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Review Article

Our Current Understanding of SARS-CoV-2 and Strategies for Management of COVID- 19; A Comprehensive Review

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Abstract

From past few years, the world is ravaged by a new pandemic whose magnitude of damage was never anticipated before. The pandemic, caused by a virus was first reported in Wuhan city of China. It was initially thought to be seasonal disease but was later declared a pandemic due to the damage caused worldwide. The disease caused by Severe Acute Respiratory Syndrome Coronavirus 2 (SARS-CoV-2) was christened as Coronavirus Disease 2019 COVID-19 by World Health Organisation (WHO). Coronaviruses are common in bats but can infect humans too. It hijacks the replication machinery of the human cells by attaching itself to the special receptors present on the cell surfaces like ACE-2 to gain entry into cell. It then proceeds to replicate its genetic material and ultimately increase the viral count inside the body. COVID-19 has pneumonia like symptoms. Some possible symptoms experienced are high fever, severe cough, body pain, loss of taste (ageusia) or smell capacity, sore throat. In some cases diarrhoea, skin rashes, or fingers discolouration, eyes pain or irritation, shortening in breath and acute chest pain. Scientists all around the world are engaged in devising strategies and methods to tackle the pandemic. Some possible strategies that can be or were or are employed are discussed in this review article.

Keywords: SARS-CoV-2; COVID-19 Vaccines; Drugs and Convalescent Plasma; ACE-2 Receptor; M^{pro}; RdRp

Introduction

Almost every living species, be it human, bird, plant or microorganisms (bacteria, fungi, etc.) are infected by virus at least once in a lifetime. This may occasionally trigger rare pandemic or seasonal epidemic outbreaks [1]. In previous centuries, we have already seen some diseases of the respiratory system, particularly from the Coronavirus family. The two regional epidemics we faced were- severe acute respiratory syndrome coronavirus (SARS-CoV) in the year 2001 but re-emerged in 2002 (Southern China) and Middle East respiratory syndrome coronavirus (MERS-CoV) in 2012. In 2003, due to SARS almost 774 people died, while due to MERS 858 people died between 2012 and 2019 [1]. A new virus was detected in 2019 in Wuhan city of China. The disease was designated as Novel Coronavirus Disease 2019 (COVID-19). As the virus was not seen in humans previously, hence it was termed as novel coronavirus or SARS- Cov-2. SARS-CoV-2 is a zoonotic virus that has bats as its storage houses [3].

This disease has wreaked great havoc since it started spreading. Total of 318,648,834 people got infected, with 5,518,343 of them dying as of January 16, 2022 (according to WHO Coronavirus (COVID-19) Dashboard). There is an urgent need to counter SARS-CoV-2. Vaccines and some therapeutics are being developed to fight the pandemic. On August 23, 2021, Pfizer-BioNTech was first vaccine to be granted EUA (Emergency Use Authorization) by FDA (Food and Drug Administration) for prevention of covid-19 in individuals of age 16 and above in the United States of America [4]. After that more and more vaccine candidates were being made available for use.

SARS-CoV-2 structure

There is a subfamily from which Coronavirus belongs that is Coronavirinae in the family of Coronaviridae and the subfamily contains four genera: Alphacoronavirus, Betacoronavirus, Gamma-coronavirus, and Deltacoronavirus. Coronavirus RNA is larger than any other RNA viruses and have a single-stranded RNA molecule of positive-sense (+ss RNA) and will make their negative sense inside the host cell [5]. The capsid outside the genome of virus is created by nucleocapsid protein (N) and the genome is further packed by an envelope which is composed of three structural proteins. As we know, SARS-CoV-2 belongs to Betacoronavirus genera, genome size was sequenced recently and was found that approximate genome size of SARS-CoV-2 was 29.9 kb [6].

Figure 1: Diagrammatic representation of structure of SARS-CoV-2.

The S protein enters the endoplasmic reticulum (ER) through an N-terminal signal region and is extensively N-linked glycosylated [7]. The spike-like structure is made up of homotrimers [8] of the virus-encoded S protein. Host receptor attachment is facilitated by this trimer of S glycoprotein [9]. The most prominent structural protein is the M protein (~25–30 kDa) with three transmembrane domains, which interpret shape of the viral envelope [10]. It has a short glycosylated ectodomain at the N-terminus and a significantly bigger C-terminal end domain spanning approximately 6–8 nm within the virus particle [11]. According to a research [10], the M protein usually present as a dimer and can acquire two different conformations, allowing it to persuade membrane curvature and binds to the nucleocapsid.

The spike protein of SARS-CoV-2 specifically recognises the ACE2 receptor of the host cell through RBD domain present on the spike protein. The RBD domain can be an important for targeting virus through antiviral agents and antibodies [12]. The majority of SARS-CoV-2 and ACE2 binding sites are found in receptor binding motif (RBM). RBM attaches to the ACE2's tiny lobe, present on the bottom side. RBM's surface is somewhat curved inward to accommodate ACE2 [13].

(A)

Figure 2: (A) diagram showing RBD binding domain, part of S2 subunit of the spike protein and FP (Fusion peptide) of viral particle. (B)This schematic diagram depicts the binding of SARS-CoV-2 to entry into host cells. S protein binding.

The E protein is the smallest of the main structural proteins (~8–12 kDa). This transmembrane protein has an ectodomain at the N-terminus and an end domain at the C-terminus with ion channel activity. E is extensively produced inside the infected cell during the replication cycle, but only a tiny fraction of it is integrated into the viral envelope [14]. The bulk of the protein is involved in viral assembly and budding [15]. The viral envelope is made up of M and E proteins, and the interaction between them is sufficient enough to generate and release virus-like particles (VLPs) [16]. The only protein that binds to the RNA genome is the N protein [17]. Two domains that make up the protein are: N-terminal domain (NTD) and

a C-terminal domain (CTD) [18]. According to the findings, effective RNA binding may need the participation of both of these domains. It is also involved in viral assembly and budding, which results in the production of an entire virion [19].

Figure 3: Functions of various proteins of SARS-COV-2.

SARS-CoV-2 replication is controlled by a replication system composed of multiple sub-units. Viral non-structural proteins (nsp) make up the system, with RdRp in nsp-12 serving as the complex's core. A major component of coronavirus replication/transcription is RNA- dependent RNA polymerase (RdRp), which catalyses viral RNA synthesis. RdRp is a critical antiviral therapeutic target [20].

SARS-CoV-2's main protease (M pro) is critical in facilitating viral gene replication and transcription. M pro hydrolyses the polyprotein at eleven least conserved sites [21].They are in charge of cleaving the viral polyprotein into numerous structural and non-structural proteins prior to the creation of the replication organelle, which is located near to virus assembly sites [22].

The main protease and RdRp play critical roles in replication of the virus. Spike protein is required for virus to infiltrate host cells. Consequently, the M^{pro}, s protein, and RdRp are promising therapeutic targets, suggesting possibilities of antibody, drug, and vaccine development [20].

How COVID-19 infects humans (mechanism)

Human coronavirus causes a viral infection which is contagious. It can also be spread by inhaling or ingesting virus droplets, which causes sneezing and coughing. The primary source of infection is touching the infected surface. As we know that the N protein helps the virus for its replication and hijacking the host cell. In MHV and IBV virions, the N-terminal of the N protein attaches to genomic

and sub-genomic RNAs and processes viral replication and transcription [1]. Now it becomes a significant open scientific issue for development of a therapeutic drug which can avert the interactions between N-terminal of the N-protein and single stranded positive RNA strand that will ultimately help to cease viral replication and transcription. Scientists have found that two major classes of chemicals, theophylline and pyrimidine medicines, may be potential inhibitors of RNA binding to the N terminal domain of the coronavirus N protein, opening up new paths for in vitro evaluations [23]. The SARS- CoV-2 virus's entrance, replication, and RNA packaging in the human cell have previously been characterized and displayed in the schematic below.

Figure 4: The mechanism of SARS-CoV-2 entry, replication process and RNA packing in the human cell.

Figure 5: The functional domains of S protein and organization of genomes for SARS-CoV-2 are shown schematically. The single-stranded RNA genomes of COVID-19 viral particle contain two large genes, ORF1a and ORF1b, which code for several Non-structural proteins (nsp1 to nsp16). Structural genes encode some important structural proteins like spike (S), envelope (E), membrane (M), and nucleocapsid (N). Auxiliary genes are represented by various shades of green colour. The structure of the S protein is shown beneath the genomic sequence. S1 and S2 are the two subunits that make up the S protein. The S1/S2 cleavage sites are also indicated separately. The Several domains are present in S-protein, like: the presence of cytoplasm domain (CP), fusion peptide domain (FP), heptad repeat domain (HR) is present, and receptor-binding domain (RBD), signal peptide domain (SP) is also present as well as transmembrane domain (TM) [1].

The spike (S) protein of coronavirus attaches on the surface of many human cells through angiotensin converting enzyme 2 (ACE2) receptors, present on surface of different cell like the cells of lungs having the same receptors. There are two proteases of host cell which can cleave the coronavirus S protein at the site of S1/S2 subunit border (S1/S2 site) by trypsin and furin proteases. The S2 domain (S2′ site) is cleaved at a later stage, to release the fusion peptide. The mechanism of will be activated because of this event. The angiotensin-converting enzyme 2 receptor contains the structural information (AA sequence) of the attachment region. This can be utilized to aid molecular targeting in the antibody development. This approach could create a treatment to prevent viral infection in this way. Endocytosis is the process through which a human cell ingests the virus. Once in the cytoplasm, SARS-CoV2 viral particle is thought to employ a unique three-step approaches for membrane fusion, first involves the receptor- binding and persuade changes in conformation of Spike (S) glycoprotein, proteolysis of cathepsin L (a human lysosomal proteases, encoded by CTSL gene and helps in the viral particle entry) by intracellular proteases, and endosomes membrane fusion mechanism gets activated [24]. The virus particle releases inside the cytoplasm once endosome opens, and the viral nucleocapsid (N) gets uncoated by proteasomes, which can help in degradation of exogenous proteins like the SARS viral nucleocapsid protein and can also catalyse the endogenous proteins hydrolysis [25]. An another substitute of two-step approaches has been put forward, in which the virion uses its S1 subunit for the attachment of viral particle to the receptor on the surface of target host cell, then the Spike protein is cleaved by proteases of host cell, and at the low pH through the use of S2 subunit viral fuses with the host target membrane.

[26] Finally the single stranded RNA viral genetic material, is released entirely inside the cytoplasm. The two processes of replication and transcription takes place, carried out by the mediator complex- replication and transcription complex (RTC). The non-structural proteins (Nsp) are responsible for making this complex and is encoded in the viral genome. In the infected cell's cytoplasm RTC is assumed to have given rise to double-membrane structures.

[27] To produce replicase proteins the open reading frame 1a/b (ORF 1a/b) genome is translated after the positive RNA genome.

Those proteins utilize the genome to create negative sense RNAs, which are subsequently used to create new entire genomes. The structural viral proteins M, S, and E are made in the cytoplasm, incorporated into the endoplasmic reticulum (ER), and then transported to the ER- Golgi intermediate compartment (ERGIC) [28]. Encapsidation (when viral nucleic acid is wrapped within a capsid) of replicated genomes by N protein generates nucleocapsids

in the cytoplasm, which consolidate within the ERGIC membrane to self-assemble into fresh virions. After being delivered to the cellular membranes in smooth-walled vesicles, fresh virions are discharged from infected cells by exocytosis. Meanwhile, viral production stresses the endoplasmic reticulum, and finally cell dies. On the other hand, the exact mechanism of action for novel COVID-19 is still a mystery [28].

Current strategies to protect humans against SARS-CoV-2:

Prior experience of handling other such diseases and current understanding of the SARS-CoV- 2 virus, we can surely counter it by deployment of vaccines, therapeutic drugs, and some other therapies like Convalescent plasma therapy. Under Vaccine we have main seven types of vaccines like live attenuated viral vaccines, Recombinant viral-vectored vaccines, inactivated viral vaccines, Protein/subunit vaccines, Virus-like particles, Nucleic acid-based vaccines, m- RNA vaccine. but in this mini-review article we will cover some of them like- adenovector based, inactivated viral based, protein/subunit-based, virus like particle-based, m-RNA based vaccines and how these vaccines help body to generate immunity against virus particles. Apart from vaccines, during the critical situation one we can use Convalescent plasma therapy and it is a possible substitute to treat the disease. If person ever been infected from the virus and after the treatment period of 14 days the report comes negative then that person is eligible to donate its Convalescent plasma, if the person feels healthy because the plasma will contain neutralizing antibody against virus in high amount. We can also use Drugs to stop the viral replication inside the body and the blocking the virus to attach the human cell receptors. For now, we have included three different drugs like- Remdesivir, Favipiravir, Carmofur. Though the exact treatment is not currently available, but we can try a combination of proven treatments for this disease.

Adenovector based vaccines for SARS-CoV-2

Adenovirus (Ad) is adjustable pharmaceutical vaccine delivery technology. This technology is appealing because to a number of difficulties relating to vaccination effectiveness, and manufacturing capabilities [29]. It is possible to change the genetic makeup to include a gene of interest reflecting the pathogen-specific immunogenic antigen/s, and ad biology is well understood. Even Adenovirus in wild that induce moderate symptoms in native carriers can be modified quickly so as to reduce undesirable complexities [30]. Before studying the vaccine in detail, we should understand the biology of adenoviruses.

Figure 6: Structure of adenovirus particle.

The structural properties of Ads are as following: - they are non-enveloped viruses; the symmetry of head is icosahedral, and the type of genetic material is double-stranded (ds) DNA. The diameter of a virion particle is about approximately 90–120 nm (10-9m). The genome size of Ads is in the range of 30–45 kb, and this property makes them suitable to make any biological alternation or modification. Ads belongs to the family of Adenoviridae and a DNA viruses, which are frequently very specific for species [31]. The three major capsid proteins are responsible in the formation of outer structural part of Ads virus: the first one is hexon protein, it is an important structural component helps in the formation of the body of virus; the second one is penton base, helps in the penetration function of viral particle inside the host cell; and the third one is fibre which surrounds the icosahedron because it lies at each single twelve vertices of the viral particle. There are two main components of fibre protein – the N-terminal 'stem' protein which facilitate the binding of fibre to the capsid, and the other one is C-terminal domain 'knob (CTD)', and it is a globular protein which occupies the top portion of an N- terminal protein. There are some pivotal role of structural proteins in the attachment and penetration or entry and remarkable impact on the potency in transduction of gene and in tropism quality of Ad vectors [32].

Taking an example for adenovector vaccines for COVID-19, the prime boost method is used in the Sputnik-V COVID19 vaccine, with two different HAd (Human adeno virus) vectors (HAd26 and

Figure 7: Basic framework of non-replicating Adenovector Vaccine.

HAd5) and they both expresses the spike protein in the transduced cells to cleverly overcome the impact of pre-existing immunity against HAd5 vector vaccine, due to which this technique was adopted. The Sputnik-V COVID19 vaccine's preclinical animal trials are not published yet [33]. Both the humoral and CMI (cell-mediated immunity) responses get triggered among the participants after the vaccine doses. The IgG antibody titers also increases in those COVID-19 patients who recovered from the infection. Not only the IgG but Nab (Neutralising antibody) titers also greatly increased all over the study period. In addition, certain T cell responses peaked 28 days after immunization. A total of 19,866 participants have been included in the Phase III trial, who were given two doses of the Sputnik-V vaccine or a placebo. Vaccinated individuals showed strong antibody responses, including increased NAb and S-specific CMI responses [34].

Despite of Sputnik-V there are also some other Adenovirus vector-based vaccines available, like Johnson and Johnson and AstraZeneca. All three having same antigen that is SARS CoV-2 spike protein. But they differ from each other only based on the vector which they are using to generate the immunity inside the human body, whether it is of human type or chimpanzee. That's create a difference in the protecting efficiency of the vaccines.

Figure 8: The graphic depicts the creation of the S protein in animal cells generated by an adenovector vaccination. Through the endocytosis process, an adenovector vaccine containing the entire S gene in the viral DNA, enters the cell. The capsid traffics to the nucleus after endosomal evacuation into the cytoplasm. Adenoviral DNA enters the nucleus and remains as extrachromosomal DNA and triggers the production of S-specific mRNA for further spike protein translation. Ribosomes, which are associated with the endoplasmic reticulum (ER) are responsible for the translation of S m-RNA, and after the endosomal escape into cytoplasm, the freshly generated Spike protein is transported into the lumen of this compartments. The expression of S m-RNA was shown on the plasma membrane where S protein is present, which was transported through the exocytic pathway. There is also a breakdown of intracellularly produced protein

Vaccine Name	Company/Sponsor	Vector Used	Antigen	Route	Phase	Protection Efficacy	NCT
Gam-COVID-Vac/ Sputnik-V	Gamaleya National Institute for Research in Epidemiology and Microbiology	HAd5 and HAd26	SARS-CoV-2 S protein	i.m.	I II III	91.6%	NCT04436471 NCT04640233 NCT04530396
Ad26.COV2.S	Johnson and Johnson/ Janssen	HAd26	SARS-CoV-2 S protein	i.m.	I II III	85%	NCT04509947 NCT04436276 NCT04505722

AZD1222 nCoV-19	University of Oxford/ AstraZeneca	ChAd-Y25	SARS-CoV-2 S protein	i.m.	I/II III	82%	NCT04324606 NCT04516746

Table 1: Some adenovector based COVID-19 vaccines under trials. Legend: - ChAd is chimpanzee adenovirus; HAd5 is human adenovirus type 5; HAd26 is human adenovirus type 26 and i.m is intramuscular; NCT is national clinical trial, and the S is spike protein. Courtesy: https://www.ncbi.nlm.nih.gov/pmc/articles/PMC8510854/#!po=22.1429

Inactivated viral vaccines for COVID-19

COVID-19 vaccines with beta-propiolactone inactivation have mostly been developed in China. Clinical III trials have already started for these vaccines. In the lungs of immunized and SARS-CoV-2-infected mice, these inactivated vaccines revealed zero signs of immune- pathological alterations.

The Indian Bharat Biotech had already developed inactivated SARS-CoV-2 virus-based vaccine (Covaxin) and it is the first inactivated vaccine that has already entered in the second phase trials outside of China. The animal trials revealed strong responses by the immune cells and protective efficacy, with increased SARS-CoV-2 specific IgG antibody and neutralizing antibodies (NAB), as well as reduced viral multiplication in monkeys' nasal cavity, throat portion, and lungs. Histopathological examination revealed no indication of pneumonia occurrence in the vaccinated groups, and no any severe effects were identified in animals immunized with the two-dose vaccination program [35].

Protein subunit based vaccines for SARS-COV-2

Antibody responses and $CD4^+$ T_H cells are largely induced by subunit vaccines. As a result, many of these vaccines contain full-length or parts of the SARS-CoV-2 S protein in order to elicit neutralising antibodies [36]. Proteins are ineffective immunogens as well as inefficient CD8+ T cell activators that require not only an adjuvant but also many doses Moreover, this platform is unsuited for immunisation of the respiratory mucosa. The use of unaltered alum as an adjuvant, as with attenuated viral vaccinations, distorts the immune response towards TH2 cell-like reactions [37], that is harmful to the host's defence against SARS-CoV-2 and may play a role in onset of the disease [38]. SARS-CoV-2 and SARS-CoV share a lot of commonalityin their respective B-cell and T-cell epitopes. Cross-immune responses to mutant viruses may be elicited by a vaccination targeting a conserved epitope [39]. SARS-CoV mutations mostly attacked epitopes that have been substantially expressed by MHC-I, according to an analysis of T-cell and B-cell epitopes. Zero mutations were discovered near RBD. Recombinant SARS- CoV-2 S protein is a promising vaccine contender when combined with additional epitopes [35].

SARS-CoV-2 subunit vaccine candidate from Novavax is based on Matrix-M -adjuvant recombinant protein vaccine with nanoparticle technology employing the Sf9 system, was the quickest created subunit vaccine. In non-human primate trials, it elicited significant titers of neutralising antibodies and S protein specific IgG, as well as a Th1 oriented immune response, whereas two doses of 5 g adjuvant NVX-CoV2373 provided excellent shielding, demonstrating the ability to protect people [40]. The vaccine's S protein is firmly held in the ideal prefusion shape, and each nanoparticle contains up to 14 spike proteins, according to detailed structural analysis [41].

Virus like particle based vaccines for SARS-COV-2

VLPs are particles are self-assembling particles and are composed of various structural viral proteins that are expressed together [42]. In the case of enveloped viruses like coronavirus, the VLPs develops when the structural viral proteins M, S, and E, with or without N, are simultaneously expressed in eukaryotic host cells [43]. Resulting into the production of active budding VLP from the producer eukaryotic cells. The VLP are non-infectious because they lack the infectious viral genome but structurally identical to the infectious virus. VLPs can able to bind and enter ACE2+ cells in the same way because of the presence of spike protein on the surface of virus like particles, as the parent virus have [44]. In contrast to the protein based vaccinations, the surface S protein of VLPs cross-links the B cell receptor and directly activates the B cells. Like protein based and inactivated viral vaccines, the VLP vaccines usually needed an adjuvant which helps body to generate immunity and are manage multiple times [42]. In spite of this, the technology for VLPs is well established, biology of coronavirus VLP and their safety points are now well understood. The Good Manufacturing Practice (GMP) standards for the large-scale production of VLP based vaccines is forthright [45].

mRNA based vaccines for SARS-CoV-2

Figure 9: A) Vaccine mRNA schematic illustration having a spike protein gene and a UTR gene (untranslated region, which will not be translate). B) The mRNA vaccination is responsible for the synthesis of S protein in the transduced cell. Through the process of Endocytosis, the full-length S mRNA encapsulated in a lipid nanoparticle (LNP) gets enter inside the cell, but direct fusion of lipid nanoparticle is not shown in the diagram. Ribosomes which are associated with the endoplasmic reticulum (ER) are responsible for the translation of S m-RNA, and after the endosomal escape into cytoplasm, the freshly generated Spike protein is transported into the lumen of this compartments. The expression of S m-RNA was shown on the plasma membrane where S protein is present, which was transported through the exocytic pathway. There is also a breakdown of intracellularly produced protein and enters in the Major histocompatibility complex I and II pathways (MHC) (the detailed pathways is not shown) [2].

A full-length S protein sequence with two steady proline mutations in S2 domain sequence to retain the natural prefusion structure, encoded by the nucleoside modified m-RNA and that was used in the mRNA-based vaccines. These vaccines are delivered using lipid nanoparticles. To generate efficient immune response in the body, an mRNA vaccine is delivered inside the body which contains the antigen particles. Then by using the protein translatory mechanism of the cell and then proper amount of antigen forms. Corresponding to that antigen a good amount of immune response generates by the body immunity system [46].

The Pfizer vaccine produces a full-length spike of SARS-CoV-2 that has been retain in the prefusion symmetrical arrangement. Pfizer vaccine was linked to decreased ubiquity and severity of immunity system responses, especially in older age persons. In experimental studies it was revealed on November 9, Pfizer's vaccine candidate was found to be more than 90% effective in preventing COVID19 in people without evidence of past SARSCoV2 infection in the first interim efficacy analysis of the clinical investigation of stage III [47].

Convalescent plasma therapy against SARS-CoV-2

For more than a century, there is a type of adaptive immunotherapy that has was used to prevent and cure a variety of infectious diseases i.e., convalescent plasma (CP) therapy. Patients who was once suffered from COVID-19 and then recovered after the proper treatment, having a high titer of neutralizing antibody and that makes the person eligible to donate its CP [48]. Unlike vaccines and monoclonal antibodies the Convalescent plasma therapy, requires only a small development or infrastructure, and depending only on a survivor, who are willing to donate its CP and an infrastructure for blood collection and delivery of convalescent plasma in other suffering patients. During the starting period of COVID-19 pandemic there were neither vaccines nor monoclonal antibodies available that is why Convalescent plasma was preferred flexible alternative. Convalescent plasma is also able to adapt themselves under any changes in circumstances. As it can be seen now several new variants of SARS-CoV-2, so the other immunity therapies may require redevelopment so to target the new strain of virus more specifically, but the convalescent plasma donated by recovered patient of variant SARS-CoV-2 infections can an immediately alternative flexible therapy for those patients who are diagnosed with that variant infection. There are three main fundamental principles of any passive antibody therapy to strictly become an effective therapy for any viral infection just like to effectively neutralize SARS-CoV-2 there are of three principles. The first one is that the specific antibodies must present in Convalescent plasma against the viral pathogen,

and the second one the sufficient level of anti-SARS-CoV-2 antibody should be present and the last one is that the CP should be transfused early in the disease course so to preventing the spread and occurrence of the infection [49].

Several animal research conducted concurrently with human clinical investigations during the COVID-19 pandemic indicated that convalescent plasma is effective. When administered to infected animals, convalescent sera from Syrian hamsters, exhibited significant antiviral effect [50]. Effectiveness of convalescent plasma increases if the transfusion is from the same species. This helped in improving inflammation, lung pathology and viral shedding in green monkeys infected with SARS-CoV-2 [51]. Moreover, when animals exhibiting the human ACE2 receptor were fed human convalescent plasma, they were shielded from SARS-CoV-2 infection [52]. These research show that virus-neutralizing antibodies in animal and human convalescent plasma help facilitate safeguarding against animal SARS-CoV-2 in the studied animal models.

For study purpose there were ten severe patients were enrolled, which was confirmed by a real- time viral RNA test. There was an addition treatment was given with other maximal supportive care and antiviral medications, in the additional therapy the patients were received 1 dose of 200 mL of convalescent plasma (CP) that was taken from recently survived donors with high concentration or titer of neutralizing antibody. The level of neutralising antibody increased rapidly after CP transfusion. Within three days, the clinical symptoms had greatly improved, as had the oxyhaemoglobin saturation. When compared to pretransfusion, several indicators improved, including lymphocyte counts and C-reactive protein levels. Within 7 days, varied degrees of absorption of lung lesions was seen in radiological scans. In those seven suffering patients who had previously had viremia, the viral load was undetectable following transfusion. There were no serious side effects. From this study it was founded that CP therapy was very well supported and could increase the potentially of neutralizing viremia in acute COVID-19 disease cases [48].

Anti-viral drug therapy for SARS-CoV-2

Remdesivir is an analogy to adenosine nucleotide and it a kind of prodrug (in vial). It interacts with the viral polymerase enzyme that is RNA-dependent RNA polymerase (RdRp) and block the enzyme, inhibits the RNA transcription process and ultimately viral replication can be stop. In vitro condition the Remdesivir drug was shown to be very effective against SARS-CoV-2 virus [53]. Remdesivir treatment began immediately after inoculation in a rhesus macaque model of SARS-CoV-2 infection; it was shown that people who was suffering from the disease had low level of viral particles in the lungs and less damage as compare to the control animals, after treating with the remdesivir drug [54].

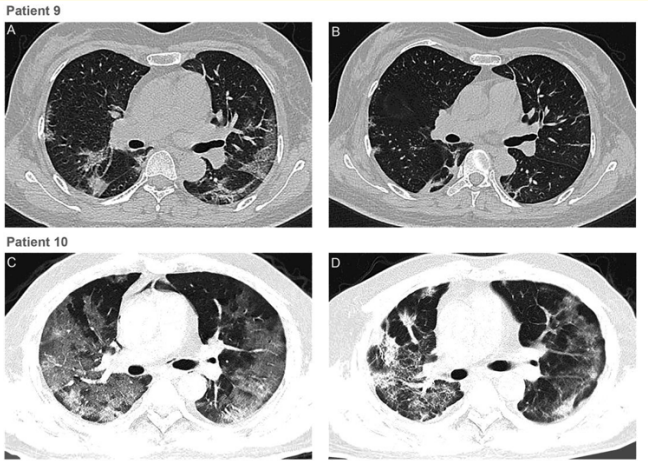

Figure 10: Chest CTs of two patients. (A) Chest CT of patient 9 obtained on [7-day post onset of illness (dpoi)]. before CP transfusion (10-dpoi) showed ground-glass opacity with uneven density involving the multi-lobal segments of both lungs. (B) CT Image of patient 9 taken (13-dpoi) showed the absorption of bilateral ground-glass opacity after CP transfusion. (C) Chest CT of patient 10 was obtained on (19-dpoi) before CP transfusion (20-dpoi). The brightness of both lungs was diffusely decreased, and multiple shadows of high density in both lungs were observed. (D) Chest CT of patient 10 on (29-dpoi) showed those lesions improved after CP transfusion.

Image courtesy: https://www.pnas.org/content/117/17/9490.

Figure 11: This schematic diagram depicts Remdesivir (pro drug) entry inside the cell, then converts into an active drug (RDT-TP), which inhibits the action of viral replication enzyme (RdRp) ultimately stopping RNA replication inside the host cell.

Conclusion

For hospitalised adults and paediatric patients (having age of 12 year and weight nearby 40 kg) an intravenous drug (Remdesivir) was approved by Food and Drug Administration (FDA) for the treatment of COVID-19. FDA also approved the remdesivir drug for the treatment of COVID-19 in hospitalised paediatric patients having weight of approximately 3.5 kg to 40 kg and age of 12 years and weight 3.5 kg [1,55-57]. Scientists suggested that according to some of the studies the remdesivir in combo with dexamethasone drug has more therapeutic advantage for SARS-CoV-2 infected patients [58,59]. Majorly, randomised experiment, remdesivir + dexamethasone was not directly compared to dexamethasone alone. It was theoretically proven in some studies that the combination therapy has an advantageous factor for some SARS-CoV-2 infected or COVID-19 patients. Some immunomodulators, like baricitinib [60] and tocilizumab was studied in the combination with Remdesivir drug [61].

It would become active in target cells after converting to the triphosphate form (RTP) [62]. Remdesivir suppresses RdRp action by covalently binding the primer strand to stop the RNA chain, similar to certain other nucleotide analogue prodrugs. The nsp12-nsp7-nsp8 complex functions as an RNA polymerase when ATP is added to it [1]. It's worth noting that the remdesivir in complex is monophosphate (RMP). A phosphate, the primer strand and three magnesium ions are all covalently bound to the RMP. The three magnesium ions are in close vicinity of active site and help to catalyse the reaction [1]. RMP and the base of the primer strand in the upstream have base-stacking interactions. RMP and the template strand's uridine base have hydrogen bonds as well [1,63].

RdRp pathway can be inhibited by the use of favipiravir just like remdesivir. Structurally, favipiravir shares similarity with endogenous guanine. Favipiravir showed few side effects in the first trials of any compound conducted against SARS-CoV-2 in China [64].

Carmofur has been authorised for usage against cancer of colon or rectum. Carmofur is modified 5-fluoroyracil (5-FU). Carmofur, an antineoplastic medication, can block the major protease (M Pro) of SARS-CoV-2. Carmofur suppresses the function of the SARS-CoV-2 main protein in vitro, most likely by causing conformational changes in M pro's catalytic residue site [65].

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