ELSEVIER

Since January 2020 Elsevier has created a COVID-19 resource centre with free information in English and Mandarin on the novel coronavirus COVID-19. The COVID-19 resource centre is hosted on Elsevier Connect, the company's public news and information website.

ELSEVIER

Review

Exploring the multifocal therapeutic approaches in COVID-19: A ray of hope

Arun Kumar [*], Asmita Deka Dey, Tapan Behl, Swati Chadha, Vishal Aggarwal

Chitkara College of Pharmacy, Chitkara University, Punjab, India

ARTICLE INFO

ABSTRACT

The ongoing global pandemic of severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2) is marked as one of the most challenging infectious diseases in the history of mankind with affliction of ~29,737,453 confirmed cases globally. Looking at the present scenario where there is a parallel increment in curve with time, there is an utmost emergency to discover a perennial solution to this life-threatening virus which has led the Human race in an unusual state of affair. The entire health care fraternity is engaged in endeavouring an ultimate way out to hit this pandemic but no such research made till now has been approved yet, to have the potential to bring an end to this fatal situation. Although a few possible treatment choices exist at the moment yet the requirement to search for a still better therapeutic option remains persistent. Global laboratories are working day and night in search for an effective vaccine, many are undergoing clinical trials but their commercialization is no less than a year away. The present review highlights the current potential therapies *viz.,* vaccines, immunotherapies, convulsant plasma therapies, corticosteroids, antithrombotic, intravenous immunoglobulins, nocturnal oxygen therapy etc. that may prove beneficial in attenuating the pandemic situation. However, comparison and presentation of collective data on the therapeutic advancements in mitigating the pandemic situation needs further clinical investigations in order to prove boon to mankind.

1. Introduction

Over the span of last 6 months, the entire world has been put on halt by a new strain of corona virus which was not seen previously in human and was termed as "Novel Corona virus-19" (nCOVID-19). The corona virus is an unsegmented, crown shaped, and positive-sense single stranded RNA virus belonging to the family *Coronaviridae* and subfamily *Coronavirinae* [1]. On the basis of distinct genetic attributes, the sub family of coronavirus is further classified into four genera namely: alpha, beta, gama, and delta coronaviruses. However, only alpha and beta genus are originated from bat and are responsible for the viral infection in human population. The virus SARS-COV-2 responsible for the current outbreak belongs to the beta genus [2]. A significant feature of the virus is its crown-like structure which comprises of the spike glycoprotein on its outer surface termed as spike protein or S protein which is further cleaved into two subunits S1 and S2 [3]. The virus binds to the host cell receptor at Receptor Binding Domain (RBD) which lies in S1 subunit, while the S2 subunit is involved in fusion of host and viral membranes, thereby leading to penetration of virus inside

the host cell [4]. An idiosyncratic feature of SARS-COV-2 is the presence of furin cleavage site at the interface of S1 and S2 subunits which promotes the insertion of O-linked Glycans to T678, S673, and S686 [5].

By means of receptor mediated endocytosis, the virus makes its way into the host cell particularly via type-2-alveolar cells [6]. Due to the existence of polybasic furin cleavage site and O-linked glycans, mutation takes place on receptor binding site of S protein and thus promote the efficacious binding of SARS-COV-2 virus to the main receptor angiotensin converting enzyme 2 (ACE2) receptor [7]. Upon binding to the specific receptor, virus initially infects the lower airway and finally activates the immune cells to secrete inflammatory cytokines and chemokines into pulmonary vascular endothelial cells leading to Cytokine Release Syndrome (CRS) [8]. Interleukin-10 (IL-10), IL-7, IL-12, Monocyte Chemotactic Protein 1 (MCP1), Tumour Necrosis Factor- α (TNF-α) and Granulocyte Colony Stimulating Factor (GCSF) are the cytokines which are produced in larger quantity as when compared with other cytokines. Several studies have reported that high levels of IL-12, IL-7, IL-10, GCSF, MIP1α and TNF-α in blood has been found in some patients admitted in intensive care unit [9,10].

The first COVID-19 case was stated in December 2019 from Wuhan, Hubei Province, China [11]. Initially five cases were reported (total of five cases and one death) with Acute Respiratory Distress Syndrome during the time span of December 18, 2019 to December 29, 2019 [12,13]. Due to high degree of infectivity of SARS-COV-2, the world witnessed an unprecedented rise in the number of infected patients, starting from a handful of cases in China to catastrophically spreading across the boundaries infecting 216 countries worldwide. As per the weekly epidemiological update, presented by World Health Organisation (WHO), a total of 29,737,453 confirmed cases and 937,391 confirmed deaths have been reported till 17 September 2020, with United States being the most affected country with a total of 6,530,324 established cases and 194,434 death cases followed by India with 5,118,523 cases and 83,198 death cases [14,15].

Looking at the current scenario where there is a parallel increment in the curve with time, there is an utmost emergency to discover a perennial solution to this life-threatening virus which has led the human race in an unusual state of affair. The entire health care fraternity is engaged in endeavouring an ultimate way out to hit this pandemic, but no such research made till now has been approved yet to have the potential to bring an end to this situation. Meanwhile the drug discovery processes are going on in full swing, a number of antecedent antiviral drugs are sent for pre-clinical and clinical trials for SARS-COV-2 treatment. According to Coronavirus Treatment Acceleration Program (CTAP) Dashboard provided by The U.S. Food and Drug Administration (FDA), a total of 590 + drug development programs are in planning stage, 310 + reviewed trials, yet no treatment is approved by FDA. However, two drugs Remdesivir and hydroxychloroquine achieved authorization for emergency use [16,17]. Remdesivir, an antiviral drug for Ebola virus has proven its ability in speeding up the recovery time in patients suffering from severe condition. However, this drug cannot be delivered in patients with severe hepatic disease and chronic renal impairment as it produces side effects like respiratory failure, hypertension, nausea, and elevation in the levels of liver enzyme [18,19]. The results of randomized, open-label, phase III clinical trials conducted for the investigational drug, Remdesivir, by Gilead Sciences, reported that the intake of the drug successfully decreased the mortality rate of hospitalized patient [20]. Apart from this, Chinese Randomized Clinical Trial (RCT) supported study, carried out by Shenzhen in February 2020 suggested that the treatment with Favipiravir developed by Toyama Chemicals, could ameliorate the symptoms in initial and early stages. However, it failed to show similar outcome in cases with high severity [21]. Chloroquine, an anti-malarial drug also reflected as one of the promising drugs in in-line treatment, but its overdose was observed to be associated with acute toxicity. The hydroxyl derivative of chloroquine, hydroxychloroquine serves its immunomodulatory action and turned out to be a better option against SARS-COV-2 with respect to safety concerns. The drug not only demonstrated the potential of decreasing elevated levels of cytokines in the serum but also inhibited the phagolysosome fusion by lowering the intracellular pH [22]. In a longitudinal study, carried out by Henry Ford Health System in Southern Michigan [23] a remarkable rise in the survival rate of hospitalized patients was observed upon administration of hydroxychloroquine alone as well as in combination with Azithromycin in the first 24–48 h of exposure towards the virus. However, the use of hydroxychloroquine combined with Azithromycin was contradicted in many reports and hence it was interpreted to use this therapy only in patients under medical aid. Though many drugs tried to prove themselves to be efficient enough but Hydroxychloroquine and Remdesivir are implied potent drug candidate employed for treatment of viral infection [24]. Scientists have also demonstrated that influenza drug EIDD-2801, acting as a prodrug of the synthetic nucleoside derivative N4-hydroxycytidine, works on the principle of imitating nucleoside and this has successfully proven to be a better therapeutic and prophylactic agent against the devastating disease [25].

Unfortunately, all these treatment approaches are only contributing scanty towards the win and further examination of the medical therapies are still a necessity. On account of major health concern, present review article mainly focuses on presenting a collective data on the advancements towards curtailment of the pandemic so that worldwide researchers get an idea of the current status which will embolden them to meet current medical needs. Here we provide an insight into the mechanism and utility of newly emerging strategies *viz.,* Vaccines, Immunotherapies, Convulsant Plasma Therapy, Corticosteroids, Antithrombotic Therapy, Intravenous immunoglobulins, Nocturnal Oxygen Therapy, Mesenchymal Stem Cell Therapy and Radiation Therapy along with the associated Clinical Trials and Patents filed worldwide.

2. Advances in COVID-19 therapies

2.1. Vaccination

Innumerable bunch of repurposed and anti-viral drugs trial against SARS-COV-2 are predicted to help control the disease yet none is able to completely eliminate the virus from the biological environment. Under such circumstances, "Vaccination" proves to be a prime solution to control any infectious disease. Clinical researchers all over the world have raced for the development of an effective and efficient vaccine and so far, a total of 170 vaccine candidates are being monitored by WHO [26]. Several research scientists suggested that the Bacillus Calmette-Guerin (BCG) vaccination exploited against tuberculosis has shown to offer a protective effect against the viral strain. Aron et al. [27] in an epidemiological study conducted lately, ascribed the nation-wise deviation in the SARS-COV-2 associated morbidity and fatality to the BCG immunisation strategy in varied countries. The survey demonstrated that the countries having appropriate BCG immunisation scheme have lower SARS-COV-2 associated mortality rate in contrast to the nations with no BCG vaccination scheme thus suggesting possible defence provided by BCG vaccination against SARS-COV-2. Additionally, a recently published study by Berg et al. [28] proposed that the BCG vaccine might likely be involved in flattening the epidemic curve and thus control the transmission of the disease. The study assessed the rate of per day rise in the number of positive reported cases in around 135 nations and also analysed the associated mortality in 134 nations during the first 30 days of time span. Kinoshita and Tanaka [29] conducted a study wherein they analysed the co-relation between the BCG vaccination and SARS-COV-2 virus in Japanese RT-PCR positive patients. They demonstrated that neonatal BCG vaccine coverage in the younger generation resulted in positive effects with defensive impact against the native SARS-COV-2 transmission in Japan. At present, 22 clinical trials are registered in "clinicaltrials.gov" with BCG vaccine and among which 12 candidates are recruited to prevent and minimize the risk of SARS-COV-2 infection in older generation and the healthcare professionals [30]. However, the safety of BCG vaccine still remains an unexplained mystery. As reported last on 12 April 2020, owing to the lack of evidence, WHO discourages the recommendation of BCG vaccination against SARS-COV-2 [31]. However, Simone et al. [32] carried out a retrospective cohort study to examine the safety profile of BCG immunisation in the SARS-COV-2 disease. They conducted a comparative analysis in three cohorts of volunteering participants, either BCG vaccinated in past 5 years or had not been vaccinated ever in their life. The survey resulted in positive outcomes and they reported that no increased risk of hospital admission was observed and thus reassuring the safety of the vaccine. The study also assured the non-involvement of BCG vaccination in the increment of cases or the severity of SARS-COV-2 viral infection in the healthy population. As of September 9, 2020, WHOs draft landscape of SARS-COV-2 candidate vaccine, reported 145 candidate vaccines under preclinical evaluation and 35 candidates under clinical evaluation among which 9 most advanced vaccines are undergoing the final phase III clinical trials. The candidate vaccines are investigated using different platforms and technologies including viral-vectored, nucleic acids (DNA and RNA), protein subunit and inactivated vaccines [26]. The mRNA-1273

candidate vaccine jointly developed by ModernaTX, Inc. and the National Institute of Allergy and Infectious Diseases (NIAID) is a lipid nanoparticle (LNP) encapsulating mRNA-based vaccine which expresses a perfusion stabilised SARS-COV-2 spike protein [33,34]. At present, the vaccination is undergoing a randomized phase III trial (NCT04470427), which began to the experimental in July 27, 2020 enrolling 30,000 participants in two cohorts with one being placebo-controlled. The individuals belonging cohort shall receive a dose of intramuscular injection (IM) (100 μg) on the first day and on the 29th day while the placebo-controlled group shall receive a dose of IM injection of placebo-matching mRNA-1273 on the first and the 29th day. The trial is focused to evaluate the immunogenicity, efficacy and the safety profile of the vaccine candidate in its route to prevention from SARS-COV-2 viral infection for a period of 2 years following the second dose of the vaccine and the study is estimated to be completed by October 27, 2020 [35,36]. Another forefront candidate in the race of vaccine development is the ChAdOx1-nCOV19 vaccine, a recombinant chimpanzee adenovirus-vectored vaccination developed by the University of Oxford, UK in collaboration with AstraZeneca. The candidate vaccine has already been reported to be capable of generating an anti-viral response in the animal model studies [37]. The ChAdOx1-nCOV19 is undergoing a randomized control Phase III clinical trial (NCT04536051) with 5000 volunteers with high risk of SARS-COV-2 exposure, enrolled in two cohorts. The study is estimated to be completed by September 2020 [38]. However, the safety of the vaccine remains a question among the health professionals as due to the occurrence of adverse effects in one of the participants the clinical trials for the vaccine was put on halt and are yet to be resumed in countries like US, India and South Africa [39].

Although the process of vaccine development is progressing in an accelerated fashion yet uncertainty prevails in the industrialisation of every new drug candidate registered for clinical trials and as per experts the estimated time is suggested to be 12–18 months [40]. However, in this regard the United States have taken a noteworthy step by initiating the Operation Warp Speed (OWS), an alliance with organisations including Department of Health and Human Services (HHS), the Food and Drug Administration (FDA), the Department of Defence (DOD), the National Institute of Health (NIH) and the Centres for Disease Control and Prevention (CDC). The chief purpose of this alliance is to expedite the examining, supplying, development and dispensing processes of effective and secure vaccine, diagnostics and therapeutics by utilising the resources of the federal jurisdiction to encounter SARS-COV-2 [41]. Moreover, the OWS has picked up the most promising counter-measure participants to provide economic and financial support along with harmonizing and accelerating their development and trial processes. Meanwhile the growth of the vaccines rises forward, the HHS-DOD alliance is establishing the foundation for dispensing, funding and logistical assistance [42]. So far, for developmental purpose, the HHS-DOD partnership has provided $456 million to Johnson & Johnson's (Janssen) vaccine candidate, $483 million to the ModernaTX's applicant vaccine, $1.2 billion to the candidate vaccine of AstraZeneca and $1.6 billion, $1.95 billion and $2 billion funds to the vaccine candidates of Novavax, Pfizer and Sanofi-GlaxoSmithKline (GSK) partnership respectively. Moreover, late in September 16, the HHS-DOD alliance revealed two documentation describing the complete strategy in detail for the delivery of safe and secure SARS-COV-2 vaccine to the natives of America as early and safely as possible [43]. With all the indeterminacies existing in terms of vaccination, the Gamaleya National Centre of Epidemiology and Microbiology developed, two adenovirus-vectored Sputnik V vaccine came as a ray of hope for the entire global health system. The phase ½ results demonstrated that the vaccine was effective in inducing a strong immune response in the 76 enrolled participants. However, in spite of the completion of phase III clinical trials the vaccine has gained approval but its safety and efficacy still remain uncertain and does have received a multitude of criticism from various organisation [44]. Table 1. shows the list of some ongoing clinical trials for SARS-COV-2.

Table 1
Ongoing Clinical Trials for SARS-COV-2 [45].

Vaccine	Country of Origin (Pharma Sponsor)	Phase of Trial	Funding
CoronaVac	Sinovac, China	Phase 3	Sinovac research and development co., Ltd
mRNA-1273	Moderna, USA	Phase 3	Operation Wrap speed; NIAID, BARDA (483 Million Dollar)
AZD1222	Oxford University; AstraZeneca; IQVIA	Phase 3	Operation Warp speed; UK Ministry of health; The University of Oxford; BARDA
BNT162	Pfizer, BioNTech	Phase3	Pfizer, BioNTech
BCG live attenuated Vaccine	University of Melbourne and Murdoch Children's Research Institute	Phase 2/3	University of Melbourne and Murdoch Children's Research Institute
Ad5-nCoV	CanSino Biologics	Phase 3	CanSino Biologics
ZYCOV-D	Zydus Cadila (India)	Phase 2	Department of Biotechnology, India
Covaxin	Bharat's BioTech; National Institute of Virology	Phase 2	Indian Council of Medical Research, India

2.2. Immunotherapy in COVID-19

Owing to the perilous threat on the world health sector by the current SARS-COV-2 pandemic, repurposing of drugs and therapies has become a mandatory field of research. The novel coronavirus imposes a major menace on the human immune system. A beneficial therapy that might have the ability to reduce the action of the virus is Immunotherapy. Immunotherapy which is an exciting area of research for cancer treatment has changed the world's perspective towards cancer cure. The therapy was first discovered by the Father of Immunotherapy, William B. Coley, back in 1890s [46]. Immunotherapy is a form of biotherapy that fights against cancer by boosting the body's own immune system to recognize, target and remove cancer cells. Besides curing cancer, immunotherapy also holds a glorious history of healing viral infections including the members of coronavirus family comprising of SARS-CoV and MERS-CoV [47]. At the moment, among the various immunotherapy proposals, Monoclonal Antibody Therapy and Vaccination are the major area of concern for treatment against SARS-COV-2. On account of its safety profile, purity, receptor specificity and diminished risk of contamination by blood-borne pathogens, Monoclonal Antibodies are preferred passive immunotherapy for the infection. With 77.5% similarity in the spike glycoproteins, the attachment of the Receptor Binding Domain (RBD) present in the S1 subunit with the ACE-2 receptor in the host cell marks the onset of the infection in both SARS-CoV and SARS-COV-2 [48-51]. The trimeric spike glycoprotein located in the viral membrane is the key target of anti-coronavirus neutralizing antibodies [52,53]. Although, the viral strains are structurally alike, the SARS-CoV specific, ACE-2 receptor targeted antibodies fails to combine with the receptors of SARS-COV-2 thereby generating an urge for further development in the therapy [54]. Monoclonal antibodies have the ability to recognise the epitopic region in S1 subunit and are aimed to cease the interaction between the RBD and ACE-2 receptor preventing the fusion of the membranes [55]. Three Human Monoclonal antibodies (HmAb) viz. B38, H4 and 47D11 showed promising outcome in neutralizing the SARS-COV-2 viral infection. 47D11 is the first SARS-COV-2 blocking HmAb designed by Wang and his co-workers [56]. With the help of ELISA (cross) reactivity, a cohort of 51 SARS-S hybridoma's extracted from immunized transgenic H2L2 mice, were assessed of antibody containing supernatants. However, ELISA cross reactivity with SARS2-S1 subunit was displayed only by four hybridoma cell line supernatants. Furthermore, one supernatant (47D11), indicated cross neutralizing activity of SARS-S and SARS2-S pseudo typed VSV infection. For further examination purpose, the human variable heavy and light chain

regions were cloned into a human IgG1 isotype backbone to reformate the chimeric 47D11 H2L2 antibody to a fully human immunoglobin. 47D11 exhibited binding properties to SARS-COV-2 and SARS-CoV thereby limiting the viral infection of vero cells. The 47D11 targeted the S1b RBD of SARS-2 and prevented the interaction between the S-Protein and ACE-2 receptor, however further investigation in this research design is essential. Moreover, on 12 March 2020, Wang and his colleagues filed a patent application on monoclonal antibodies targeting SARS-CoV 2, with results awaiting. Wu et al. [57] presented a report on the neutralizing abilities of four human origin monoclonal antibodies (B38, H4, B5 and H2), extracted from convalescent patients. With an IC_{50} value ranging from 0.177 µg/ml to 1.375 µg/ml, all the four antibodies exhibited neutralizing activities. The antibodies were designed to block the binding between the RBD and ACE-2 receptor by forming their own complexes with the S1-RBD. A competition assay using Biolayer Interferometry (BLI) and a blocking assay using Fluorescence- Activated Cell Sorting (FACS) was performed to examine the ability to block the viral interactions, wherein the results demonstrated complete competition with ACE-2 receptor by B38 and H4, partial competition by B5 while no competition by H2 antibody. The study also proposed the fact that with partial overlapping, B38 and H4 were able to recognize the different epitopes on RBD. The authors assured that this evaluation further could be helpful in the development of smaller molecules or peptide drugs and inhibitors.

Though Monoclonal Antibody therapy proves to be a promising candidate in neutralizing the viral strain, yet no antibodies have been marketed till now. Production of large-scale monoclonal antibodies is expensive, time consuming and intense thus limiting its utilization during the pandemic [58]. However, looking at the present condition with no effective therapeutic solution, the knowledge of neutralizing antibodies will provide the researchers a better outlook for vaccine development process.

Hyperbolised immune response often known as Cytokine Storm Syndrome (CSS), contributed primarily by elevated serum levels of IL-6 is a hallmark of severely ill SARS-COV-2 patients with an increasing susceptibility to death. A fetching treatment strategy for quenching the inflammatory cascade is by inhibiting or modulating the IL-6 signalling pathway to mimic the SARS-COV-2 associated inflammatory response [59]. The 2010 FDA approved IL-6 antagonist, Tocilizumab (TCZ) has been approved in the Diagnosis and Treatment protocol for Novel Coronavirus Pneumonia (Trial Version 7), (issued by: National Health Commission of china) for use in critical patients with high level of IL-6 and lesions in bilateral lungs [60]. Upon treatment with Tocilizumab, initially the IL-6 levels temporarily remain in an elevated state for next few days as the receptors are blocked by the antagonist, however with time the drug effectively manages to lower the inflammatory response. Xiaoling Xu et al. [61] proposed that Tocilizumab showed effective results in improving clinical symptoms of hypoxygenmia in a retrospective observational study of 21 severely affected SARS-COV-2 patients. Improvement in body temperature and respiratory functions were observed along with lowered oxygen intake flow. No adverse events and deaths were reported and about 90.5% patients were discharged after 13.5 days. Reports from the literature also suggested that early administration of Tocilizumab controlled the worsening of the symptoms. Perez and co-workers [62] in 2020 described an overall mortality rate of 12.9% (all at ICU) in a retrospective cohort of 306 hospitalized patient treated with TCZ. The median time for TCZ administration was 10 days after infection onset and 2 days after admission. During the evaluation, two patients were hospitalised with one in ICU, and the cumulative follow up was 83 days. No readmission and follow-up losses were reported. Alattar and his co-workers [63] presented the clinical records of 25 patients in which 36% of the cohort were successful in attaining primary outcomes, 52% were admitted still in ICU and 12% was the confirmed death rate. Capra et al. [64] published that TCZ administered patients displayed a better survival rate in a relative study between 26 standard care patients and 62 TCZ plus standard care delivered subjects.

The Italian Medicines Agency on March 19,2020 launched an independent phase II study TOCIVID-19, to estimate the potency and safety of Tocilizumab in treatment of SARS-COV-2 pneumonia. Sarilumab, with trade name Kevzara manufactured by Regeneron/ Sanofi is another IL-6 receptor antagonist undergoing a randomized, placebo-controlled phase II/III study to evaluate the efficacy of low and high dose Sarilumab in hospitalized patients with SARS-COV-2 [65]. Although IL-6 inhibitors have presented promising outcomes in increasing the survival rate of hospital aided patients yet safety risk and substantial cost limits the widespread use of Tocilizumab in the fight against SARS-COV-2 pandemic [66].

Based on all the available evidences, immunotherapy can be stated as an upcoming defence against this viral disease. Several studies have reported that combination of immunotherapy with anti-viral drugs will produce excellent outcomes with former decreasing the viral load and reducing stimulus intended for inflammatory responses and the latter improving the dysregulated inflammatory response preventing lung injury.

2.3. Convalescent plasma therapy

Convalescent plasma (CP) therapy has long been utilised effectively for treatment of multiple infectious diseases which includes the 2003 SARS-CoV-1 epidemic, 2009–2010 H1N1 influenza virus pandemic, and 2012 MERS-CoV epidemic [67-69] for which current medication has no precisely actual treatment. In the present deficiency of an exact antiviral drug and vaccination for SARS-COV-2, clinical trials have been steered and meant for exploring the therapeutic efficacy of CP in treating pandemic. Sun et al. [70] conducted a meta-analysis on 40 study reports on CP treatment for infectious diseases and reported that the approach was found to be effective in reducing the mortality risk together with rare occurrence of unfavourable effects, boost antibody production, foreshorten the course of disease and leads to a decrease in the viral load. The authors concluded that based on previous evidences of CP treatment the same might have therapeutic effect in the case of SARS-COV-2. A very newly available study by research scholars from China established the effectiveness of CP in regulating SARS-COV-2 (Table 2) [71]. The study recommended that SARS-COV-2 patients exhibited cryptograms of enhancement approximately by 1 week following CP transfusion. Abolghasemi et al. [72] reported a multicentred clinical study conducted on 189 SARS-COV-2 patients among which 115 participants were to be administered with CP and the remaining 74 were added in a control group. The results of the study stated that 98.2% of the individuals delivered with CP therapy were discharged early from the medical compared to 78.7% in the control group. A significant decrease in the duration of hospital stay was observed in the CP group (9.54 days) in contrast to the controlled group (12.88 days). In addition to this, merely 7% of the participants in CP group had the need for intubation while in the controlled group 20% of the cohort faced the requirement for intubation. Thus, this study provided a strong testification to uphold the efficaciousness of Convalescent Plasma Therapy in the treatment for SARS-COV-2 disease. The clinical efficiency, potential economic efficacy and the ease of access of CP cumulated from SARS-COV-2 patients who have the subsisted transmittable virus by building defensive antibodies are some of the advantages of CP therapy for SARS-COV-2. Given the scientific efficiency of CP, the FDA has approved clinical consent for employing CP for the treatment of critically ill SARS-COV-2 patients (FDA, 2020).

2.4. Corticosteroids therapy

On the grounds of the fact that corticosteroids are mainly responsible for the suppression of inflammation, a study was carried out in which a total of 41 patients were included, out of which 21% received corticosteroids. The initial idea of using steroids in treatment of acute respiratory distress was given by Stockman and his co-workers (through a

Table 2
Role of Convalescent plasma in patients with respiratory infection by coronavirus (SARS, MERS, and SARS-COV-2).

Viral Etiology	Patient Condition Case Design	No of individuals	Interventions	Outcomes	Reference
SARS-COV2	Critically ill Case Series	5	200 ml was transfused twice, for a time period of 10–22 days	In 4/5 patients, body temperature gets normalized. Increase in PAO2/FIO2 and decrease in SOFA score was observed within 12 days.	[73]
SARS-COV2	Severely ill Case Series	10	200 ml was transfused, for a time median of 16.5 days	Reduction in viral load and inflammation was observed and breathing was improved	[74]
SARS-COV2	Case Series	4	In one or two successive transfusions, 200–400 ml of volume was transfused. A total of 2400 ml provided by dividing the volume in eight consecutive transfusions.	Clinical improvement and discharged from hospital.	[75]
SARS-COV2	Case Series	5	200–250 mL of Convalescent plasma was transfused in two successive transfusions, then Single dose of 200 ml was transfused	Decreased viral load and improvement in antibodies.	[73]
SARS-COV2	Clinical trail	19	Single dose of 200 ml of Convalescent plasma was transfused	Reduction of viral load and improvement in lungs function.	[76]
SARS-COV2	Case Series	6	200–250 mL of Convalescent plasma was transfused in two successive transfusions	IgG and IgM antibodies increased and Suppression in viral load was observed.	[77]
SARS-COV2	Case report	2	Unknown	IgG and IgM antibodies increased and Suppression in viral load was observed.	[78]
SARS-COV2	Critically ill Case Series	4	200–2400 ml was transfused in 1–8 transfusions for an average of 15.5 days	All four patients were well again and discharged from hospital.	[79]
SARS-COV1	Stable Case Report	1	200 ml was transfused twice, for a time period of 14–16 days	Unremarkable recovery	[67]
SARS-COV1	Progressive disease, Retrospective non-randomized comparison	40 (19 CP)	200–400 ml was transfused, for average time period of 11.4 days.	Fast recovery in those patients infused with CP than patients who received continued methyl prednisone (non-CP)	[80]
SARS-COV1	Severely Ill Case Series	3	500 ml was transfused, for average time period of 10.5 days.	Progression have seen in infected healthcare worker and had failed to show recovery with available treatments.	[81]
SARS-COV1	Case Series	80	An average of 279.3 ml was transfused, for a time range of 7–30 days	By 22nd day, highest discharged rate was observed in patients who received CP before 14th day. Patient stay long in hospital who received CP after 14th day	[82]
SARS-COV1	Retrospective comparison of case	19	200–400 ml was transfused, for 11 days and 42 after onset of symptoms	Adverse events are recorded and long stay in hospital was observed.	[80]
SARS-COV1	Case series	80	279 ml of CP was transfused per day 14	Long stay in hospital was observed and mortality rate is more.	[82]
SARS-COV1	Case series	40	Unknown Dose of CP	Mortality	[83]
SARS-COV1	Case series	3	Unknown Dose of CP	Adverse events were recorded, viral load increased, mortality	[84]
SARS-COV1	Case series	1	50 mL of CP single dose was infused on day 17 of onset of symptoms.	Long stay in hospital was observed and mortality rate is more.	[85]
SARS-COV1	Case report	1	CP 250 mL of CP, 2 doses was transfused on day 7 on the onset of symptoms.	Mortality	[86]
SARS-COV1	Case report	1	200 ml of CP was infused on day 14 on onset of symptoms	Mortality	[67]
MERS-COV	Case Series	3	Dose of Cp was unspecified.	Antibodies was produced.	[87]
MERS-COV	Case Report	1	250 ml was transfused, for time period of 19 days	Respiratory distress was observed within 2 hours of transfusion.	[88]
MERS-COV	Case Series	3	CP was transfused, for a time period of 8–18 days	Neutralization in antibody activity was observed in 2/3 patients.	[87]

meta-analysis; where he carried out the effect of steroids in patients of SARS-COV-1). The observations showed that corticosteroid therapy is associated with majority of side effects as it delays the viral clearance, can be responsible for diabetes, psychosis and avascular necrosis [89]. Corticosteroids are used for the treatment of sepsis and ARDS. Despite of their history, the effectiveness and safety of corticosteroids is still controversial. Numerous clinical trials along with meta-analysis have shown that corticosteroids are linked with increased mortality and is employed in conditions where hospitalization for longer period is required (as in SARS, MERS). The associated adverse effects are due to suppression of host immune responses. Various studies demonstrate that corticosteroids are associated with some beneficial effect in viral-associated infections (mainly in critical or serious cases). A retrospective study carried out on 401 patients showed that corticosteroids are associated with reduced cases of fatality and shortens hospital stay. Higher doses are linked with numerous adverse effects such as delayed viral clearance, secondary infections as well as emergence of viral

resistance. As per the guidelines provided by Diagnosis and Treatment of COVID-19 (7th edition), China (NHPFC, 2020), lower and moderate quantity of corticosteroids results in therapeutic effect for a critically ill patient with COVID-19 pneumonia [90].

The preliminary data obtained through retrospective cohort study that was carried out in China reported that 48% of patients died who were given corticosteroids as therapy whereas the other 23% patients survived who were given other therapies. On the basis of this evidence, World Health Organisation (WHO) restricted the use of corticosteroid treatment against SARS-COV-2 but can be used only if indicated (intended for other indications). Corticosteroids are responsible for suppressing lung inflammation. The dose of methylprednisolone (that was administered) was based on the severity of disease. The guidance provided by WHO suggests that corticosteroids should only be administered only when advised to do so. The clinical outcomes do not support the use of corticosteroids during corona virus infection. A retrospective study was carried out with 309 adults suffering from MERS, who were

allowed to administer corticosteroids. From the observational studies, it can be concluded that patients administered with corticosteroids requires vasopressors, ventilation therapy as well as renal replacement therapy. There is no such distinctive reason which can be employed for the implication of corticosteroids in patients with SARS-COV-2 [89,91,92]. The various corticosteroids that are prescribed are mentioned in Table 3.

In a study conducted by Xiaofan Lu [91], the role of corticosteroids (as adjuvant therapy) was observed in serious ill patients (suffering from SARS-COV-2). The study was conducted on the patients with coronavirus disease, as at chronic stages it can lead to the development of pneumonia which on further leads to the development of Acute Respiratory Distress Syndrome (ARDS). Along with this, multiple organ dysfunction can be observed leading to high mortality rates. In such conditions, corticosteroids are employed as adjuvant therapies. The study was carried out on 244 patients (critically suffering from SARS-COV-2), all of them were administered antiviral drugs (lopinavir/ritonavir, ganciclovir, oseltamivir, arbidol etc.). Amongst these 244 patients, 151 patients were supplemented with adjuvant corticosteroid treatment (hydrocortisone in 200 mg/day). This investigation warrants the limited use of corticosteroid therapy in severely afflicted patients with SARS-COV-2. Along with this proper caution must be taken in consideration and prudent dosage must be given only under specific condition. Another study carried out by Lei Zha and his co-workers [89] aimed at evaluating the efficacy of corticosteroids in patients suffering from SARS-COV-2. In their study SARS-COV-2-designed hospitals (WUHU) were chosen and 11 patients out of 31 (infected with SARS-COV-2) received corticosteroids as treatment therapy. The observations clearly reported that no as such association was there between viral clearance time and corticosteroid (as carried out through COX proportional hazards regression analysis). Thus, through this, it can be evaluated that no association is there between corticosteroid therapy and SARS-COV-2.

2.5. Anti-thrombotic therapy

The initial phase of SARS-COV-2 is marked with sustained high fever and cough for a time span of 8 days. After 8 days, about 20% of the patients develop dyspnoea along with pulmonary infiltrates (in 10% of patients) and around 1/4th of the patients is at a critical ill stage (admitted to hospital and suffering from ARDS) after 10 days from onset of symptoms. The common laboratory-based problem comprises of lymphopenia, elevated levels of lactate dehydrogenase and higher amount of D-dimer, ferritin, C-reactive protein as well as IL-6. IL-6 is

related with pro-coagulant profile as well as with the severity of the disease. The lungs get affected at the initial stage which is supported by autopsy reports. This ARDS further propensities to severe complicated form known as Severe Acute Respiratory Syndrome Coronavirus 2 (SARS-COV-2), in which patients require medical assistance (including Intensive Care Units/ICU or mechanical ventilation) for its treatment. The reason for the assistance is not only lung damage but it also damages other vital organs such as heart and kidney [95,96]. The above findings support that SARS-COV-2 is multi-organ disease that acts via different mechanism; such as systemic inflammation that cause organ failure. This can further be described by the fact that hospitalized patients for SARS-COV-2 comprises of complicated and complex pneumonia; which can further lead to systemic inflammation as well as thrombotic events like ischemic stroke and myocardial infraction. From studies it can be reported that patients with pneumonia showed changes in platelet activation as well as clotting. This occurs during initial phase of disease and further leads to precipitation of systemic or local thrombosis. Although it is not clear, that whether this thrombosis is linked with lungs, kidney or coronary circulation. Numerous studies have reported the behaviour of clotting as well as platelet count in hyper-coagulation state. Laboratory test carried out for measuring the clotting activity includes Prothrombin Time (PT) and Activated Partial Thromboplastin Time (APTT); along with this whole blood viscoelastic analysis can be carried out through the implication of Thermoelectrometry (ROTEM) and Thromboelastography (TEG) [96,97].

2.5.1. General consideration for COVID-19 and thrombotic disease

Numerous investigational agents are evaluated for its management and implication in SARS-COV-2 pandemic; mainly for the patients with severe disease. Table 4 shows the various drugs employed in SARS-COV-2 can have interaction with anti-coagulant or antiplatelet agents and are associated with risk in some cases while beneficial in other cases. For instance, bevacizumab acts as a monoclonal antibody which binds with vascular endothelial growth factor and observations show that it is connected to amplified risk of cardiovascular events (myocardial infraction, venous thromboembolism and cerebrovascular accidents). Another can be hydroxychloroquine (Emergency used Authorized Drug from U.S. Food and Drug Administration) required for SARS-COV-2 treatment exerts antithrombotic effect against the anti-phospholipid antibodies. Patients admitted in ICU with lower risk of bleeding should be administered low intensity pharmacological prophylaxis comprising of low-molecular weight heparin (dalteparin 5000 IU/day OR nadroparin 65 IU/kg/ day, OR enoxaparin 40 mg/day) along with low-dose unfractionated heparin (5000 units two times a day) mainly

Table 3
Clinical status of corticosteroid therapy for the management of SARS-COV-2.

Clinical Trial No.	Aim	Dose for Group No. I	Dose for Group no. II	No. of patients	Indicator	Reference
ChiCTR2000030481	The clinical value of corticosteroid therapy timing in the treatment of novel coronavirus pneumonia (COVID-19): a prospective randomized controlled trial	Early corticosteroid intervention was provided.	Late corticosteroid intervention was administered.	75	Time of duration of COVID-19 nucleic acid RT-PCR test results of respiratory specimens change to negative.	[91,92]
NCT0424459	The efficacy of different hormone doses in 2019-nCoV severe pneumonia	Methylprednisolone was administered intravenously (duration: 7 days; dose: 40 mg/d	Methylprednisolone was administered through *IV* drip (dose: 40–80 mg/d; duration: 7 days)	–	Rate of initiation of critical stage and disease remission	[92]
ChiCTR2000029386	Effectiveness of glucocorticoid therapy in patients with severe novel coronavirus pneumonia: a randomized controlled trial	Intravenous injection of methylprednisolone (Dosage: 1–2 mg/kg for 3 days)	No glucocorticoid therapy was administered	24	SOFA score	[93]
ChiCTR2000029656	A randomized, open-label study to evaluate the efficacy and safety of low-dose corticosteroids in hospitalized patients with novel coronavirus pneumonia (COVID-19)	Standard treatment along with methylprednisolone through injection	Standard treatment without methylprednisolone	50 patients	Chest imaging, complication	[94]

Table 4

Various drugs employed for SARS-COV-2 can have possible interaction with anti-coagulant or antiplatelet agents and associated risk factors.

Interaction between therapies in COVID-19 and anti-coagulant agent						
Therapies	Vitamin K Antagonists	Dabigatran	Apixaban	Betrixaban	Edoxaban	Rivaroxaban
Tocilizumab	No interaction	No interaction	Increased expression of enzyme 3A4	No interaction	No interaction	Leads to increased expression of 3A4
Lopinavir/ritonavir	It causes induction of CYP2C9 which leads to decrease concentration of plasma concentration. Dosage adjustment required.	Causes inhibition of P-gp which increases the plasma concentration.	Causes inhibition of CYP3A4 and P-gp inhibition	Inhibition of P-gp and ABCB1 and thus increased dose concentration. Dose should be decreased to 80 mg once followed by 40 mg once daily	Inhibition of P-gp inhibition.	Should not be co-administered as it causes inhibition of CYP3A4 and P-gp
Methylprednisolone	No interaction	No interaction	No interaction	No interaction	No interaction	No interaction
Interferon	Mechanism for specific interaction is not elucidated yet.	No interaction	No interaction	No interaction	No interaction	No interaction
Hydroxychloroquine and Chloroquine	No interaction	No interaction	No interaction	No interaction	No interaction	No interaction
Sarilumab	No interaction	No interaction	Reported increase in the expression of CYP3A4	No interaction	No interaction	Reported increase in expression of CYP3A4.

intended for preventing venous thromboembolism. Various drugs employed for the treatment of SARS-COV-2 can interact with oral anti-platelet agents. For instance, protease inhibitors Lopinavir/ ritonavir which can inhibit metabolism of CYP3A4, which can cause metabolism of clopidogrel and thus it reduces effective dosage of clopidogrel. Such interactions can cause problem and thus the drug selected should go through an alternative pathway. For example: Prasugrel, does not undergo any such interaction and should be used only when recommended. The employed drugs can also interact with anti-coagulants, for instance: Lopinavir/ Ritonavir can affect the dosage of numerous anticoagulants. Vitamin K antagonist such as Betrixaban, Apixaban should not be co-administered with Ritonavir/ Lopinavir as it interferes with its dosage amount [97-99].

Heparin acts as a glycosaminoglycan that prevents the clot formation and resolves the clots present inside blood. It binds and activates enzyme inhibitor antithrombin III (AT). This activated AT inactivates thrombin, proteases as well as Factor Xa thereby inhibiting coagulation. The presence of heavy molecular chain makes it safer for its usage during breastfeeding and whole pregnancy. The major side effects related are heparin-induced thrombocytopenia and osteoporosis. The effect of anticoagulant heparin was investigated by Tang et al. in patients suffering from severe SARS-COV-2 disease and showed an effect in the management of SARS-COV-2 pandemic [100].

2.6. Intravenous Immunoglobulin

The novel corona virus disease poses a unique challenge to clinicians, results in stress and puts financial burden on both healthcare system as well as patients, owing to a greater proportion of mortality and infectivity (Ro) cases. At present, due to lack of harmony with respect to dealing processes for SARS-COV-2 as suggestions/treatments offered are not well precise and mostly unreliable. Assumed abrupt and with shattering spread of SARS-COV-2 virus, there exists an utmost necessity in order to discover previously prevailing and existing healing possibilities until novel treatments and vaccines gets industrialized [101]. Intravenous Immunoglobulin (IVIG), was initially approved in United States, back in 1980 and is an extremely efficacious treatment option for the anticipation of deadly infections in patients with immune deficiencies (mainly primary and secondary). IVIG is widely employed in the treatment of long-lasting/life threatening infections, namely parvovirus infection intricated by anaemia. Currently, understanding, treatment and rationale of SARS-COV-2 infection using IVIG is imperfect and intonation of inflammation, respectively. Numerous anti-inflammatory properties of IVIG may decrease the response (mainly inflammatory)

in life-threatening cases (for example: SARS-COV-2 infection, together with the existence of auto-reactive antibodies which binds cytokines to variable domains of other antibodies) and is shown in Fig. 1. Moreover, IgG dimers present in IVIG forms a barrier in activating FcγR on innate immune effector cells [102]. IVIG is a biological invention obtained from plasma of number of patrons and exploited for treatment of primary immunodeficiency, secondary immunodeficiency, and autoimmune disorders. IVIG offers passive immunization and fortification against comprehensive range of microbes, pathogens, and viruses. Hyperimmune globulin extracted from patrons with high antibody titters towards specific pathogens and is employed efficaciously in treatment of contagions, like cytomegalovirus and H1N1 influenza [101].

The access of SARS-COV-2 inside target cell is facilitated due to presence of transmembrane spike (S) protein which fixes it towards Angiotensin Converting Enzyme-2 (ACE-2) receptor. The S protein forms a homotrimer which bulges from pathogen surface. The binding with receptor site is initiated by S1 subunit with aid of RBD that further results in the S2 subunit activation and imparts the blending amongst the viral and the cell membrane [102]. As per Fig. 1 cellular infection preventive role of S glycoprotein might be due to binding of antibodies to S1 and S2, as proved in cell cultures by incubating viruses in incidence of counterbalancing antibody along with quantitative decrement in viral intracellular RNA levels. Neutralizing antibodies deactivates the viral imitation *via* delaying receptor binding, averting membrane fusion, or avoiding uncoating of the virus once inside the cytoplasm [103].

Unindustrialized studies are illustrating the response of antibodies in patients with SARS-COV-2 viral infection. To and co-workers [104] assessed the role of serum antibody results in 23 SARS-COV-2 patients in Hong Kong, Republic of China. A greater number of subjects were found to be positive for anti-RBD IgG (10 days) and all the patients were positive for anti-RBD IgG 14 days following symptom onset. The immune responses towards SARS-COV-2 infection was studied in patients (285) with the SARS-COV-2 disease. In this regiment, average period required for growth of anti-viral IgM and IgG was 13 days after the onset of symptoms, and the entire group of patients developed antiviral IgG within 19 days. Over a four-fold log variance was observed in level of antiviral IgG and no relationship was seen between anti-viral IgG levels and experimental consequence measures (e.g. lymphocyte counts, C reactive proteins count, or extent of hospitalization) [105]. Recently, Quniti et al. [106] from Italy have described their involvement in seven SARS-COV-2 patients with primary immunodeficiency, X-linked agammaglobulinemia. Amongst them, five patients were suffering from Common Variable Immune Deficiency (CVID) and with unknown genetic diagnoses. All patients were started with IVIG therapy.
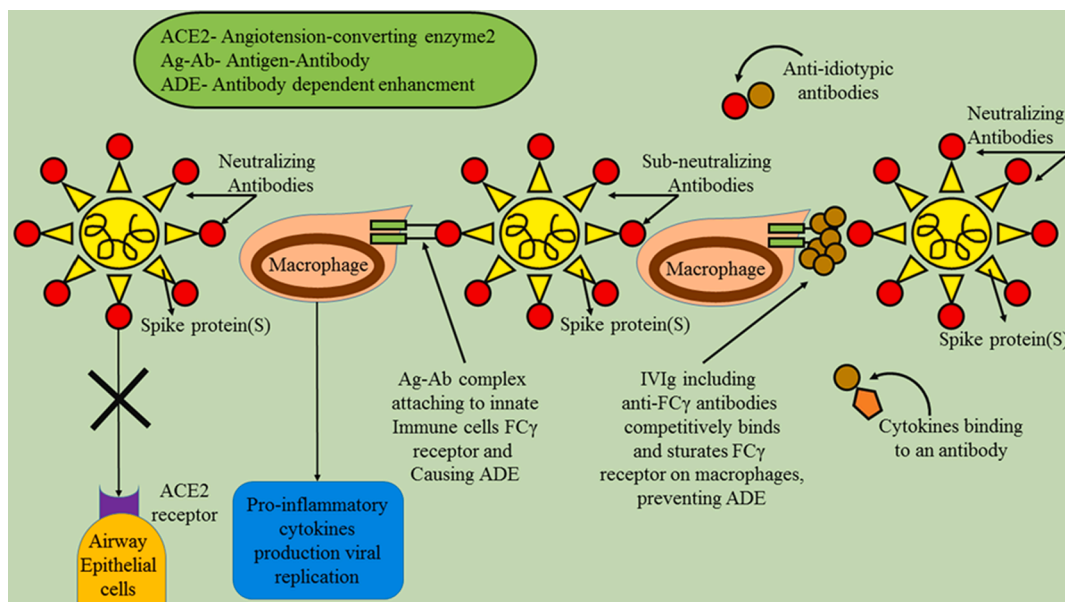
Fig. 1. Proposed mechanisms of neutralizing antibodies prevent attachment of SARS-CoV2 to ACE2 receptor, and thus inhibiting viral entry into the cell. Furthermore, Ag-Ab complexes consisting of viral antigens and anti-viral sub-neutralizing antibodies can activate Fcγ receptors on innate immune cells (e.g. macrophages) in the lung, triggering an exaggerated inflammatory response and causing antibody dependent enhancement (ADE). Additionally, a proposed mechanism whereby IVIG applies anti-inflammatory action causes saturation of Fcγ receptor binding, anti-idiotypic binding to anti-viral antibodies, and binding of proinflammatory cytokines.

Remarkably, both agammaglobulinemia patients had insignificant illness for petite duration. Out of five, four patients required machine-driven aeriation and one demised. It has been seen that COVID patients were observed to have more comorbidities. Alternately, SARS-COV-2 illness is typically linked with more unadorned immune deficiency as compared to X-linked agammaglobulinemia and variable B and T cell flaws, signifying a vital role for cellular immunity against SARS-COV-2.

There exist a case studies on IVIG treatment for three SARS-COV-2 patients in China. The patients taken into consideration were suffering from severe infection, having lymphopenia with raised levels of inflammatory markers. All the patients were given 0.3–0.4 g/kg/day of IVIG for 5 days. They all resulted in regularization of temperature in two days of treatment, and mitigation of breathing signs within five days. Perplexing factors incorporates, simultaneous usage of antivirals in two out of the three patients with steroids in one patient, in addition to the non-existence of case-matched control patients [107].

2.7. Nocturnal oxygen therapy

As per recent publications and observing the attributes of SARS-COV-2, it has been found that oxygen enriched environment play havoc with the viral replication and thus oxygen therapy should be prescribed in SARS-COV-2 infected patients, independent of hypoxia and can be effective in thwarting further disease progression. Viruses depend on host cell resources and metabolism to accomplish their life cycle. For the purpose of replication, several viruses reprogram the host cell metabolism. For instance, Adenoviral cytomegalovirus, Kaposi's Sarcoma-associated herpes virus, Vaccinia virus prevents oxidative phosphorylation whereas it induces the process of glycolysis, which offers broad supply of carbon for production of amino acids along with nucleotides essential for virus replication [108-111]. Several studies have reported that vaccinia virus, hepatitis B virus, H1N1 virus can stabilize hypoxia inducible factor 1α (HIF-1α) by its degradation at normal oxygen conditions [112]. It is a widely known fact that HIF-1α induces metabolic transformation to glycolysis from biogenesis. In fact, studies also disclose that human B19 erythrovirus gene expression and multiplication of hepatitis C virus can be boosted by hypoxia. The above results

clearly demonstrate that HIF-1α plays an important part in enhancing viral replication. However, the activity of HIF-1α gets reduced via hydroxylating two proline residues within HIF-1α under normoxic conditions [113-115]. No data or evidence is there which proves that supplemented oxygen is responsible for minimizing HIF-1α expression in the cells affected by the virus, scholars have documented a substantial decrease in HIF-1α expression in the kidney subjected to *in-vivo* hyperoxic conditions [116]. As a result, hypothesis states that primary effective oxygen therapy for SARS-COV-2 patients is anticipated to obstruct the coronavirus-2 replication process by down-regulating HIF-1α expression.

Median duration of SARS-COV-2 patients from first sign to dyspnoea was 5 days [117], approximately associated with a cytokine storm and lead to injury or failure of many organs. Till now, the mechanism has not been fully explored but it is predicted that early vigorous replication of the virus possibly interrupts the immune response and promote the consequent inflammation. Type 1 interferon is a prime constituent of our innate immunity. It can activate transcription factors and promote host cells to confront the viral contamination. But unfortunately, SARS-CoV, having similarity with SARS-COV-2 is verified to impede production of IFN-1 in animal models [118]. Therefore, it is of foremost importance towards grasping mechanism of action of the virus replication to resolve the response of interferon so as to take effective measures. Investigators have recently indicated the accumulation of lactate due to glycolysis or via enhanced levels of Lactate Dehydrogenase (LDH) enzyme may act as promising mechanism for virus to down-regulate the assembly of interferon [119]. It is noteworthy that clinical studies have displayed that high levels of LDH or lactate have been found in a few patients infected with the virus, specifically the ones with poor prognosis [120]. As per the clinical data from SARS-COV-2 infected patients in Wuhan, China, LDH increased by 29/40 (73%), ICU care12/13 (92%) and ICU care 17/27 (63%) [121]. Therefore, inhibition of glycolysis and lactate reduction production is expected to initiate the antiviral immunity in the first phase of viral infection. As described above, oxygen may influence the functioning of HIF-1α and minimize glycolysis. Furthermore, oxygen may also turn down the deposition of lactate by speeding its deterioration. Thus, early effective oxygen therapy for SARS-COV-2 patients is anticipated to be helpful for the release of interferon and the stimulation

of antiviral immune response. The cytotoxic T cells and Natural Killer cells (NK) are a vital element of our immunity. They are supposed to exert its key role in antiviral community. The level of immune cells inside body fluid of most infected patients with SARS-COV-2 has been reduced. Not long ago, medical scientists found that peripheral blood lymphocyte subset in SARS-COV-2 patients also found that the depletion in CD8 + T, CD4 + T, and NK cells was 68.3%, 60.16%, and 36.59% correspondingly, which tremendously weakens the immune system [122]. In order to deal with early SARS-COV-2, till date, no distinct master plan has been recommended to meliorate the body's immune system. Around the same period, the preventive influence of oxygen treatment in extreme conditions has contributed to the effects of oxygen on the immune system. It is also tempting to believe that ample oxygen will boost the antiviral potential in patients with early SARS-COV-2 infection by amplifying the abundance and functionality of immune cells.

Studies on SARS-CoV may also help to explain SARS-COV-2. Analysis also shows that SARS-CoV genome was located in heart of 35% (7 of 20) of patients, suggesting heart attack was related with previous deaths [123]. Studies on renal functions of patients with SARS-COV-2 virus also explored that acute renal damage fostered by SARS-CoV was associated with peaked mortality rates [124]. Additionally, the collected clinical data suggest that rate of renal damage is unarguably greater in patients with SARS-COV-2 as compared with SARS-CoV [125]. Such several lines of proof suggest that SARS-COV-2 is capable of infecting the heart and lungs with ACE-2 and can inflict significant harm in patients. Minimizing the manifestation of ACE-2 in organs at the initial phase of infection with SARS-COV-2 is therefore required for prevention of virus invasion. Studies have shown that ACE-2 transcription is enhanced due to hypoxia, by up-regulating SIRT1 expression on Huh cells which increases ACE-2 expression in a HIF-1α dependent manner on CD 34$^+$ cells [126,127]. Hypoxia was also shown to increase expression of ACE-2 inside pulmonary vascular smooth muscle cells. Therefore, administration of hypoxia is also likely to postpone the development of SARS-COV-2 in the early stages. Oxygen abundance can elevate the partial pressure of O_2 in arterial blood by increasing O_2 pressure and boost tissue oxygenation which is known to boost myocardial ischemic functioning [128,129]. Thus, early effective oxygen treatment in SARS-COV-2 patients can counteract the rapid annexation of virus.

As the cytokine storm is presently esteemed to be a major reason of the most important SARS-COV-2 explosion, initial steps must be occupied to prevent or minimize unrestricted secretion of inflammatory cytokine. Production of cytokines in the *sapiens* blood indicates the diurnal rhythmicity. Pro-inflammatory cytokines production (mainly TNF-a, IL-1, IFN-γ, and IL-12) occurs higher at night and in the early morning when plasma cortisol is very low [130]. A successive research during a human *in-vivo* trial has shown that whole blood stimulation demonstrated elevated cytokine and chemokine levels at night and early in the morning in a healthy volunteer [131]. Consequently, the elimination of nocturnal pathogen, replication is anticipated to disrupt the synthesis of inflammatory factors. Whether viral proliferation is associated with time-of-day, particularly once virus infects host cell, additional investigation is still required here [132,133]. In accordance with the mentioned studies, it can be hypothesized that nocturnal oxygen therapy could prolong the progression of SARS-COV-2 disease. Since it is not a new concept, it is safe, reliable and user friendly in clinical practice.

2.8. Mesenchymal Stem cell therapy

With the growing demand for the key to this unsolved mystery of SARS-COV-2 pandemic, innumerable researches, clinical trials are conducted in the laboratories worldwide, countless literatures are being published yet neither any pharmacological approach nor any therapy-based treatment procedure has been able to address the crisis. In recent times, stem cell therapy has established itself as one of the most

effective and promising treatment strategies for diseases that were earlier esteemed to be incurable [25]. One such emerging therapy expected to show results is Mesenchymal Stem cell Therapy. Mesenchymal stromal cells (MSC's) have potential utility in a range of cellular therapies with application related to tissue engineering, immunomodulation and vehicle for gene therapy. Based on the capability of stem cell to show resistance to tissue damage, immunomodulatory effect along with promoting tissue repair, dedicated researchers worldwide have begun to consider its benefits in the treatment of SARS-COV-2 pneumonia [134]. The robust anti-inflammatory activity produced by the mesenchymal stem cells, forms the basis for the mechanism of action in treating SARS-COV-2 patients [135]. Immunomodulatory activity and proliferation ability of MSC paves the way for SARS-COV-2 treatment [136]. MSCs can take the edge off SARS-COV-2 induced cytokine storm by reducing the production of proinflammatory cytokines. Moreover, by increasing the production of anti-inflammatory cytokine IL-10, MSCs efficiently inhibits influx and accumulation of neutrophils into lungs and further reduces the secretion of TNF-α [137]. Mesenchymal Stem cell curtails injury and increases matrix metalloprotein (MMP)-9, IL-1 RA, Granulocyte-Macrophage Colony Stimulating factor (GM-CSF), etc to promote the repair and multiplication of alveolar epithelial cells through its own secretion Keratinocyte Growth Factor (KGF) as shown in Fig. 2. [138]. Besides MSCs, Hepatocyte Growth Factor (HGF) as well as Vascular Endothelial Growth Factor (VEGF) synergistically stabilizes endothelial barrier function by restoring the permeability of pulmonary capillaries [139]. MSCs provides protection to endothelial layer of the lungs and controls inflammation by limiting apoptosis of pulmonary vascular endothelial cell and lowering proinflammatory factors [140]. With lungs being the prime target of coronavirus infection, MSCs in serum are primarily concentrated near the lungs where they secrete signalling molecules known as Paracrine factors. The Paracrine factors plays major role in revitalizing and safeguarding alveolar epithelial cells thwarting fibrosis and ameliorating the lung function. All these clinical changes made by MSC therapy indicates itself to be an effective approach for SARS-COV-2 cure and are depicted through Fig. 3 [141].

Liang and co-workers [142], first experimented the administration of MSC therapy in a 65-year-old critically ill female patient. Prior to infusion, laboratory test results indicated an atypical level of neutrophils, lymphocytes, and white blood cells in the peripheral blood for which patient received glucocorticoid and antiviral therapy. The ongoing treatments were also able to lower body temperature and the patient suffered no shortness of breath. By day 11, revaluated physical condition of the patient revealed that she was diagnosed with Acute Respiratory Distress with multiple organ injury, immunosuppression, moderate anaemia, hypertension, electrolyte disturbance, gastrointestinal bleeding and several other critical symptoms. All the existing treatments were withdrawn and the patients received three infusions of human umbilical cord mesenchymal stem cells (hUCMSCs) at an interval of 3 days. The first infusion did not show any unfavourable effect assuring that the cells were well tolerated. 24 hours late the second administration, vital signs of the patient were seen to be stabilized with levels of C-reactive protein (CRP), alanine transaminase (ALT), aspartate transaminase (AST) and serum bilirubin back to normal. Further, the levels of white blood cells, neutrophils, lymphocytes, CD3 + T cells, CD4 + T cells and CD8 + T cells were brought to normal. The throat swab test of patient reported negative after 2 days of the third infusion. Pre and post administration CT scans indicated complete recovery of pneumonia and the patient was discharged on 30th day. In another pilot study of intravenous MSC transplantation conducted with 7 RT-PCR confirmed SARS-COV-2 patients with different severity by Leng and his colleagues [143] in Beijing You an Hospital, China. This showed remarkable outcomes in mitigating the symptoms of viral infection. Additionally, three more severely affected patients were matriculated for placebo control. Before, IV infusion, all the patients exhibited clinical signs of high fever, shortness of breath, low oxygen saturation and weakness. The patients were administered with 1×10^6 clinical grade
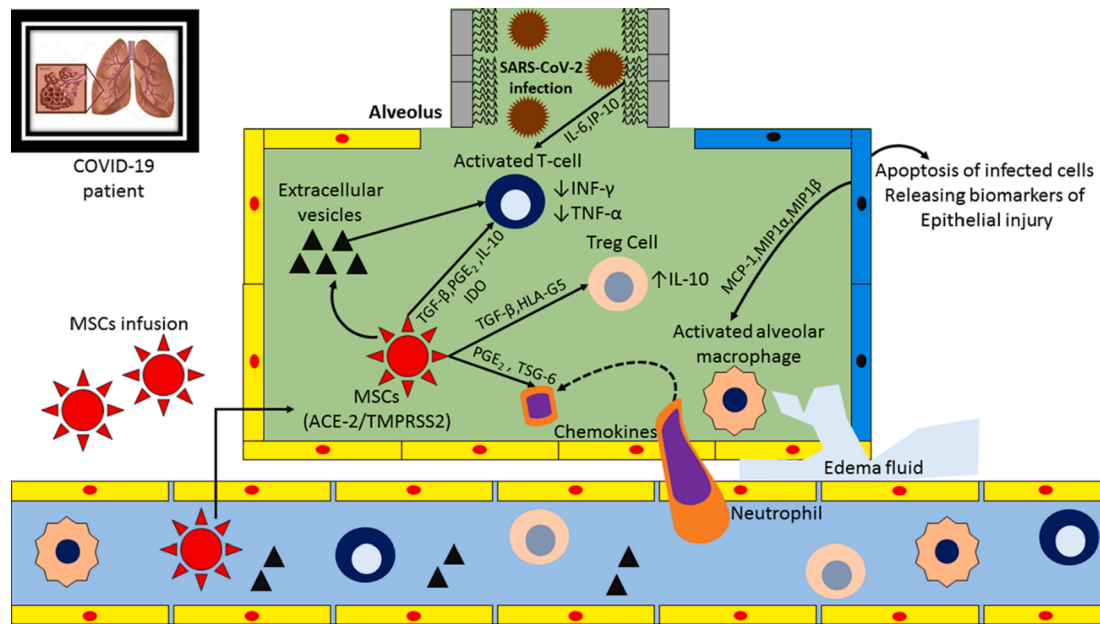
Fig. 2. The Mechanism of action of Mesenchymal Stem Cell infusion against SARS-COV-2 induced Pneumonitis. On contamination with the virus, the capillary endothelial and the epithelial cells get infected, resulting in inflammatory signalling, cell injury and secretion of chemokines and cytokines. The inflammatory atmosphere triggers the activation of local macrophages, endothelial and dendritic cells. The condition further leads to the secretion of soluble factors and foster the relocation of circulating granulocytes, lymphocytes and the monocytes. The pathological changes results in a feed forward control process marked by tissue damage, inflammation and organ dysfunction. Through paracrine pathways and contact-dependent, MSCs can be bought in use to withstand the inflammation associated with Corona virus 2 disease.
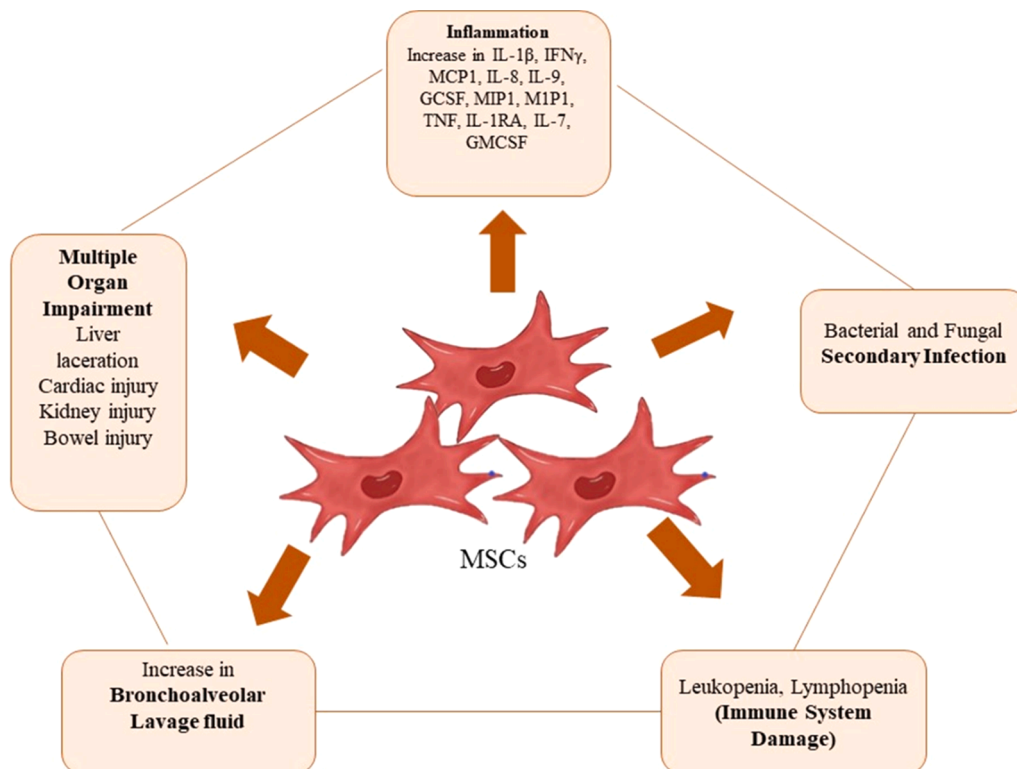

Fig. 3. Target for MSCs in SARS-COV-2 pneumonia. The SARS-COV-2 pneumonia induced ARDS leads to several changes in the pathological conditions contributing much towards the risk of mortality. The MSC based Therapy holds the potential to normalise these unfavourable conditions and thereby proving it as a promising therapeutic option in combating SARS-COV-2 pneumonia.

human MSCs per kilogram body weight. Results showed that all symptoms had disappeared by 2–4 days of transplantation. The oxygen saturation level at rest rose to $\geq$ 95% along with cytokine secreting immune cells CXCR3 + CXCR3 + NK cells, CD4 + cells, and CD8 + cells, CXCR3 + embedded in a week. No adverse reactions, secondary infections or hypersensitivity were witnessed during and after the

treatment. However, this was not the case with the three patients under placebo control. Only one of them showed improvement, other demonstrated symptoms of ARDS and third patient succumbed to the infection. Additionally, with the help of single-cell transcriptome analysis, authors also expressed the absence of TMPRSS2 in the MSC, which aids the viral entry into the host, thus suggesting it to be an immune to Coronavirus2 disease. Within the time period of February 20th 2020 to March 30th 2020, Chen et al. [144] carried out a retrospective analysis with 25 subjects to examine the efficacy and the ill effects associated with MSC therapy on severely affected patients. 80% (20 patients) of the group were male and 20% (5 patients) were female. The criteria of enrolment included patients with oxygen saturation level $\leq$93% in resting phase, respiratory distress, RR $\geq$ 30 beats/min and PaO2/ FiO2 ratio $\leq$300 mmHg. All the patients received a dose of 1×10^6 mononuclear cells per kilogram of weight of clinical grade MSCs. Intramuscular injection of Promethazine Hydrochloride was given as precautionary measure against secondary allergy. 7 out of 25 cases received MSC transplantation once. While at an interval of 5 days, another 7 cases received therapy twice and the remaining 11 cases

received thrice. 64% of the cohort showed improvement in the CT scan and all the cases achieved betterment in clinical signs paving the way towards recovery phase. However, certain side effects associated with the treatment particularly cardiac failure, liver dysfunction and allergic rashes were observed in 3 patients. The results of this study demonstrated no significant change in the inflammatory indexes, IgG and IgM. However, a notable elevation in the serum levels of Lactate (LAC), Cardiac Troponin T (cTnT), and Creatine Kinase-MB (CK-MB) was witnessed with no clear rationale to this change. Chen and his colleagues suggested the utilisation of MSC therapy as promising approach but with cautions in patients with coronary heart disease and metabolic acidosis.

As of August 12, 2020, about 50 clinical studies for examining the efficacy of mesenchymal stem cell therapy in SARS-CoV-2 treatment have been registered under clinicaltrials.gov some of which are mentioned under Table 5. Recently, in the United States, FDA has approved Stem Cell Therapy as treatment of choice for SARS-COV-2 [145]. Although, several studies have reported the safety and efficacy of Mesenchymal Stem Cell Therapy in combating SARS-COV-2 induced inflammatory storm yet no complete evidence of the therapy as

Table 5
A few ongoing Clinical trials for Mesenchymal Stem Cell Therapy registered in clinicaltrials.gov.

Clinicaltrials.gov identifier	Title	Status	Study Design	Estimated Enrolment	Primary outcome	Estimated Completion date	Study location
NCT04461925	Treatment of Coronavirus COVID-19 Pneumonia (Pathogen SARS-CoV-2) with Cryopreserved Allogeneic P_MMSCs and UC-MMSCs	Recruiting	Phase I/II	30	Oxygenation Index, Changes in hospital stay duration, Changes in Mortality rate	December, 2021	Ukraine
NCT04313322	Treatment for COVID-19 patients using Wharton's Jelly Mesenchymal Stem Cells	Recruiting	Phase I	5	Improvement in clinical symptoms, Side effects measured with CT scan, RT-PCR results, turning negative (time frame: 3 weeks)	September 30, 2020	Jordan
NCT04457609	Administration of Allogenic UC-MSCs as Adjuvant Therapy for critically ill COVID-19 Patients	Recruiting	Phase I	40	Presence of dyspnoea, Presence of sputum, fever, Blood pressure, ventilation status, Heart rate, respiratory rate improvement, Oxygen saturation	September, 2020	Indonesia
NCT04447833	Mesenchymal Stoma cell therapy for treatment of Acute respiratory distress syndrome	Recruiting	Phase I	9	Treatment related adverse events of interest	June 30, 2025	Sweden
NCT04366271	Clinical Trial of Allogenic Mesenchymal cells from umbilical cord tissue in patients with COVID-19	Recruiting	Phase II	106	Mortality due to lung involvement due to SARS-CoV-2 virus infection at 28 days of treatment.	May 31, 2021	Spain
NCT04252118	Mesenchymal Stem Cell Treatment for Pneumonia Patients infected with COVID-19	Recruiting	Phase I	20	Evaluation of pneumonia improvement, Number of patients with treatment related adverse events as assessed by CTCAE v4.0	December 2021	China
NCT04366063	Mesenchymal Stem Cell therapy for SARS-CoV-2 related Acute Respiratory Distress Syndrome	Recruiting	Phase II/III	60	Adverse events assessment, Blood Oxygen Saturation	December 10, 2020	Iran
NCT04371601	Safety and Effectiveness of Mesenchymal Stem Cells in the treatment of pneumonia of coronavirus disease 2019	Active, Not recruiting	Early Phase I	60	Changes of oxygenation index (PaO$_2$/FiO$_2$), Blood gas test	December 31, 2022	China
NCT04390152	Safety and Efficacy of Intravenous Wharton's jelly Derived Mesenchymal Stem Cells in Acute Respiratory Distress Syndrome	Not yet Recruiting	Phase I/II	40	Intergroup mortality difference with treatment.	July, 2021	Colombia
NCT04416139	Mesenchymal Stem Cell for Acute Respiratory Distress Syndrome due to COVID-19	Recruiting	Phase II	10	PaO2/FiO2 ratio changes, Clinical Cardiac changes, Respiratory rate changes, Changes in body temperature	May 1, 2021	Mexico
NCT04333368	Cell Therapy using Umbilical Cord-derived Mesenchymal Stromal Cells in SARS-CoV-2 relates ARDS	Recruiting	Phase I/II	40	Respiratory efficacy evaluated by the increase in Pao2/FiO2 ratio from baseline to day 7 in the experimental group compared with placebo group.	July 31, 2021	France
NCT04490486	Umbilical Cord Tissue (UC) Derived Mesenchymal stem cells (MSCs) versus placebo to treat Acute Pulmonary inflammation due to COVID-19	Not yet recruiting	Phase I	21	Percent of participants with treatment related Serious Adverse events (SAE)	June 1, 2024	United States
NCT04302519	Novel Coronavirus Induced Severe Pneumonia Treated by dental Pulp Mesenchymal Stem Cells	Not yet recruiting	Early Phase I	24	Disappear time of ground glass shadow in the lungs	July 30, 2021	China

successful approach is available. Further, several confusions with the source of MSC, doses to be delivered, route of administration still persists which are to be explored prior to its complete approval.

2.9. Advanced radiotherapy

Radiotherapy, as a cancer treatment has been in use for over a century. The therapy has successfully presented outstanding outcomes in healing the silent killer disease. Radiotherapy is a treatment procedure based on the application of radioactive agents or ionising radiation energies to destroy the cancer cells and to put an end to the growth and proliferation of tumoral cells [146]. In view of the current deadly pandemic, Radiotherapy has also been sought as a therapeutic tool to halt the complications associated with the disease. Upon the exposure to the coronavirus, two distinct yet overlapping pathological subsets seems to appear, initially triggered by the virus itself followed by the host response. During the second stage, patients generally establish lung disorders developing viral pneumonia accompanied by hypoxia, cough and fever. The Chest Radiograph images or the Computed Tomography displays ground glass opacities with bilateral infiltrates. The necessity of medical aid in majority of SARS-COV-2 patients arise at this stage [147]. Pneumonia tends to be a severe complication that follows the onset of the infection followed by Cytokine Storm Syndrome, with minority of patients leading to Acute Respiratory Distress Syndrome (ARDS) resulting in death owing to respiratory failure [148]. Pneumonia has long been a serious threat to the global health. Prior to 1939, Serum Therapy was the principal cure for pneumonia. However, in 1930s radiotherapy came into light as a potential therapeutic option for the illness. Calabrese and co-workers [149] demonstrated the utilisation of Low Dose Radiotherapy (LD-RT) to treat pneumonia back in 20th century. The authors reviewed and presented a report of 15 studies on around 700 patients suffering from bacterial, interstitial, atypical and sulphanilamide-resistant pneumonia treated with LD-RT. They reported

that an average of 30% to 10% decrease in the pneumonia mortality rate was observed when low dose radiation therapy was provided. By the beginning of the second decade of the 20th century, radiotherapy was widely accepted by the radiological community with significant achievement in healing severe diseases like carbuncles [150], sinusitis [151], arthritis [152], etc. SARS-COV-2 pneumonia poses a major threat on the survival rate of the affected patients especially for the ones falling in the high-risk categories (geriatric patients, hypertension, cardiovascular complications, diabetes and elevated levels of inflammatory Dimer D/ Ferritin) [153]. Cytokine storm plays a significant role in the critical cases of SARS-COV-2 pneumonia. Suppressing the cytokine storm by inhibiting or neutralising IL-6 and IL-1 is a key factor for reducing the lethality of the infection [154]. On the basis of several clinical accomplishments in the past, and given current insufficiencies in treatment for the disease, scientific scholars have undoubtedly initiated an exploratory attempt of assigning LD-RT to treat SARS-COV-2 pneumonia. Low Dose Radiotherapy (0.5 Gy) is a non-toxic, cost effective, evidence based anti-inflammatory therapeutic tool that could improve the respiratory complications and normalise the immunity cascade in the patients suffering from SARS-CVO-2 pneumonia. The therapy emerges as a better alternative for patients who are sensitive to common anti-inflammatory treatments [155]. Usually doses greater 200 cGy exerts pro-inflammatory response however, recent studies have evinced that low doses less than 100 cGy are able to provoke anti-inflammatory effects [156,157]. Calabrese et al. [158] proposed that LD-RT induces polarization of macrophages into a M-2 anti-inflammatory phenotype. As shown in Fig. 4, the anti-inflammatory phenotype initiates the obstruction of leukocyte-endothelial cell interaction, reduces the endothelial adhesion molecule production, lowers the inflammatory mediators and also decreases the expression of pro-inflammatory cytokines [148]. Moreover, by inducing polynuclear apoptosis, secreting anti-inflammatory cytokine TGF-β1, reducing the applications of macrophages and through several other mechanisms, LD-RT potentially
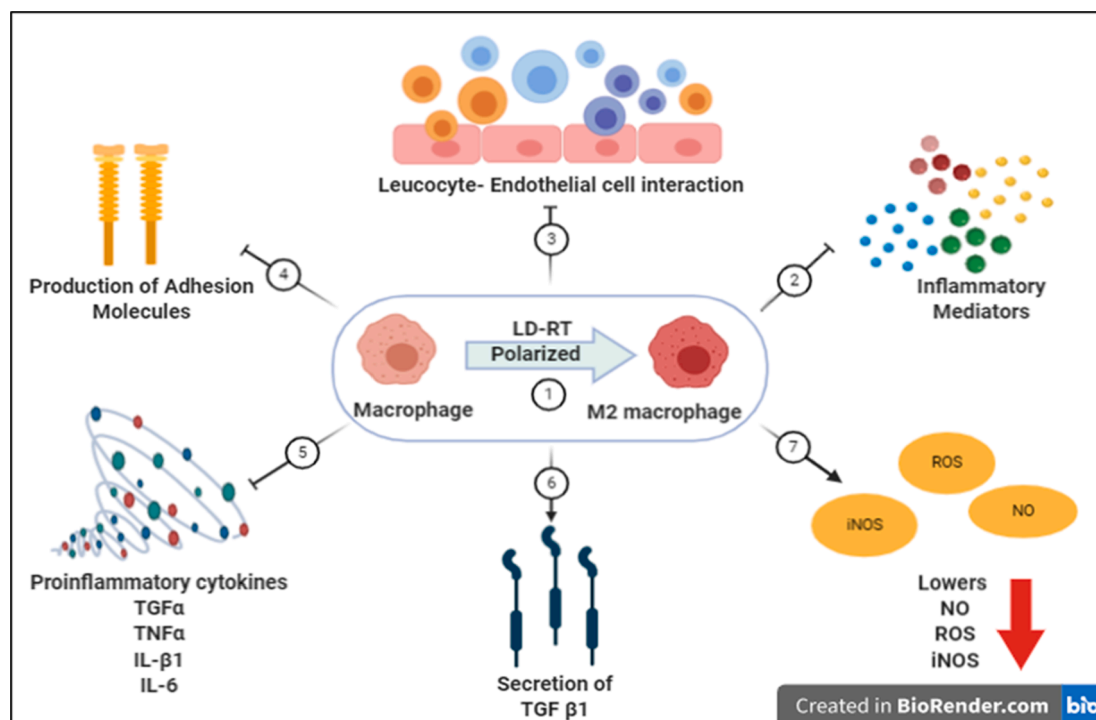

Fig. 4. Mechanism of action of Low Dose Radiotherapy (LD-RT) in combating the COVID-19 related Cytokine Storm. (1) LD-RT causes the polarization of macrophages to anti-inflammatory phenotype M2 macrophage. (2) The phenotype inhibits the inflammatory mediators (3) obstructs the leucocyte-endothelial cell interaction, (4) decreases the production of Endothelial Adhesion molecules (L and E selectins) and (5) hinders the expression of proinflammatory cytokines (TGF-α, TNFα, IL-β1, IL-6). Further (6) by promoting the secretion of anti-inflammatory factor TGF-β1 LD-RT successfully (7) lowers the levels of Nitrogen oxide (NO), reactive oxygen species (ROS) and inducible nitric oxide synthetase (iNOS).

reduces the elevated levels of Nitric Oxide (NO), decreases the inducible nitric oxide synthetase (iNOS), L and E selectins, lowers the Tumour Growth Factor- alpha (TGFα), TNF-α or IL-β1 secretions, and decreases the levels of Reactive Oxygen Species (ROS) [159,160]. Based on all of these changes, LD-RT treatment (30–100 cGy) to the lungs of SARS-COV 2 patients could taper off the pneumonia associated inflammation by creating an anti-inflammatory environment and also lessen the probability of death [161]. Thus, the therapy might be a treatment of choice for palliating the infection. At present there are 14 clinical trials registered for Low dose radiotherapy under clinicaltrials.gov. With the key objective of assessing the duration for clinical recovery in reliance to reduction in the requirement for supplementary oxygenation in SARS-COV-2 patients, Emory University has started the randomized Phase 3 clinical trials for Low Dose Radiation therapy with a total of 52 participants. The study design includes two arms with Arm 1 receiving supportive care plus the treatment of choice by the physician while the arm 2 will receive the best supportive care along with low dose RT. The completion date is estimated to be 30 May, 2022 (NCT04433949). Recently, on September 1, 2020, the Instituto Mexicano del Seguro Social has registered for a trial (NCT04534790) to evaluate the clinical improvements upon treatment with low dose RT. The study will include 30 participants divided into two groups *viz.,* control group (will not receive radiotherapy) and the experimental group (shall receive radiotherapy 1 Gy to Whole lung). The responsible authority promises to complete approximately by April 5, 2021 [30]. Even though, radiation therapy has showed successful results in the past and is expected to provide similar outcomes at present, yet employing radiotherapy in non-cancer diagnosis poses a risk of secondary malignancy [162]. Dhawan et al. recommended that RT should be considered as treatment only for severe patients under critical stage (for whom other options are ineffective) and not for all patients. Thus, cautious use of radiotherapy should be implemented if approved as a cure for SARS-COV-2 pandemic [160]. Hopefully, the researchers will find an answer to this pandemic, overcoming all the limitations in the medical treatments evaluated so far, retrieving the global health system and gaining normalcy in the entire globe.

3. Conclusion

In the era of SARS-COV-2, the livelihoods of people are at a stake. No matter various therapies are assigned to combat this devastating situation yet more and more findings are required to meet the global demand. With numerous publications, research ideas and pre-existing drugs the clinical representatives have so far managed to reduce the intensity of the situation. At present there are more than 100 s of pharmacological drugs and therapy-based treatments undergoing clinical trials. Hopefully, the world will soon be gifted with a solution to terminate this novel coronavirus 2019 disease and a chance to restore the global health.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Appendix A. Supplementary material

Supplementary data to this article can be found online at https://doi.org/10.1016/j.intimp.2020.107156.

References

[1] Y. Chen, Q. Liu, D. Guo, Emerging coronaviruses: Genome Structure, replication and pathogenesis, J. Med. Virol. 92 (2020) 418–423, https://doi.org/10.1002/jmv.25681.

[2] P. Chibber, A. Haq, I. Ahmed, N. Iqbal, G. Singh, Advances in the possible treatment of COVID-19: A review, Eur. J. Pharmacol. 883 (2020), 173372, https://doi.org/10.1016/j.ejphar.2020.173372.

[3] B.J. Bosch, R. van der Zee, A.M. de Haan, J.M. Rottier, The Coronavirus Spike Protein Is a Class I Virus Fusion Protein: Structural and Functional Characterization of the Fusion Core Complex, J. Viro. 77 (2003) 8801–8811, https://doi.org/10.1128/JVI.77.16.8801-8811.2003.

[4] F. Li, Structure, Function, and Evolution of Coronavirus Spike Proteins, Ann. Rev. Virol. 3 (2020).

[5] K. Dhama, S. Khan, R. Tiwari, S. Sircar, S. Bhat, Y. Malik, K. Singh, W. Chaicumpa,D. Bonilla-Aldana, A. Rodriguez-Morales, Coronavirus Disease 2019 – COVID-19, 2020. 10.20944/preprints202003.0001.v2.

[6] D. Wang, Z. Li, Y. Liu, An overview of the safety, clinical application and antiviral research of the COVID-19 therapeutics, J. Inf Health. (2020) 2–6, https://doi.org/10.1016/j.jiph.2020.07.004.

[7] K.G. Andersen, R. Andrew, L.W. Holmes Edward, G. Robert, The Proximal origin of SARS-CoV-2, Nat. Med. 26 (2020) 450–452.

[8] C. Zhang, Z. Wu, J.W. Li, H. Zhao, G.Q. Wang, Cytokine release syndrome in severe COVID-19: interleukin-6 receptor antagonist tocilizumab may be the key to reduce mortality, Int. J. Antimicro. Agents 55 (2020). https://dx.doi.org/10.1016%2Fj.ijantimicag.2020.105954.

[9] Y. Liu, C. Zhang, F. Huang, Y. Yang, F. Wang, J. Yuan, Z. Zhang, Y. Qin, X. Li, D. Zhao, Elevated plasma level of selective cytokines in COVID-19 patients reflect viral load and lung injury, Nat. Sci. Rev. 7 (6) (2020), https://doi.org/10.1093/nsr/nwaa037.

[10] A.H. Rothana, N. Siddappa, The epidemiology and pathogenesis of coronavirus disease (COVID-19) outbreak, J. Autoimm. 109 (2020) 1–3, https://doi.org/10.1093/nsr/nwaa037.

[11] H. Abdulmohsen, A. Rohaimi, F.A. Otaibi, Novel SARS-CoV-2 outbreak and COVID19 disease; a systemic review on the global pandemic, Genes Dis. (2020), https://doi.org/10.1016/j.gendis.2020.06.004.

[12] T. Singhal, A review of coronavirus disease-2019 (COVID-19), Ind. J. Pediatr. (2020) 1–6.

[13] L.L. Ren, Y.M. Wang, Z.Q. Wu, Z.C. Xiang, L. Guo, T. Xu, Identification of a novel coronavirus causing severe pneumonia in human: a descriptive study, Chinese Med. J. 133(9) (2020) 1015–1024. https://dx.doi.org/10.1097%2FCM9.0000000000000722.

[14] Weekly Epidemiological Update- 14 September 2020. Available from: who.int.

[15] COVID-19 Dashboard. Available from: who.int.

[16] Coronavirus Treatment Acceleration Program (CTAP) Dashboard, fda.gov.

[17] S. Zheng, The critical role of futility analysis in the pursuit of effective treatments for COVID-19, Contemporary Clin. Trials Comm. (2020), 100581.

[18] Y. Song, M. Zhang, L.Y. Wang, Y. Zhou, M. Zhou, Y. Lu, COVID-19 Treatment: Close to a Cure? – A Rapid Review of Pharmacotherapies for the Novel Coronavirus, Int. J. Antimicro. 56 (2) (2020), 106080, https://doi.org/10.1016/j.ijantimicag.2020.106080.

[19] S. Mulangu, L.E. Dodd, R.T. Davey, O.T. Mbaya, M. Proschan, D. Mukadi, A Randomized Controlled Trial of Ebola Virus Disease Therapeutics, N. Engl. J. Med. 381 (24) (2020) 2293–2303, https://doi.org/10.1056/NEJMoa1910993.

[20] Remdesivir Clinical Trials report, Gilead Sciences.

[21] V. Pilkington, T. Pepperrell, A. Hill, A review of the safety of Favipiravir – a potential treatment in the COVID-19 pandemic? J. Virus Erad. 6 (2) (2020).

[22] P.K. Samudrala, P. Kumar, K. Choudhary, N. Thakur, G.S. Wadekar, R. Dayaramani, M. Agrawal, A. Alexander, Virology, pathogenesis, diagnosis and in-line treatment of COVID-19, Eur. J. Pharmacol. 883 (2020), 173375, https://doi.org/10.1016/j.ejphar.2020.173375.

[23] S. Arshad, P. Kilgore, Z.S. Chaudhry, G. Jacobsen, D.D. Wang, K. Huitsing, I. Brar, COVID-19 Task Force Treatment with hydroxychloroquine, azithromycin, and combination in patients hospitalized with COVID-19, Int. J. Inf. Dis. 97 (2020) 2–3, https://doi.org/10.1016/j.ijid.2020.06.099.

[24] A. Hussin Rothana, N. Siddappa, The epidemiology and pathogenesis of coronavirus disease (COVID-19) outbreak, J. Autoimm. 109 (2020) 1–3, https://doi.org/10.1016/j.jaut.2020.102433.

[25] T. Hampton, New Flu Antiviral Candidate May Thwart Drug Resistance, JAMA 323 (2020) 17, https://doi.org/10.1001/jama.2019.20225. PMID: 31910262.

[26] Draft Landscape of COVID-19 Candidate Vaccine- 9 September 2020. Available at: www.who.int.

[27] A. Miller, M.J. Reandelar, K. Fasciglione, V. Roumenova, Y. Li, G.H. Otazu, Correlation between universal BCG vaccination policy and reduced morbidity and mortality for COVID-19: an epidemiological study, medRxiv. (2020) 2020.2003.2024.20042937.

[28] M.K. Berg, Q. Yu, C.E. Salvador, I. Melani, S. Kitayama, Mandated Bacillus Calmette- Guérin (BCG) vaccination predicts flattened curves for the spread of COVID-19, (2020). doi: 10.1101/2020.04.05.20054163.

[29] M. Kinoshita, M. Tanaka, Impact of routine infant BCG vaccination in young generation on prevention on prevention of local COVID-19 spread in Japan, J. Inf. (2020), https://doi.org/10.1016/j.jinf.2020.08.013.

[30] clinicaltrials.gov.

[31] Bacillus Calmette-Guerin (BCG) vaccination and COVID-19: Scientific Brief. Available at: www.who.int.

[32] S.J. Moorlag, R.C. van Deuren, C.H. van Werkhoven, M. Jaeger, P. Debisarun, E. Taks, Safety and COVID-19 symptoms in individuals recently vaccinated with BCG: a retrospective cohort study, Cell Rep. Med. 1 (5) (2020), 100073, https://doi.org/10.1016/j.xcrm.2020.100073.

[33] World Health Organization. Draft landscape of COVID-19 candidate vaccines – 15 May 2020. (2020).

[34] National Institute of Allergy and Infectious Diseases (NIAID). Phase I, Open-Label, Dose-Ranging Study of the Safety and Immunogenicity of 2019-nCoV Vaccine (mRNA-1273) in Healthy Adults. (2020). Available at: https://clinicaltrials.gov/ct2/show/record/NCT04283461.

[35] Moderna, Inc, A study to evaluate the efficacy, safety and immunogenicity of MRNA-1273 vaccine in Adults aged 18 years and older to prevent COVID-19, (NCT04470427), (2020). Available at: www.clinicaltrials.gov.

[36] J. Garamone, Operation Warp Speed on Track for End of Year Vaccine Delivery. Available at: https://www.defense.gov/Explore/News/Article/Article/2311177/operation-warp-speed-on-track-for-end-of-year-vaccine-delivery/.

[37] N. van Doremalen, T. Lambe, A. Spencer, S. Rammerstorfer, J.N. Purushotham, J. R. Port, V.A. Avanzato, T. Bushmaker, A. Flaxman, M. Ulaszewska, ChAdOx1 nCoV-19 vaccine prevents SARS-CoV-2 pneumonia in rhesus macaque, Nat. (2020) 1–8.

[38] A Study of a Candidate COVID-19 Vaccine (COV003), Sponsored by. University of Oxford, (NCT04536051) Available at: www.clinicaltrials.gov.

[39] Phase 3 Clinical Testing in the US of AstraZeneca COVID-19 Vaccine Candidate Begins. Available at: nih.gov.

[40] L. Riva, S. Yuan, X. Yin, L.M. Sancho, N. Matsunaga, Discovery of SARS-COV-2 antiviral drugs through large-scale compound repurposing, J. Nature (2020), https://doi.org/10.1038/s41586-020-2577-1.

[41] Coronavirus: Operation Wrap Speed. Available from: https://www.defense.gov/Explore/Spotlight/Coronavirus/Operation-Warp-Speed/.

[42] M. Slaoui, M. Hepburn, Developing Safe and Effective Covid Vaccines- Operation Wrap Speed's Strategy and Approach, The New Eng. J. Med. (2020), https://doi.org/10.1056/NEJMp2027405.

[43] Fact Sheet: Explaining Operation Warp Speed. Available from: https://www.hhs.gov/coronavirus/explaining-operation-warp-speed/index.html.

[44] Talha Khan Burki, The Russian vaccine for COVID-19, The Lancet (2020), https://doi.org/10.1016/S2213-2600(20)30402-1.

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

[46] A Brief History of Immunotherapy, targeted oncology, August 22, 2014.

[47] A. AminJafari, S. Ghasemi, The possible of immunotherapy for COVID-19: A systematic review, Int. Immunopharmacol. (2020), 106455, https://doi.org/10.1016/j.intimp.2020.106455.

[48] A. Zumla, F.W. Jasper, I. Esam, S.C. David, K.Y. Yuen, Coronaviruses—drug discovery and therapeutic options, Nat. Rev. Drug Dis. 15 (2016) 327–347.

[49] L. Jahanshahlua, N. Rezaeic, Monoclonal antibody as a potential anti-COVID-19, Biomed. Pharmaco-ther. 129 (2020), https://doi.org/10.1016/j.biopha.2020.110337.

[50] D. Wrapp, Cryo-EM structure of the 2019-nCoV spike in the prefusion conformation, Science 367 (2020) 1260–1263, https://doi.org/10.1126/science.abb2507.

[51] A.C. Walls, Structural, function and antigenicity of the SAS-CoV-2 spike glycoprotein, Cell. 181 (2020) 281–292, https://doi.org/10.1016/j.cell.2020.02.058.

[52] J. Reguera, C. Santiago, G. Mudgal, D. Ordon, L. Enjuanes, J.M. Casasnovas, Structural bases of coronavirus attachment to host aminopeptidase N and its inhibition by neutralizing antibodies. PLoS Path. 8 (2012) e1002859. https://doi.org/10.1016/j.cell.2020.02.058.

[53] X. Yu, S. Zhang, L. Jiang, Y. Cui, D. Li, D. Wang, N. Wang, Structural basis for the neutralization of MERS-CoV by a human monoclonal antibody MERS-27, Sci. Rep. 5 (2015) 13133.

[54] X. Tian, C. Li, A. Huang, S. Xia, S. Lu, Z. Shi, Potent binding of 2019 novel coronavirus spike protein by a SARS coronavirus-specific human monoclonal antibody, Emerging Micro. Inf. 9 (2020) 382-5. https://doi.org/10.1080/22221751.2020.1729069.

[55] E.N. van den Brink, J. Meulen, F. Cox, M.A. Jongeneelen, A. Thijsse, M. Throsby, Molecular and biological characterization of human monoclonal antibodies binding to the spike and nucleocapsid proteins of severe acute respiratory syndrome coronavirus, J. Virol. 79 (2005), https://doi.org/10.1128/JVI.79.3.1635-1644.2005.

[56] C. Wang, W. Li, D. Drabek, N.M. Okba, R. van Haperen, A.D. Osterhaus, A human monoclonal antibody blocking SARS-CoV-2 infection, Nat. Comm. 11 (2020) 1–6.

[57] Y. Wu, F. Wang, C. Shen, W. Peng, D. Li, C. Zhao, Y.Gong,. A noncompeting pair of human neutralizing antibodies block COVID-19 virus binding to its receptor ACE2, Sci. 368(6496) (2020) 1274-8. 10.1126/science.abc2241.

[58] E. Sparrow, M. Friede, M. Sheikh, S. Torvaldsen, Therapeutic antibodies for infectious diseases, Bull. World Health Organ. 93 (2017) 235.

[59] P.A. Ascierto, SITC Statement on anti-IL-6/IL-6R for COVID-19- Society for Immunotherapy of Cancer (SITC), 2020.

[60] National Health Commission and National Administration of Traditional Chinese Medicine. Diagnosis and treatment protocol for novel coronavirus pneumonia (Trial Version 7). Chin. Med. J. 2020:133.

[61] X. Xu, M. Han, T. Li, W. Sun, D. Wang, B. Fu, Effective treatment of severe COVID-19 patients with tocilizumab, Proceed. Nat. Acad. Sci. 117 (20) (2020) 10970–10975, https://doi.org/10.1073/pnas.2005615117.

[62] O. Pérez, M. Andres, J.M. Ramirez, J. Payá, J.C. Rodríguez, Experience with tocilizumab in severe COVID-19 pneumonia after 80 days of follow-up: A retrospective cohort study, J. Auto-imm. (2020), 102523, https://doi.org/10.1016/j.jaut.2020.102523.

[63] R. Alattar, T.B. Ibrahim, S.H. Shaar, S. Abdalla, K. Shukri, Tocilizumab for the Treatment of Severe COVID-19, J. Med. Virol. (2020), https://doi.org/10.1002/jmv.25964.

[64] R. Capra, N. De Rossi, F. Mattioli, G. Romanelli, C. Scarpazza, M.P. Sormani, S. Cossi, Impact of low dose tocilizumab on mortality rate in patients with COVID-19 related pneumonia, Eur. J. Int. Med. (2020), https://doi.org/10.1016/j.ejim.2020.05.009.

[65] F.I. Arnaldez, S.J. Day, C.G. Drake, B.A. Fox, B. Fu, W.J. Urba, V. Montesarchio, The Society for Immunotherapy of Cancer perspective on regulation of interleukin-6 signaling in COVID-19-related systemic inflammatory response, J. Immunother. Cancer. 8 (2020).

[66] M. Zhao, cytokine storm and immunomodulatory therapy in COVID-19: Role of Chloroquine and anti-IL-6 monoclonal antibodies, Int. J. Antimicro. 56 (2020).

[67] I. Ray, D.F. Sánchez, C.A. Robert, M.P. Robert, Convalescent Plasma Therapy: An Effective Therapeutic Option to Treat COVID-19? A Narrative Review, Int. J. Clini. Trans. Med. 8 (2020) 7–21, https://doi.org/10.2147/IJCTM.S269691.

[68] I.F.N. Hung, K.K.W. To, C.K. Lee, Convalescent Plasma Treatment Reduced Mortality in Patients With Severe Pandemic Influenza A (H1N1) 2009 Virus Infection, Clin. Inf. Dis. 52 (2011) 447-456. https://doi.org/10.1093/cid/ciq106.

[69] J.M. Jenkins, M.S. Campos, J.K. Baillie, P. Cleary, F.M. Khaw, W.S. Lim, S. Makki, K.D. Rooney, The Effectiveness of Convalescent Plasma and Hyperimmune Immunoglobulin for the Treatment of Severe Acute Respiratory Infections of Viral Etiology: A Systemic Review and Explanatory Meta-Analysis, J. Inf. Dis. 211 (2015) 80–90, https://doi.org/10.1093/infdis/jiu396.

[70] M. Sun, Y. Xu, H. He, A potentially effective treatment for COVID-19: A systemic review and meta-analysis of convalescent plasma therapy in treating severe infectious disease, Int. J. Infect. Dis. 98 (2020) 334–346, https://doi.org/10.1016/j.ijid.2020.06.107.

[71] J.D. Roback, J. Guarner, Convalescent Plasma to Treat COVID-19 Possibilities and Challenge, JAMA. 323 (2020) 1561–1562, https://doi.org/10.1001/jama.2020.4940.

[72] H. Abolghasemi, P. Eshghi, A.M. Cheraghali, A.A. Fooladi, F.B. Moghaddam, S. Imanizadeh, M.M. Maleki, M. Ranjkesh, Clinical efficacy of convalescent plasma for treatment of COVID-19 infections: Results of a multicenter clinical study, Trans. Apheresis Sci. 15 (2020) 102875. https://doi.org/10.1016/j.transci.2020.102875.

[73] C. Shen, Z. Wang, F. Zhao, Y. Yang, J. Li, J. Yuan, F. Wang, D. Li, M. Yang, Treatment of 5 critically ill patients with COVID-19 with convalescent plasma, JAMA. 323 (16) (2020) 1582–1589, https://doi.org/10.1001/jama.2020.4783.

[74] K. Duan, The feasibility of convalescent plasma therapy in severe COVID-19 patients: a pilot study, medRxiv. (2020). https://doi.org/10.1101/2020031620036145.

[75] Z. Bin, L. Shuyi, T. Tan, H. Wenhui, D. Yuhao, C. Luyan, Treatment With Convalescent Plasma for Critically Ill Patients With SARS-CoV-2 Infection, Chest. (2020), https://doi.org/10.1016/j.chest.2020.03.039. In press.

[76] K. Duan, B. Liu, C. Li, H. Zhang, Yu T, Qu J, Effectiveness of convalescent plasma therapy in severe COVID-19 patients, Proc. Nat. Acad. Sci. U.S.A. (2020), https://doi.org/10.1073/pnas.2004168117.

[77] M. Ye, D. Fu, Y. Ren, F. Wang, D. Wang, F. Zhang, Treatment with convalescent plasma for COVID-19 patients in Wuhan, China, J. Med. Virol. (2020). https://doi.org/10.1002/jmv.25882.

[78] J.Y. Ahn, Y. Sohn, S.H. Lee, Y. Cho, J.H. Hyun, Y.J. Baek, Use of convalescent plasma therapy in two COVID-19 patients with acute respiratory distress syndrome in Korea, J. Korean Med. Sci. 35 (2020) e149. https://doi.org/10.3346/jkms.2020.35.e149.

[79] B. Zhang, S. Liu, T. Tan, Treatment with convalescent plasma for critically ill patients with SARS-CoV-2 infection, Chest (2020).

[80] Y.O. Soo, Y. Cheng, R. Wong, et al., Retrospective comparison of convalescent plasma with continuing high-dose methylprednisolone treatment in SARS patients, Clin. Micro. Inf. 10 (2004) 676–678, https://doi.org/10.1111/j.1469-0691.2004.00956.x.

[81] T.S. Chiueh, L.K. Siu, J.C. Lin, P.K. Chan, M.Y. Peng, H.L. Wan, J.H. Chen, B. S. Hu, Experience of using convalescent plasma for severe acute respiratory syndrome among healthcare workers in a Taiwan hospital, J. Anti-micro. Chemother. 56 (2005) 919–922, https://doi.org/10.1093/jac/dki346.

[82] Y. Cheng, R. Wong, Y.O. Soo, W.S. Wong, C.K. Lee, M.H. Ng, P. Chan, K.C. Wong, C.B. Leung, G. Cheng, Use of convalescent plasma therapy in SARS patients in Hong Kong, Eur. J. Clin. Micro. Inf. Dis. 24 (2005) 44–46.

[83] Q.H. Nie, X.D. Luo, W.L. Hui, Advances in clinical diagnosis and treatment of severe acute respiratory syndrome, World J. Gastro-enterol. 9 (2003) 1139–43. https://doi.org/10.3748/wjg.v9.i6.1139.

[84] K.M. Yeh, T.S. Chiueh, L.K. Siu, J.C. Lin, P.K.S. Chan, et al., Experience of using convalescent plasma for severe acute respiratory syndrome among healthcare workers in a Taiwan hospital, J. Anti-micro. Chemo-ther. 56 (2005) 919–922, https://doi.org/10.1093/jac/dki346.

[85] X. Zhou, M. Zhao, F. Wang, T. Jiang, Y. Li, W. Nie, et al., Epidemiologic features, clinical diagnosis and therapy of first cluster of patients with severe acute respiratory syndrome in Beijing area, Zhonghua Yi Xue Za Zhi. 83 (2003) 1018–1022.

[86] L. Kong, Letter to editor. Trans. Apher. Sci. 29 (2003) 101. https://doi.org/10.1016/S1473-0502(03)00109-5.

[87] J.H. Ko, H. Seok, S.Y. Cho, Y.E. Ha, J.Y. Baek, S.H. Kim, et al., Challenges of convalescent plasma infusion therapy in Middle East respiratory coronavirus infection: A single centre experience, Anti-vir, Ther. 23 (2018) 617–622, https://doi.org/10.3851/IMP3243.

[88] S. Chun, C.R. Chung, Y.E. Ha, et al., Possible transfusion-related acute lung injury following convalescent plasma transfusion in a patient with middle east respiratory syndrome, Ann. Lab. Med. 36 (2016) 393–395.

[89] L. Zha, S. Li, L. Pan, B. Tefsen, Y. Li, N. French, L. Chen, G. Yang, E.V. Villanueva, Corticosteroid treatment of patients with coronavirus disease 2019 (COVID-19), Med. J. Aus. 212 (2020) 416-20.

[90] J. Zhang, B. Xie, K. Hashimoto, Current status of potential therapeutic candidates for the COVID-19 crisis, Brain, Beh. Imm. (2020).

[91] M. Tobaiqy, M. Qashqary, S. Al-Dahery, A. Mujallad, A.A. Hershan, M.A. Kamal, N. Helmi, Therapeutic management of patients with COVID-19: a systematic review, Infec. Preven. Prac 2 (2020), 100061, https://doi.org/10.1016/j.infpip.2020.100061.

[92] P. Zhai, Y. Ding, X. Wu, J. Long, Y. Zhong, Y. Li, The epidemiology, diagnosis and treatment of COVID-19, Int. J. Antimicrobial Agents 28 (2020), 105955.

[93] Y.H. Zhou, Y.Y. Qin, Y.Q. Lu, F. Sun, S. Yang, V. Harypursat, S.Q. Tang, Y.Q. Huang, X.Q. He, Y.M. Zeng, Y. Li, Effectiveness of glucocorticoid therapy in patients with severe novel coronavirus pneumonia: protocol of a randomized controlled trial, Chin. Med. J. 10 (2020). 10.1097/CM9.0000000000000791.

[94] M.P. Lythgoe, P. Middleton, Ongoing clinical trials for the management of the COVID-19 pandemic, Trends Pharmacol. Sci. (2020), https://doi.org/10.1016/j.tips.2020.03.006.

[95] B. Bikdeli, M.V. Madhavan, D. Jimenez, T. Chuich, I. Dreyfus, E. Driggin, C. Der Nigoghossian, W. Ageno, M. Madjid, Y. Guo, L.V. Tang, COVID-19 and Thrombotic or Thromboembolic Disease: Implications for Prevention, Antithrombotic Therapy, and Follow-Up: JACC State-of-the-Art Review, J. Amer. Coll. Cardio. 75 (2020) 2950–2973, https://doi.org/10.1016/j.jacc.2020.04.031.

[96] R. Chaudhary, R.P. Kreutz, K.P. Bliden, U.S. Tantry, P.A. Gurbel, Personalizing Antithrombotic Therapy in COVID-19: Role of Thrombo-elastography and Thrombo-elastometry, Thromb. Haem. (2020), https://doi.org/10.1055/s-0040-1714217.

[97] J.M. Connors, J.H. Levy, Thrombo-inflammation and the hypercoagulability of COVID-19, J. Thromb. Haem. (2020), https://doi.org/10.1111/jth.14849.

[98] S.H. Brouns, R. Brüggemann, A. Linkens, F.J. Magdelijns, H. Joosten, R. Heijnen, A.J. ten Cate-Hoek, J. Schols, H. Ten Cate, B. Spaetgens, Mortality and the use of Antithrombotic Therapies among Nursing Home Residents with COVID-19, J. Amer. Geriat. Soc. (2020), https://doi.org/10.1111/jgs.16664.

[99] F. Violi, D. Pastori, R. Cangemi, P. Pignatelli, L. Loffredo, Hypercoagulation and antithrombotic treatment in coronavirus 2019: a new challenge, Thromb. Haem. 120 (2020) 949. https://dx.doi.org/10.1055%2Fs-0040-1710317.

[100] J. Thachil, The versatile heparin in COVID-19, J. Thromb. Haem. 5 (2020) 1020–1022, https://doi.org/10.1111/jth.14821.

[101] A. Alan, B. Saddiq, D. Craig, S. Raif, S. Janet, R. Douglas, Immunoglobulins in the treatment of COVID-19 infection: Proceed with caution!, Clin. Immunol. 216 (2020), 108459, https://doi.org/10.1016/j.clim.2020.108459.

[102] A.C. Walls, Y.J. Park, M.A. Tortorici, A. Wall, A.T. McGuire, D. Veesler, Structure, function, and antigenicity of the SARS-CoV-2 spike glycoprotein, Cell 181 (2) (2020) 281–292 (e6). https://doi.org/10.1016/j.cell.2020.09.037.

[103] J. ter Meulen, E.N. van den Brink, L.L. Poon, W.E. Marissen, C.S. Leung, F. Cox, et al., Human monoclonal antibody combination against SARS coronavirus: synergy and coverage of escape mutants, PLoS Med. 3 (7) (2006), e237, https://doi.org/10.1371/journal.pmed.0030237.

[104] K.K. To, O.T. Tsang, W.S. Leung, A.R. Tam, T.C. Wu, D.C. Lung, et al., Temporal profiles of viral load in posterior oropharyngeal saliva samples and serum antibody responses during infection by SARS-CoV-2: an observational cohort study, Lancet Infect. Dis. 20 (5) (2020) 565–574, https://doi.org/10.1016/S1473-3099(20)30196-1.

[105] Q.X. Long, B.Z. Liu, H.J. Deng, G.C. Wu, K. Deng, Y.K. Chen, et al., Antibody responses to SARS-CoV-2 in patients with COVID-19, Nat. Med. (2020) https://doi.org/10.1038/s41591-020-0897-1 [Epub ahead of print].

[106] I. Quinti, V. Lougaris, C. Milito, F.Cinetto, A. Pecoraro, I, Mezzaroma, I., Plebani, A. (2020). A possible role for B cells in COVID-19?: Lesson from patients with Agammaglobulinemia. Journal of Allergy and Clinical Immunology. 146, 1, 2020. doi: 10.1016/j.jaci.2020.04.013.

[107] W. Cao, X. Liu, T. Bai, H. Fan, K. Hong, H. Song, et al., High-dose intravenous immunoglobulin as a therapeutic option for deteriorating patients with coronavirus disease 2019, Open Forum, Infect Dis. 7 (3) (2020) ofaa102, https://doi.org/10.1093/ofid/ofaa102.

[108] M. Thai, N.A. Graham, D. Braas, Adenovirus E4ORF1-induced MYC activation promotes host cell anabolic glucose metabolism and virus replication, Cell Metab. 19 (2014) 694–701, https://doi.org/10.1016/j.cmet.2014.03.009.

[109] Y. Yu, T.G. Maguire, J.C. Alwine, ChREBP, a glucose-responsive transcriptional factor, enhances glucose metabolism to support biosynthesis in human cytomegalovirus-infected cells, Proceed. Nat. Acad. Sci. 111 (2014) 1951–1956, https://doi.org/10.1073/pnas.1310779111.

[110] M. Mazzon, C. Castro, L.D. Roberts, J.L. Griffin, G.L. Smith, A role for vaccinia virus protein C16 in reprogramming cellular energy metabolism, J. Gen. Virol. 96 (2014) 395-407. https://dx.doi.org/10.1099%2Fvir.0.069591-0.

[111] B.R. Cullen, O. Yogev, D. Lagos, T. Enver, C. Boshoff, Kaposi's Sarcoma Herpesvirus MicroRNAs Induce Metabolic Transformation of Infected Cells, PLoS Path. 10 (2014), https://doi.org/10.1371/journal.ppat.1004400.

[112] L. Ren, W. Zhang, P. Han, Influenza A virus (H1N1) triggers a hypoxic response by stabilizing hypoxia-inducible factor-1alpha via inhibition of proteasome, Virol. 530 (2019) 51–58, https://doi.org/10.1016/j.virol.2019.02.010.

[113] S. Pillet, N. Le Guyader, T. Hofer, Hypoxia enhances human B19 erythrovirus gene expression in primary erythroid cells, Virol. 327 (2004) 1–7, https://doi.org/10.1016/j.virol.2004.06.020.

[114] N. Vassilaki, K.I. Kalliampakou, I. Kotta-Loizou, Low Oxygen Tension Enhances Hepatitis C Virus Replication, J. Virol. 87 (2012) 2935–2948, https://doi.org/10.1128/JVI.02534-12.

[115] C.P. Bracken, M.L. Whitelaw, D.J. Peet, The hypoxia-inducible factors: key transcriptional regulators of hypoxic responses, Cell. Mol. Life Sci. (CMLS) 60 (2003) 1376–1393.

[116] C.R. Popescu, M.R. Sutherland, A. Cloutier, G. Benoît, M. Bertagnolli, C. Yzydorczyk, N. Germain, V. Phan, M. Lelièvre-Pegorier, et al., Hyperoxia exposure impairs nephrogenesis in the neonatal rat: role of HIF-1α, PLoS One 8 (2013), e82421 https://doi.org/10.1371/journal.pone.0082421.

[117] D. Wang, B. Hu, C. Hu, Clinical Characteristics of 138 Hospitalized Patients With 2019 Novel Coronavirus–Infected Pneumonia in Wuhan, China, JAMA. (2020).

[118] E. Kindler, V. Thiel, SARS-CoV and IFN: Too Little, Too Late, Cell Host Micro. 19 (2016) 139–141, https://doi.org/10.1016/j.chom.2016.01.012.

[119] W. Zhang, G. Wang, Z.G. Xu, Lactate Is a Natural Suppressor of RLR Signaling by Targeting MAVS, Cell. 178 (2019) 76–89 e15, https://doi.org/10.1016/j.cell.2019.05.003.

[120] L. Hunt, A. Gupta-Wright, V. Simms, Clinical presentation, biochemical, and haematological parameters and their association with outcome in patients with Ebola virus disease: an observational cohort study, Lancet Inf. Dis. 15 (2015) 1292–1299, https://doi.org/10.1016/S1473-3099(15)00144-9.

[121] C. Huang, Y. Wang, X. Li, Clinical features of patients infected with 2019 novel coronavirus in Wuhan, China, Lancet. 395 (2020) 497-506. https://doi.org/10.1016/S0140-6736(20)30183-5.

[122] S. Wan, Q. Yi, S. Fan, Characteristics of lymphocyte subsets and cytokines in peripheral blood of 123 hospitalized patients with 2019 novel coronavirus pneumonia (NCP), MedRxiv. (2020). https://doi.org/10.1101/2020.02.10.20021832.

[123] G.Y. Oudit, Z. Kassiri, C. Jiang, et al., SARS-coronavirus modulation of myocardial ACE2 expression and inflammation in patients with SARS, Eur. J. Clin. Inv. 39 (2009) 618–625, https://doi.org/10.1111/j.1365-2362.2009.02153.x.

[124] R. Reddy, I. Asante, S. Liu, et al., Circulating angiotensin peptides levels in Acute Respiratory Distress Syndrome correlate with clinical outcomes: A pilot study, PLoS One. 14 (2019), e0213096, https://doi.org/10.1371/journal.pone.0213096.

[125] Z. Li, M. Wu, J. Guo, Caution on Kidney Dysfunctions of 2019-nCoV Patients, MedRxiv. (2020). 2020.02.08.20021212.

[126] N.E. Clarke, N.D. Belyaev, D.W. Lambert, A.J. Turner, Epigenetic regulation of angiotensin-converting enzyme 2 (ACE2) by SIRT1 under conditions of cell energy stress, Clin. Sci. 126 (2014) 507–516, https://doi.org/10.1042/CS20130291.

[127] W. Ottestad, M. Seim, J.O. Mæhlen, COVID-19 with silent hypoxemia, Tidsskrift for Den norske legeforening (2020), https://doi.org/10.4045/tidsskr.20.0299.

[128] A.M. Manning, Oxygen therapy and toxicity. The Veterinary clinics of North America. Small animal practice. 32(5) (2002) 1005. https://doi.org/10.1016/s0195-5616(02)00043-8.

[129] R.F. Kelly, T.L. Hursey, J.E. Parrillo, G.L. Schaer, Effect of 100% oxygen administration on infarct size and left ventricular function in a canine model of myocardial infarction and reperfusion, Amer. heart J. 130 (5) (1995) 957–965, https://doi.org/10.1016/0002-8703(95)90194-9.

[130] N. Petrovsky, L.C. Harrison, The chronobiology of human cytokine production, Int. Rev. Immunol. 16 (1998) 635–649, https://doi.org/10.3109/08830189809043012.

[131] N. Petrovsky, P. McNair, L.C. Harrison, Diurnal rhythms of pro-inflammatory cytokines: regulation by plasma cortisol and therapeutic implications, Cytokine. 10 (1998) 307–312, https://doi.org/10.1006/cyto.1997.0289.

[132] D.S. Leland, C.C. Ginocchio, Role of cell culture for virus detection in the age of technology, Clin. Micro. Rev. 20 (2007) 49–78, https://doi.org/10.1128/CMR.00002-06.

[133] H. Yj, SARS-CoV-2 Reverse Genetics Reveals a Variable Infection Gradient in the Respiratory Tract, Cell (2020).

[134] M. Khoury, J. Cuenca, F.F. Cruz, Current status of cell-based therapies for respiratory virus infections, applicability to COVID-19, Eur. Respir J. (2020).

[135] S. Liu, D. Peng, H. Qiu, Mesenchymal stem cells as a potential therapy for COVID-19, Stem cell Res. Ther. 11 (2020).

[136] M. Jeyaraman, R. Somasundaram, et al., Mesenchymal stem cells (MSCs) as novel therapeutic option for nCOVID-19- A review, J. of Reg. Med. 9 (2020).

[137] S.H. Mei, S.D. McCarter, Y. Deng, Prevention of LPS induced acute lung injury in mice by mesenchymal stem cells overexpressing angiopoietin 1, PLoS Med. 4 (2007), https://doi.org/10.1371/journal.pmed.0040269.

[138] M. Shyamsundar, D.F. McAuley, R.J. Ingram, Keratinocyte growth factor promotes epithelial survival and resolution in a human model of lung injury, Am. J. Respir. Crit. Care Med. 189 (2014).

[139] L.A. Teuwen, V. Geldhof, A. Pasut, COVID-19: the vasculature unleashed, Nat. Rev. Immunol. (2020).

[140] Y. Yang, Q.H. Chen, A.R. Liu, Synergism of MSC-secreted HGF and VEGF in stabilising endothelial barrier function upon lipopolysaccharide stimulation via the Rac1 pathway, Stem Cell Res. Ther. (2015).

[141] K. Xiao, F. Hou, X. Huang, B. Li, Mesenchymal stem cells: current clinical progress in ARDS and COVID-19, Stem cell Res. Ther. 11 (2020).

[142] B.S. Bing, Clinical remission of a critically ill COVID-19 patient treated by human umbilical cord mesenchymal stem cells- A case report, Med. 99 (2020).

[143] Z. Leng, R. Zhu, W. Hou, Transplantation of ACE2-mesenchymal stem cells improve the outcome of patients with COVID-19 pneumonia, Aging Dis. (2020).

[144] X. Chen, Y. Shan, Y. Wen, J. Sun, H. Du, Mesenchymal stem cell therapy in severe COVID 19: A retrospective study of short-term treatment efficacy and side effects, J. Infect. (2020).

[145] A. Can, H. Coskun, The rationale of using mesenchymal stem cells in patients with COVID-19 related acute respiratory distress syndrome: What to expect, Stem. Cells Trans. Med. (2020).

[146] Radiotherapy overview presented by www.nhs.uk.

[147] K. Siddiqi, R. Mehra, COVID-19 illness in native and immunosuppressed states: A clinical-therapeutic staging proposal, J. Heart Lung Trans. 39 (2020). https://dx.doi.org/10.1016%2Fj.healun.2020.03.012.

[148] M. Algara, J. Marin, I. Vallverdu, P. Fernandez-Letón, J. Villar, G. Fabrer, C. Rubio, A. Montero, Low dose anti-inflammatory radiotherapy for the treatment of pneumonia by covid-19: A proposal for a multi-centric prospective trial, Clin. Trans. Rad. Onco. (2020), https://doi.org/10.1016/j.ctro.2020.06.005.

[149] J. Calabrese Edward, G. Dhawan, How Radiotherapy was historically used to treat Pneumonia: Could it be useful today? Yale J. Bio. Med. 86 (2013).

[150] E.J. Calabrese, X-ray treatment of carbuncles and furuncles (boils): A historical assessment, Hum. Exp. Toxi-col. 32 (2013). https://doi.org/10.1177%2F0960327112467046.

[151] E.J. Calabrese, G. Dhawan, The historical use of radiotherapy in the treatment of sinus infections, Dose Res. (2013).

[152] E.J. Calabrese, V. Calabrese, Reduction of arthritic symptoms by low dose radiation therapy (LD-RT) is associated with an anti-inflammatory phenotype, Int. J. Rad. Bio. 89 (2013), https://doi.org/10.3109/09553002.2013.752595.

[153] C. Huang, Y. Wang, X. Li, et al., Clinical features of patients infected with 2019 novel coronavirus in Wuhan, China. Lancet 395 (2020).

[154] P. Mehta, D.F. McAuley, M. Brown, E. Sanchez, R.S. Tattersall, J.J. Manson, COVID-19: consider cytokine storm syndromes and immunosuppression, Lancet 395 (2020). https://dx.doi.org/10.1016%2FS0140-6736(20)30628-0.

[155] C. Pedro, J. Lara, D. Macias, Low dose lung radiotherapy for COVID 19 pneumonia. The rationale for a cost- effective anti-inflammatory treatment, Clin. Trans. Rad. Oncol. (2020), https://doi.org/10.1016/j.ctro.2020.04.006.

[156] F. Rodel, L. Keilholz, M. Herrmann, Radiobiological mechanisms in inflammatory diseases of low-dose radiation therapy, Int. J. Rad. Bio. (2007), https://doi.org/10.1080/09553000701317358.

[157] L. Torres, G. Royo, M. Arquez, et al., Low-dose radiation therapy for benign pathologies, Rep. Pract. Oncol. Radio-ther. 25 (2020).

[158] E.J. Calabrese, G. Dhawan, R. Kapoor, W.J. Kozumbo, Radiotherapy treatment of human inflammatory diseases and conditions: optimal dose, Hum. Exp. Toxicol. 38 (2019). https://doi.org/10.1177%2F0960327119846925.

[159] M. Arenas, S. Sabater, V. Hernández, et al., Anti-inflammatory effects of low-dose radiotherapy. Indications, dose, and radiobiological mechanisms involved, Strahlenther Onkol 88 (2012).

[160] D. Gaurav, K. Rachna, et al., Low dose radiation therapy as a potential lifesaving treatment for COVID-19-induced acute respiratory distress syndrome (ARDS), Radio-ther. Oncol. (2020), https://doi.org/10.1016/j.radonc.2020.05.002.

[161] K. Charles, M. Marc, Is low dose radiation therapy a potential treatment for COVID-19 pneumonia? Radiother. Onco. 147 (2020) https://doi.org/10.1016/j.radonc.2020.04.004.

[162] S. Boon, Radiotherapy for COVID-19: Primum non nocere, Radio-ther. Oncol. (2020) https://dx.doi.org/10.1016%2Fj.radonc.2020.05.046.