration. Clinical findings also help in understanding the diversity and possibility of the viral infection affecting different people differently.

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