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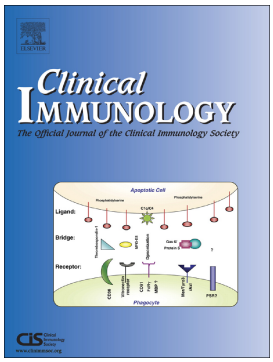

Understanding the immunological aspects of SARS-CoV-2 causing COVID-19 pandemic: A therapeutic approach

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pandemic: A therapeutic approach

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Abbreviations

ACE, angiotensin converting enzyme; Agn, angiotensin; AMs, alveolar macrophages, APCs, antigen presenting cells; ARDS, acute respiratory distress syndrome; ASCs, antigen secreting cells; AT2, alveolar type 2; BAL, bronchoalveolar lavage; CD, cluster of differentiation; cDCs, conventional dendritic cells; CCL, C-C motif chemokine ligand; CDHR3, cadherin related family member 3; CLpro, chymotrypsin-like protease; Covid-19, coronavirus disease, 2019; CTL, cytotoxic T lymphocyte; CTLA, cytotoxic T lymphocyte associated antigen; CXCL, C-X-C motif chemokine ligand; CXCR, C-X-C motif chemokine receptor; DMVs,

dsRNA, double stranded RNA; E, envelope; FGF, fibroblast growth factor; G-CSF, granulocyte colony stimulating factor; GM-CSF, granulocyte-monocyte colony stimulating factor; GZMA, granzyme; HCoV, human coronavirus; H, hydrogen; HLA, human leucocyte antigen; ICIs, immune checkpoint inhibitors; IFN, interferon; Ig, immunoglobulin; IL, interleukin; IMs, inflammatory monocytes; IMMs, inflammatory monocyte-macrophages;IP-10, inducible protein 10; IRF, interferon regulatory factor; ISG, interferon stimulated gene; LAG3, lymphocyte activation gene 3; M, membrane; mABs, monoclonal antibodies; MBL, mannose binding lectin; MCP1, membrane cofactor protein 1; MERS, middle east respiratory syndrome; MHC, major histocompatibility complex; MIP, macrophage inflammatory protein; moDCs, monocytes-derived dendritic cells; MSCs, mesenchymal stem cells; MYD88, myeloid differentiation primary response 88; N, nucleocapsid; nABs, neutralizing antibodies; NGS, of next generation sequencing; NK cells, natural killer cells; NKG2A, NK group 2 member 2A; Nsps, non-structural proteins; ORFs, open reading frames; PAMPs, pathogen associated molecular patterns; PCR, polymerase chain reaction; PD1, programmed cell death protein 1; PD-L1, programmed cell death protein ligand 1; PDGF, platelet derived growth factor; PLpro, papain like protease; Pp, polypeptides; PRRs, pattern recognition receptors; RA, rheumatoid arthritis; RBD, receptor binding domain; RBM, receptor binding motif; RLRs, RIG-I like receptors; RTC, replication transcription complex;S, spike; SARS-CoV-2, severe acute respiratory syndrome- coronavirus-2; scRNAseq, single cell RNA sequencing; SLE, systemic lupus erythematosus; ssRNA, single stranded RNA; STAT, signal transducer and activator of transcription; TIGIT, T cell immunoreceptor with Ig and ITIM domains; TIM 3, T cell immunoglobulin and mucin domain 3; TLRs, Toll like receptors; TMPRSS2, transmembrane protease serine 2; TNF, tumor necrosis factor; VEGF A, vascular endothelial growth factor A

***Keywords*:** SARS-CoV-2; immune response; COVID-19 therapy.

ABSTRACT

2), a novel variant of coronavirus has recently emerged from Wuhan in China and has created havoc impulses across the world for a larger number of fatalities. At the same time studies are going on to discover vaccine against it or repurposing of approved drugs is widely adopted are under trial to eradicate the SARS-CoV-2 causing COVID-19. Reports have also shown that there are asymptomatic carriers of COVID-19 disease who can transmit the disease to others too. But the first line defense of the viral attack is body's strong and well-coordinated immune response producing excessive inflammatory innate reaction and impaired adaptive host immune defense may leading death upon the misfunctioning. Considerable works are going on to establish the relation between immune parameters and viral entry that might alter both the innate and adaptive immune system COVID patient by up riding a massive cytokines and chemokines secretion. This review mainly gives an account on how SARS-CoV-2 interact with our immune system and how does our immune system respond to it and along with that drugs which are being used or can be used in fighting the disease and curative therapies as treatment for it has also been addressed.

1. Introduction

Evidences from the history focuses a spotlight on the incidences where coronavirus was found to the reason for the outbreak of disease and recently a new storm of coronavirus, named SARS-CoV-2 (Severe Acute Respiratory Syndrome-coronavirus-2), has been reported from Wuhan city, China. The disease is called Coronavirus disease, 2019 (COVID-19), named by WHO on Feb 11, 2020, that has first emerged in December 2019. As per the data, among the three outbreaks Middle East respiratory syndrome CoV (MERS-CoV) was the fatal most with a mortality rate of 34.77% while SARS-CoV stands out to be 10.87% of fatality and the SARS-CoV-2 has been reported to be 2.08% although is on a hike. Meanwhile the mortality rate in SARS-CoV-2 infection is lower than the previously reported two pandemics and its transmission rate is quite higher in comparison to the earlier ones [1]. As of September 4, 2020, there are 26,171,112 confirmed COVID-19 cases and death of

novel coronavirus known to infect humans. The severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) is highly contagious [3]. The most prime transmission route of COVID-19 is droplets formation of aerosols including all other possible modes of direct contact. SARS-CoV-2 incubation period is approximately 5–14 days or 24 days in some cases as per the retrospective pandemic report identified [4]. Most of the patient suspected for COVID-19 positive require the supportive care, isolation to avoid the transmission chances and stronger immunity for recovery. Though the actual mechanism is still unclear, few anti-viral drugs such as remdesivir, lopinavir, ritonavir are used for treatment [5]. The SARS-CoV-2 infection in lung with adverse symptoms namely acute respiratory distress syndrome (ARDS) and which also the leads to severe lung injury mediated by immune system [6]. The SARS-CoV-2 positive lung biopsy report revealed that the content bilateral diffuse damage of alveoli, proliferation of fibroblast and activated circulated $CD4^+/CD8^+$ lymphocytes [7]. Due to the rapid global SARS-CoV-2 transmission, investigations are much needed for the development of effective immunotherapy. In view of this context, addressing of the immunological aspects of SARS-CoV-2 spreading COVID-19 become a major focus.

2. SARS-CoV background

According to WHO, SARS-CoV-2 is from the beta lineage of the coronavirus family of group 2B with 70% genetic similarities with SARS-CoV [8]. There is four genera classification of family namely *Alphacoronavirus, Betacoronavirus, Deltacoronavirus and Gammacoronavirus* [9]. Cryo-electron tomography and cryo-electron microscopy gives an idea about the morphology of SARS-CoV. HCoV-229E and HCoV-OC43 are the two human coronavirus that are responsible for causing mild respiratory dysfunctions in humans before the rise of SARS-CoV infection in 2002, thereafter emergence of two new human coronavirus, HCoV-NL63 in 2004 and HCoV-HKU1 in 2005 has occurred, where HCoV-229E and HCoV-NL63 are found in bats [10]. Genome sequencing of SARS-CoV-2 revealed more or less 79% similarity with SARS-CoV and 50% similarity MERS-CoV according to genome sequencing that infected bat species underwent a series of genetic mutations and

the life risk situation that is prevailing all over the world because of SARS-CoV-2, raises a question forward regarding the origin of the virus. The most probable origin that has been brought to light is the zoonotic transfer of the virus from the illegally imported Malayan pangolins (*Manis javanica*) as genetic and evolutionary evidences suggest that the SARS-CoV harbored by these pangolins is 91.02% similar to the SARS-CoV-2 [12]. While angiotensin converting enzyme 2 (ACE2) host receptor sequence in bats (*Rhinolophus sinicus*), pangolins and human were taken under consideration, it revealed that the ACE2 sequence similarity between human and bats was 80.60% which is less similarity than between human and pangolins is 84.76%, indicatory that pangolins can be the original host or intermediate host of SARS-CoV-2 and therefore can promote transmission of the virus [13]. However, the genetic analysis of SARS-CoV-2 shows greater than 80% similarity compared with SARS-CoV and also more or less 50% similarity compared with MERS-CoV, both of them have a common origin i.e. bat [11]. According to phylogenetic analysis suggests that COVID-19 , seventh member of the family of beta-coronavirus, is classified as a member of the ortho-coronavirinae subfamily and can be counted within the clade of the subgenus sarbecovirus [14]. Relating to the previous epidemiological investigations we can figure out that the emergence of the new coronavirus is of zoonotic origin, keeping in mind the food habits of the Chinese people.

Being RNA virus, SARS-COV-2 has a high mutation rate that may involve in increasing virulence and pathogenecity of the infection in patients. Mutations in the surface proteins could change the tropism of the virus and increase its adaptability in new host with greater pathogenecity. Accumulation of mutations in SARA-CoV-2 may result in higher potency of pathogenecity. According to studies, high levels of mutations have been found in NSP and S proteins (Table 1). Current scenarios of COVID cases with 61.8M (million) cases and over 1.4M deaths globally, reported by WHO on 1st December 2020, shows a gradual spike in the COVID cases [15]. High level of mutations in S proteins may indicate a second wave of COVID19 with greater severity if essential steps are not taken.

The first five reported cases of COVID-19 in December,2019 were hospitalized with ARDS and one deceased. Among all human associated CoVs, four patients were having mild respiratory symptoms, while two among them, with the infection of SARS-CoV and MERS-CoV were having severe respiratory diseases [24] which mainly had been transmitted from animals to humans via an intermediate mammalian host [25]. The results of next generation sequencing (NGS) or Real-time polymerase chain reaction (PCR) of patient's sputum targeted for the envelope gene of CoV confirmed the positive infection for COVID-19 [26] and SARS-CoV-2 shares almost 80% genome similarity with SARS-CoV [4]. Patients with positive infection of SARS-CoV-29, an enveloped single stranded RNA (ssRNA) virus with positive-sense RNA, show clinical manifestations [27]. In a nutshell, the pathogenesis of COVID-19 can be categorized as systemic disorders that include fever, dry cough, headache, fatigue, high sputum production, acute cardiac injury, dysponea, lymphopenia, cytokine storm and respiratory disorders that include sore throat, sneezing, rhinorrhoea, severe pneumonia, ground-glass opacities, RNAaemia and ARDS. As per improvised current clinical symptoms, loss of smell and taste has become a new and potent symptom for COVID-19 along with other. A very recent study has shown that a higher expression of ACE2 and Type 2 transmembrane serine protease (TMPRSS2) on olfactory cells are highly affected by SARS-CoV-2 resulting in the impairment of olfactory cells [28].

SARS-Cov-2, sourcing from symptomatic along with asymptomatic patients, after infecting a healthy person, has an incubation time of 4-14 days (average 3-7 days). Respiratory droplets from affected individual infect the healthy people to transmit the disease whereas it could also be transmitted through fecal-oral route because viral nucleic acid has been detected in the faeces and urine of COVID-19 patients. Along with the disease-causing comorbidities (cardiovascular, cerebrovascular, diabetes) and people of age more than 55 are showing more susceptibility to the COVID-19 infection but *Neeltje et al*. showed that cancer patients under chemotherapy and surgery treatment are more susceptible to SARS-CoV-2. On contrary, the patients who are receiving immunotherapy using immune checkpoint inhibitors

comparatively less prone to the COVID-19 disease [29].

4. Molecular mechanism of COVID-19 as pathogen

Based on the published literatures and the observations of the COVID-19 patients, the entry of the virus occurs via nasal and larynx mucosal membranes and reaches to the lungs via respiratory tract. S (spike) protein imparts virulence by binding to the host cell ACE2 receptor followed by their entry through clathrin-mediated endocytosis [30]. Different strains of Coronavirus can recognize different host cell receptors e.g. the receptor for SARS-CoV is ACE2 which affects the pneumatocytes (Type II) and ciliated bronchial epithelial cells [31,32], the receptor for HCoV-229E is aminopeptidase N or CD13, the receptors for MERS-CoV is DPP4 (dipeptidyl peptidase4) or CD26 [32]. Based on the genetic sequence analysis, difference lies between SARS-CoV-2 and SARS-CoV-1 and thus emerged as an absolute new betacorona virus of the novel corona virus nCOVID-19. Overall structural analysis of S protein between the two SARS-CoVs showed similarity of approximately 50 ~ 53% for the RBM (receptor binding motif),around 75% for the receptor binding domain (RBD) along with 76 to 78% whole protein [33]. Assumption of using same receptors for binding comes from amino acid sequence analysis that revealed a high similarity in binding domain of ACE2 receptor in SARS-CoV [33,34]. In addition, ACE2 is an integral member of glycoprotein which is highly expressed in the lung, kidney, heart and epithelia of small intestine as well as endothelium [35]. The main function of ACE2 is the degradation of angiotensin (Ang)-II into Ang 1-7[35]. Pulmonary ACE2 maintains the balance between the circulating AngII/Ang1-7 levels. AngII, in response to hypoxia, induces pulmonary vasoconstriction and shunting in victims of lung injury and pneumonia is prevented [36].

In ARDS, ACE causes disease prognosis by increasing AngII level but ACE2 protects lung from failure by degrading AngII. Experimental evidences show that mice model where ACE2 is knockdown, drastic symptoms of ARDS is more prominent than wildtype while overexpression seems protective [37]. An increase of $CD14^{+}HLA^{-}DR^{low}$ inflammatory monocytes (IMs) and Ficolin-1^{+} monocyte-derived macrophages has been detected by single

activation of interferon (IFN) signaling and monocytes recruitment decreases the alveolar potency and aids ARDS progression [38]. S protein on SARS-CoV-2 binds with greater affinity to host ACE2 receptors in comparison to SARS-CoV-1 [39]. Apart from $ACE2^{+}$ cells, another study has focused on TMPRSS2, a cellular protease, which is required by the virus for entering into the cell as it helps the S protein on the virus surface to bind to the host ACE2 receptor, specially alveolar type-2 cells (AT2 cells) which express TMPRSS2 in large amount [40,41] whereas, the affinity towards the cadherin related family member 3 (CDHR3), a rhinovirus-C receptor at ciliated epithelial cells of the upper airway is still not cleared [42]. COVID-19 results into the inflammation in the lung tissues due to less frequent exchange between oxygen and carbondioxide upon decrease in haemoglobin. This occurs due to the role of open reading frames (ORF1ab, ORF3a, ORF10), which attacks the 1-beta chain of haemoglobin into porphyrin ORF8 and surface glycoproteins attaches. This mechanism can be treated with drugs like chloroquine, favipiravir [43]. Transcriptomic study revealed that the genome of the virus is highly complicated and undergoes innumerable transcription events that in turn contributes to the production of unknown ORFs harboring mutations and undergoes recombination event. Rapid evolution of the virus, aids the virus to be drug resistant, frequently altered host specificity, thereby contributing to the virulence of the virus [44].

5. COVID-19 affecting immune system

5.1. Antigen presentation

Whenever a pathogen enters into our body, it is recognized as antigen and presented through antigen presenting cells (APCs) via major histocompatibility complex (MHC) molecules present on their surface. The exact mechanism of presentation of coronavirus is not fully known. According to the researches on SARS-CoV, MHC I molecule mediates the antigen presentation of the virus [45] and sometimes MHC II also participates in the process [46]. Previous data has shown a variety of polymorphisms such as human leukocyte antigen

infection susceptibility of SARs virus [46,47]. The protective alleles of HLAs mainly HLA-A*0201, HLA-DR0301 and HLA-Cw1502 [48]. Similarly, polymorphism like HLA-DRB1*11:01 and HLA-DQB1*02:0 in MHC II molecules elevates the risk for developing MERS-CoV infection. Moreover, mannose binding lectin (MBL) also present SARS-CoV to the immune cells [49]. The exact MHC type for the antigen presentation of COVID-19 disease is undeciphered but available data may shed some light in conducting further researches. The prospects that needed experimental focus is exact which type of MHC molecule are involved in the antigen presentation of SARS-CoV-2?

5.2. Immune evasion

In SARS-CoV-2, pattern recognition receptors (PRRs) activates the innate immune responses via extracellular and endosomal Toll- like receptors (TLRs) in concert with cytosolic RIG-I like receptors (RLRs) [50]. Following the activation of PRRs, downstream signaling cascades stimulates the cytokines production like Type I/III IFNs as defense against virus, tumor necrosis factor alpha (TNF-α), interleukins (IL-1,IL-6, IL-18) and other proinflammatory cytokines [51]. The complex signaling pathways involving myeloid differentiation primary response 88 (MYD88) produces type I IFNs and activate the transcription factor NF-κB which induces the transcription and production of pro-inflammatory cytokines [52]. Type-I IFNs activate the downstream signal transducer and activator of transcription (STAT) proteins that catalyses generation of interferon stimulated genes (ISGs) coded antiviral proteins like IFN-induced protein with tetratricopeptide repeats-1. This phenomenon retards the replication of the virus in both neighboring and infected cells by activating an immune response against the virus. So, how COVID-19 can cause severe infection in patients? What are the immune escape strategies that are being adapted by the deadly virus? Evidences suggests that, not only SARS-CoV but MERS-CoV too produces double-membrane vesicles (DMVs) and avoid detection of their double stranded RNA (dsRNA) by host [53]. The nonspecific proteins 1 (Nsp1) of SARS-CoV repress the activation of IFN regulatory factor 3 (IRF3) and IRF7 and together with nsp3,

of IFN is blocked by accessory protein 4a of MERS-CoV upon interaction with double stranded DNA (dsDNA) directly [55]. Furthermore, studies have shown that in MERS-CoV infection ORF4a, ORF4b, ORF5 and membrane (M) proteins blocks transport of IRF3 into the nucleus and also inactivates IFNb promoter [56]. The gene expressions for antigen presentation are also downregulated after MERs-CoV infection. Thus, SARS-CoV and MERS-CoV has modified to escape from host immune surveillance. Efficient data is not available to support the theory that SARS-CoV2 also uses the same mechanism to avoid immune surveillance. Table 2 provides a comparative study on the immunological functions played by structural proteins of the virus.

5.3. Innate immune system and SARS-CoV-2

First line of defense comes from the cells of innate immune system that include residential macrophages, conventional dendritic cells (cDCs), monocytes-derived dendritic cells (moDCs), granulocytes and natural killer cells [74]. In any viral infection, the innate immune system relies on Type I interferon (IFN) responses whose downstream cascade regulate the viral replication and induce adaptive immune responses. However, nCOVID-19 may dampen the IFN Type-1 response to terminate the anti-viral response. According to studies, SARS-CoV directly affect macrophages and T cells [75]. Recent research has shown that SARS-CoV-2 induces $CD169^{+}$ tissue-resident macrophages to produce IL-6 which results into lymphocyte apoptosis via upregulation of Fas in human spleen and lymphnode [76]. According to the data of scRNAseq of COVID patients, there was expansion of $CD14^{+}IL\text{-}\beta^{+}$ monocytes [77] and IL-β associated inflammation in peripheral blood [78] and IMs, $Ficolin\text{-}1^{+}$ monocyte-derived macrophages and tissue-resident reparative alveolar macrophages (AMs) in pulmonary tissues of severe condition [79]. In severe infection, lung macrophages express high IL-1B, IL6, TNF and chemokines like C-C motif chemokine ligand (CCL) 2, CCL3, CCL4 and CCL7,C-X-C motif chemokine ligand (CXCL) 9, CXCL10, CXCL11 but CXCL16, whose product binds C-X-C motif chemokine receptor (CXCR) 6 was more highly expressed in patients with moderate infection [79]. Moreover,

neutrophils though CCR1 and CXCR2 [79]. According to earlier data, SARS-CoV-1 infection resulted in an diverging phenotype of AM phenotype which limits the trafficking of DC and activation of T cell [80] and $YM1^+$ $FIZZ1^+$ alternatively activated macrophages increased hypersensitivity in airway, thus worsening the fibrosis by SARS-infection [81]. These mechanisms, in SARS-CoV-2, need more research focus. Recent research revealed that ACE2 and SARS-CoV-2 N protein is also present $CD169^+$ macrophages of spleen and lymph node SARS-CoV-2 patients that are involved in production of IL-6 [82]. As mentioned earlier, SARS-CoV-2 undergoes the process of causing infection via ACE2 receptors but very low macrophage percentage in lungs express ACE2 receptors. So, the question arises that is there any other receptor present through which SARS-CoV-2 is infecting immune cells? Evidences revealed reduced number of natural killer (NK) cells, in peripheral blood are positively correlated with COVID severity [83–85]. In influenza infection, CXCR3 mediated NK cell infiltration [86]. In vitro study shows increased level of CXCR3 ligand (CXCL9-11) in SARS-CoV-2 infected tissue of human lung along with expanded monocyte level stimulated by CXCR3 ligand in SARS-CoV-2 infection [38]. These studies suggest that the CXCR3 pathway recruits NK cell in SARS-coV-2 infected patient the lungs from peripheral blood. Recent studies have shown that peripheral blood NK cells of SARS-coV-2 patients with deceased expression of enzymes such as granzyme B, granulysin and also reduced surface markers CD107a, Ksp37, and an impaired chemokine production of TNF-α and IFN-ɣ that suggest an impaired cytotoxicity [84,87]. Moreover, SARS-CoV-2 infection has shown less number of $CD16^+KIR^+$ peripheral blood NK cells [88]. The expression of immune checkpoint NK group 2 member 2A (NKG2A) is increased with the upregulation of genes encoding inhibitory receptors lymphocyte activation gene 3 (LAG3) and T cell immunoglobulin and mucin domain 3 (TIM3) on NK cells of COVID patients [84,87]. Thus SARS-CoV-2 impairs the activity of NK cells. The impaired immune response stimulated by SARS-CoV-2 has been summarized in Fig 1.

Antigen presentation by APCs to other immune cells subsequently activates pathogen (virus) specific B cells and T cells. Similarly in SARS-CoV, viral infection a typical pattern of IgG and IgM has been observed where the IgM antibodies disappear in the 12th week but the IgGs which are viral S-specific and N-specific, last for a longer period [89]. The near-universal presence of IgGs, IgM, IgAs and neutralizing IgGs antibodies (nABs) in COVID patients indicates a humoral immune response mediated by increase in B cells. Covid-19 patients show higher levels of antigen secreting cells (ASCs) derived from precursor naïve B cells. These B cells are regarded as double negative2 (DN2) as they lack naïve IgD, memory CD27 markers, CXCR5 and CD21 markers. The ASCs express high levels of CD11c and T-bet molecular markers and respond to TLR7. Patients in early stages with high levels of ACEs provides a protective function against eradication of virus whereas in later stages high levels ACE show poor outcomes [90]. SARS-CoV-2 specific IgG of S protein was found in the serum of patient even after 60 days of symptom onset, which decreased within 8 weeks of onset of post symptom [51]. Further studies are needed on the existence of viral specific IgG^{+} memory cells in recovered COVID patients.

Latest data has shown that in COVID-19 patients the peripheral count of CD4^{+} and CD8^{+} T cells have been greatly reduced but they were hyperactive in status. Additionally, a hike in highly proinflammatory CCR4^{+}CCR6^{+} CD4^{+} T cells (Th17 cells) producing IL-17 and granulysin expressing Tc cells were observed in patients with severe immune injury [91]. Moreover, the cytotoxic Tc cells (CD8^{+} T cells) were much higher in number e.g. 31.6% cells were perforin positive, 64.2% cells were granulysin positive and 30.5% cells were double positive for both perforin and granulysin [91]. These results implicated that the high number of Th17 and CD8^{+} T cells and their hyperactive function is responsible for severe immune inflammation in patients and produces low IFN-γ and TNF-α in CD4^{+} T cells and high granzyme B and perforin in CD8^{+} T cells in COVID-19 infected patients [92]. It has been reported that CD8^{+} T cells, developed during SARS-CoV infection, are specifically produced for the antigen S, M, E and N proteins. In SARS-CoV infection, CD8^{+} T cells have been

cells express $CD45^{+}CCR7^{+}CD62L^{-}$ central memory T cells [93]. Th1 cells which was hyperactivated releases granulocyte-monocyte colony stimulating factors (GM-CSF) and IFNγ. This recruits increased numbers of $CD14^{+}CD16^{+}$ monocytes that are inflammatory, stimulated by Il-6 [94]. In moderately infected lung macrophages produced increased chemokines, that will attract T cells, via ethe engagement of CXCR3 and CXCR6 [38]. So, innate and adaptive immune cells interact with each other and they are involved in a positive loopback in expressing higher inflammation in COVID-19 infection. $CD8^{+}$ T cells expressing high level cytotoxic genes such as *granzyme K, A, B* (*GZMK, GZMA, GZMB)* and *XCL1* along with *KLRC1* and were high in mild symptoms have been detected in bronchoalveolar lavage (BAL) of COVID patients [95]. Moreover, experimental analysis suggests that these memory cells lasts for 3-4 years after the infection has been cured and slowly diminishes in the absence of antigen after 4 years [93]. Moreover, all the subtypes of T cells found in SARS-CoV-2 infection, shows higher expression of negative immune checkpoint markers and exhaustion markers that is correlated with severe immune pathogenicity. The study of 10 patients group revealed increased levels of PD-1 in $CD8^{+}$ T cells and Tim3 in $CD4^{+}$ T cell were observed in three patients of both prodromal and symptomatic stages of SARS-CoV-2 infection [96]. Furthermore, several other investigations reported increase in the expression of both co-stimulatory and inhibitory molecules such as OX-40 and CD137 [94], CTLA-4 and T cell immunoreceptor with Ig and ITIM domains (TIGIT) [92] and NKG2A [84], were found in T cells which suppressed cytotoxic activity. Till now there is no potent evidence of any memory cells developed in cured COVID-19 patients against SARS-CoV-2.

5.5. Cytokine storm and SARS-CoV-2

Till now according to the reports, the main cause of death due to COVID-19 is severe pneumonia and ARDS. The key cause behind the occurrence of ARDS is the severe "cytokine storm" in infected patients that resulted in pneumonia, respiratory failure and other organs failure. A high cytokine storm occurring in COVID-19 patients include IL1-β, IL1RA, IL7, IL8, IL9, IL10, basic-fibroblast growth factor 2 (FGF2), granulocyte colony stimulating

inflammatory protein 1α (MIP1α), MIP1-β, platelet derived growth factor B (PDGF-B), TNFα, and vascular endothelial growth factor A (VEGFA) [26,97]. The ICU patients show high levels of pro-inflammatory cytokines such as IL2, IL7, IL10, G-CSF, IP10, MCP1, MIP1α, and TNFα, which are positively correlated with disease severity [26]. In a report from Wuhan where 99 cases had been studied, an increase in total neutrophils, decrease in total lymphocytes and increased in serum IL-6 has been observed. A delayed IFN-I signaling was observed which accumulate inflammatory monocyte-macrophages (IMMs).This resulted in high levels of cytokine and chemokine in lung, vascular leakage and impaired the response of viral-specific T cell [98]. In SARS infected patients, an elevated level of IL-6, IL-8 and inducible protein 10 (IP-10) has been found in lung tissue [99]. Increased levels of proinflammatory cytokines is mainly responsible for severe lung injury, leading to demise of nCovid victims [91]. High levels of IP10 was related with immune mediated severe lung injury and apoptosis of lymphocytes in SARS [99]. Together with the cytokines, certain chemokines such as CXCL10, IP10 CCL2, CCL3, CCL5, CXCL8, CXCL9 support the impaired systemic inflammatory response in SARS-CoV-2 [100]. In comparison with SARS-CoV, SARS-CoV-2 upregulated five chemokines namely CXCL1, CXCL5, CXCL10, CCL2 and IL-6 [101]. SARS-CoV-2 patients with more severe pneumonia and pulmonary syndrome showed correlated higher expression of GM-CSF^{+} and IL-6^{+}CD4^{+} T cells, higher co-expression of IFN-γ and GM-CSF in pathogenic Th1 cells, much higher expression of CD14^{+}CD16^{+} monocyte [94]. In a nutshell, high infiltration of all type of immune cells such as T cells, monocytes, macrophages, NK cells, DCs, and secretion of their proinflammatory cytokines into lung cause severe ARDS leading to death in the patients.

6. Ongoing therapies

Currently there is no clinically approved antiviral vaccine for the treating SARS-CoV-2. All patients are treated with supportive treatment strategies targeted to culminate the patients' symptoms (like pneumonia, fever, breathing problems) and often supported with combination of drugs. However, these strategies cannot be implemented for a long time.

other RNA viruses such as the Human Immunodeficiency Virus (HIV). Clinical trials are currently undergoing with combinational drugs mainly ritonavir and lopinavir. Several other drugs are under clinical trials such as Kevzara, a rheumatoid arthritis (RA) drug that decreases lung complications. Kevzara has been successfully tested in COVID-19 patients. As per data, there are 11 phase 4, 36 phase 2 and 4 phase 1 trails [102]. Table 3 encloses a list of commonly used combinational drugs for the treatment of COVID-19.

As it has been an absolute outbreak and pandemic disease declared by WHO, a specific cure has to be found out to cure the disease completely. According to the genomic and structural analysis of SARS-CoV-2, there are a number of therapeutic targets which are under clinical trials in different laboratories across the whole world.

6.1. Viral targets

The Washington Department of Health Administration has first introduced remdesivir which inhibit RNA dependent RNA polymerase activity intravenously and found that it has a potential to protect from SARS-CoV-2 infection. The combination of remdesivir and choloroquine has shown to prevent SARS-CoV-2 infection *invitro*. Therefore, other nucleotide analogue such as favipiravir, ribavirin can also be administered as potential inhibitors. There are certain proteases such as 3 chymotrypsin-like protease (CLpro) along with papain like protease (PLpro) that cleave viral polyproteins, can be the noble drug targets for the treatment. These also affects the replication of virus and antagonize IFN, IL-6. As SARS-CoV-2 binds with the ACE2 receptors of host cell, therefore targeting the S protein on the surface of the virus or the binding of the S protein and ACE2 can be a potential therapeutic target to combat COVID-19 infection. Fig 2 points out the role of various drugs in distinctive stages of SARS-CoV-2 replication process.

6.2. Antibody and plasma therapy

According to studies the development of recombinant monoclonal antibody (mAb)

human mAb, can bind with the RBD of SARS-CoV-2and can be used as candidate vaccine for SARS-CoV-2. Other mAbs, such as m396, CR3014, can be alternative against SARS-CoV-2. Recently, a recombinant mAb named tocilizumab has come into application that can bind to IL-6 receptor, thereby terminating its signal transduction but its efficiency is still under study [29]. In addition to it, virus neutralizing antibody isolated from convalescent serum of COVID-19 patients, who has recovered from the infection, is also administered in susceptible individuals as it proved to be promising treatment approach during the previous corona outbreaks. It can impose immediate immune response in the unaffected susceptible individuals [109]. The generation of antibodies against the S proteins of the virus is being followed by Moderna Inc., MA, USA. There is also hope for development of new mAbs, which may take less time to be available to the doctors due to their speedy trials and their high specificity.

6.3. Development of Vaccine

In this pandemic situation, approved vaccines against SARS-CoV-2 are essentially required as soon as possible for decreasing disease severity together with reduced shedding and transmission of virus. Currently, no approved vaccine is available in the market to cure this disease. In the world full of darkness, a keen ray of light has been illuminated by the recent development of a vaccine mRNA1273 by The National Institute of Allergy and Infectious Diseases (NIAID), part of the National Institutes of Health (NIH). This mRNA1273 is now under phase one trial. The vaccine may be available in the near future, but the time require for this to reach the market depends on the efficacy and success in all three phases of clinical trials.

6.4. Epitope Mapping

Significant studies have been focused on identifying various target epitopes mapping on SARS-CoV-2 for development of targeted vaccines. Apart from antibodies

fragments (epitopes). This investigation has utilized the data on genetic differences and similarities among the three strains of coronavirus by utilizing bioinformatics analysis [110,111]. By implementing immune informatics scientists discovered five cytotoxic T lymphocytes (CTLs) epitopes and eight B-cell epitopes in the viral surface glycoproteins. Among the B cell epitopes three are sequential and rest five are discontinuous. Furthermore, CTL epitopes are activated as judged by molecular dynamicity that the interaction between the CTL epitopes and HLA chains of MHC-I complexes are mediated by hydrogen (H) bonds and salt bridges, indicating their efficacy to confer immune responses [111]**.** Another study has identified five linear and two conformational B cell epitopes of SARS-CoV-2 surface proteins [112]**.**

6.5. Stem cell therapy

This noble therapeutic approach was not undertaken into study until two distinct studies conducted by China and detected that stem cell therapy can be a new aspect in the treatment of COVID-19. Intravenous infusion of mesenchymal stem cells (MSCs) can play a vital role in curing the dysfunctions of the lung i.e. complications like pulmonary edema, dysfunction of air-exchange, ARDS, acute cardiac injury which are the results increased inflammation due to the account of the virally triggered cytokine storm caused damage to lung tissues [41,113]. These MSCs, depending on their properties of modulating the immune system and regeneration or differentiating capability can counteract the increased release of cytokines and their repairing capacity thus restore the damaged tissues, followed by curing the disease. Moreover, RNA-sequencing of transplanted MSCs has revealed the presence of undifferentiated transfused MSCs and remained to ACE2 negative thus there exist no chance for the virus to affect these cells [113].

7. Ongoing interventional studies

is undertaken across the world on observing the severity of COVID-19. From the increasing number of fatalities and affected individuals reported across the world, it is clear that COVID-19 is escaping the treatment strategies undertaken to eradicate it. Due to the immense capability of SARS-CoV-2 to mutate very rapidly, a challenge has been thrown to the scientists to develop a potent vaccine that can destroy it all. Keeping pace with the abovementioned treatment strategies, several drugs, which are used for treating other diseases, under clinical trial to find a solution to the menace of COVID-19. A list of interventional drugs and vaccines under trial has been illustrated in the Table 4.

Another concept of controlling the rapid spread of the virus is to develop herd immunity which is defined as decrease in population of susceptible individuals below the threshold value required for transmission. The contagious state of SARS-CoV-2 (R_0) varies between 2%-3%. So, for acquiring herd immunity the threshold value is 67% for this virus.

8. Conclusion

The current scenario of rapidly spreading and unpredicted infectious nature of SARS-CoV-2 demands an urgency to focus on basic science and clinical research. Though there are a few resemblances of immunopathogenesis of SARS-CoV-2 with SARS-CoV-1 and MERS but the differences are prominent enough to focus on new therapeutic targets for developing vaccines. Within short time there is significant knowledge about the immunology of SARS-CoV-2 infection which can aid in potent vaccine development. The emerging cases of asymptomatic situations is demanding a better and deep evaluation about the mechanisms of immune response following SARSCoV-2 infection to develop a promising therapeutic approach. Here, we reviewed some recent literatures that interrogate the viral entry, invasion, escape and immune mechanisms, the dysfunctions of various immune cells like T cells, NK cells, monocytes lineages with a brief view on the memory cells. We also addressed antibody and plasma therapy as well as vaccine development against SARS-CoV-2. Further studies are needed to explain the immune response varying in victims encompassing both affected and

accomplish the unmet needs.

Authors contributions

All authors have contributed equally in this work.

Conflict of interest

Authors do not have any conflict of interest.

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utations	**Features**	**Outcomes**	**Ref.**
ikeD614G	A missense mutation in S protein encoding gene, where an amino acid (aa) change from aspartate to glycine at 614 position was found. With this mutation this strain contains 3 other mutations as follow: 1. C-to-T mutation at the 5′ untranslated region (UTR) at position 241, 2. C-to-T mutation at position 3037, 3. a nonsynonymous C-to-T mutation at position 14408 within the RNA dependent RNA polymerase gene.	D614G substitution was a rare mutation at the beginning of the COVID-19 spread before March 2020, found as predominant in Europe, but later it occurred about 74% in all published sequences in June 2020 and spread worldwide. This mutation enhances the viral replication in the upper respiratory tract and also has higher susceptible to neutralization by monoclonal antibodies.	[16,17]
SP2 and SP3	SARS-CoV-2 contains a polar aa instead of nonpolar aa unlike bat SARS at position 321 and glycine is replaced by serine in NSP3 at position of 543.	This may affect the mechanisms involved in viral entry and replication and increases the contagiousness of the virus.	[18]

2012/01	CoV-2 has 29 aa substitution from the original Wuhan strain with a mutation N501Y which is located in the receptor binding region.	According to till now revealed reports this new strain possesses a high transmissible rate than the original strain.	
utations Rdrp	A mutation was found in the RNA dependent RNA polymerase at the position of 14408.	It might result in drug resistant viral phenotype.	[20]
utations ORF gion	According to the present studies there are mutations in ORF region as follow: 1. C > T in ORF1ab gene at position 8782, 2. T > C in ORF8 gene at position 28144.	Better studies needed to understand the role of this mutation in viral pathogenecity.	[21]
382 riant	This variant has 382 nucleotide deletion in ORF8.	This variant, seen during the early epidemic in Wuhan, was mild infectious with lower concentration of proinflammatory cytokines.	[22]

ARS-CoV-AZ-SU2923	of 81 nucleotide in the ORF7a region found in Arizona.	to be studied.	

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ame of the ructural rotein	**Structure**	**Function on immunological aspects**		
		SARS-CoV-1	MERS	SARS-CoV-2
nstructural otein (nsp)1 –59]	It is a leader protein, cleaved chain of ORF1b.	Antagonize IFN-β production by decreasing the phosphorylation level of STAT1.	Helps in viral replication.	Detailed function not known.
sp 15 [60–64]	Nidoviral RNA uridylate specific endoribonuclease (NendoU) that belongs to EndoU family. 34 KDa, around 345 amino acids, with three domains: N terminal, middle and C-terminal domain.	Cleaves polyuridine (polyU) sequences from PUN RNAs and limits the formation of a PAMP and thus impedes the ability of activation the innate immune response to infection by MDA5.	Prevent activation of dsRNA sensors in host cell for evading immune system.	Inhibits the nuclear localization of IFR3 and antagonize the production of IFN and also target RNF41 (also known as NRDP1) to regulate innate immune system.
sp 9 and Nsp [64–66]	The crystalline structure of Nsp9 of SARS-CoV revealed that the molecule form two distinct types of	Nsp10 regulates the activity of the 2′-O-Methyltransferase (2′-O- MTase) that prevents virus detection	According to available data Nsp9 helps in viral replication.	Interacts with NF-κB repressor, NKRF and activates IL-8/IL-6 mediated

	of the protein is an open 6-stranded β-barrel that in turn comprises of two antiparallel β sheets packed orthogon.	mechanisms and viral translation inhibition by the interferon-stimulated IFIT-1 protein.		neutrophils that results in inflammatory response in patients.
sp13 3,64][67]	It is a helicase of superfamily 1 and helps in viral RNA replication via unwinding of duplex RNA and DNA leaving a 5′ single-stranded tail in a 5′ to 3′ direction.	It acts as a helicase and helps in unfold the RNA-DNA hybrid.	Nsp13 attenuates the viral replication.	Targeted TBK1 and TBKBP1 to inhibit interferon pathway to regulate innate immune response in host cell.
(Nucleocapsid) rotein [68]	N protein of SARS-CoV-2 is 29.9 kb n length, similarly to 27.9 kb SARS-CoV and 30.1 kb MERS-CoV genome.	Generation of IFN is retarded upon crosstalk between the SPRY domain of TRIM25 and C terminus of the N protein as it blocked RIG-I ubiquitination by TRIM25.	Interacts with TRIM25 and interfere the IFN production in host cell.	Detail function is not clearly known.
RF (open ading frame)	ORF-9b possess a long hydrophobic	ORF-9b manipulates host cell mitochondrial	Function in immune system	ORF9b in association with

6 [69,70]	formed due to interwined dimer with an amphipathic outer surface	MAVS signaling that results in reducing NLRP3 inflammasome activity, thus evading innate immune system.		with a signaling adaptor MAVS indirectly
RF6 [62,63]	SARS-CoV-1 and SARS-CoV-2 share only 69% amino acid similarity	It prevents primary production of interferon.	Helps in viral assembly and viral release and can act as a potential B cell epitope.	It prevents interferon production by various signaling molecules MDA5, MAVS, TBK1 and IRF3-5D, which is a phospho-mimic of the activated form of IRF3.
RF3 [71–73]	Accessory protein formed by the cleavage of ORF1 and ORF1b.	ORF3a is responsible for activation of the NLRP3 inflammasome by secreting IL-1β.	Prevent interferon production and prevent inflammation.	The hypothesis is that ORF3a of SARS-CoV-2 may be less efficient in inflammasome activation.

IFIT, interferon-induced protein with tetratricopeptide repeats; IFN, interferon; IRF, interferon regulatory factor; MTase, methyltransferase; N, nucleocapsid; NendoU, nidoviral RNA uridylate specific endoribonuclease; NF-κB, nuclear factor **kappa**-light-chain-enhancer of activated B cells; NLRP3, NLR family pyrin domain containing 3; NRDP1, neuregulin receptor degradation protein 1; Nsps, non-structural proteins; ORFs, open reading frames;PAMP, pathogen associated molecular patterns; PolyU,

polu ignal transducer and activator of transcription; TBK1, TANK binding kinase 1; TBKBP1, TANK binding kinase-1, binding protein 1; TRIM25, tripartite motif containing 25

Name of drug	Description	Function
Chloroquine and hydroxyl chloroquine [103–105]	These drugs are basically used in malaria treatment and some extent to Systemic Lupus Erythematosous (SLE) and rheumatoid arthritis (RA) treatment.	Chloroquine and hydroxychloroquine inhibits viral entry into cells. The glycosylation of host receptors, endosomal acidification and proteolytic processing are inhibited. These agents also affect immunopathology via production of cytokine inhibition of lysosomal activity and autophagy of immune cells.
Lopinavir/ritonavir [106]	Lopinavir and ritonavir are approved by US Food and Drug Administration (FDA) and in treatment of HIV.	No published data are available but invitro studies show that they act by inhibiting 3-chymotrypsin-like protease.
Remdesivir [107]	Remdesivir, also called GS-5734, is a monophosphate prodrug that forms an active C-adenosine nucleoside triphosphate analogue undergoing metabolism.	The drug was designed against microbes with activity also against RNA viruses. Remdesivir targets the RNA dependent RNA polymerase and hamper the replication cycle of RNA viruses. Remdesivir first used for the

Umifenovir [108]	Umifenovir or Arbid, an antiviral drug.	It inhibits S protein/ACE2 interaction via blocking the fusion of membrane with the viral envelope. Arbid is used for the treatment of influenza in Russia and China and is recently in the interest for treating COVID-19.

ACE2, angiotensin converting enzyme 2; HIV, human immunodeficiency virus; RA, rheumatoid arthritis; S, spike; SLE, systemic lupus erythematosus; FDA, food and drug administration

Tabl

Candidate drug	Mode of action and dose	Existing disease approval	Trial sponsor	Location	Expected Result	Phase trial
Hydroxycholoroquine (ID: NCT04329611) [114]	Hydroxychloroquine inhibits acidification of endosomes, deglycosylates receptors of recipient cells, prevents proteolytic processing thus retards entry of virus. Inhibition of cytokine production modulates the host immune system. It also inhibits in host autophagy and lysosomal functionality **Dose:** Hydroxychloroquine dose of 400 mg po bid on day 1 followed by	Malaria, rheumatoid arthritis (RA), lupus	Dr. Michael Hill	University of Calgary	Preliminary trials indicated that it is a potential and safe drug against COVID-19 pneumonia and shorten the disease course about 50%. Later it was found that both these drugs have side effects like allergic reactions, hypoglycemia, cardiomyopathy. On April, 2020 in Brazil 11 patients died due to irregular heart rates.	Phase III

	be given twice daily for 4 days					
Remdesivir (ID:NCT04292899 and NCT04292730) [115–117]	Antiviral **Dose:** RDV 200 mg on first Day followed by RDV 100 mg for next 4 days together with standard therapy.		Gilead, WHO, INSERM	China, japan	According to US NIAID, remdesivir shows faster recover from COVID-19 in 11 days compared to other drugs. A clinical trial in china, reported on 29thApril several adverse effect of remdesivir in treated patients.	In April 2020, there was 9 phase III clinical trials across the world.
Duvelisib (ID:NCT04372602) [118]	Target PI3K and control hyperactivation of innate immune system by affecting macrophage polarization, reducing inflammation in pulmonary and limit the persistence of viral load.		Washington University School of Medicine.	Washington University School of Medicine, Saint Luis, Missouri, United Sates	Current primary outcome reported on 30th April overall survival	Phase II

	for 10days, orally					
Deferoxamine (ID: NCT04333550) [119,120]	It is a natural product which is isolated from *Streptomyces pilosus*. It helps in the formation of iron complexes and its mesylate form perform as chelating agent,		Kermanshah University of Medical Science	Regenerative Medicine Research Center, Kermanshah University of Medical Science, Iran, kemanshah.	Trial ongoing	Phase I Phase II
Favipiravir (ID:NCT04336904)[121]	It targets RNA-dependent RNA polymerase (RdRp) enzymes, which are necessary for the transcription and replication of viral genomes. **Dose:** Day 1:1800mg,	Used before against Ebola virus and lassa virus.	Giuliano Rizzardini	Asst Fatebenefratelli Sacco, Milan Ilaty	the normalization of pyrexia, normal respiratory rate and relief from cough is maintained for at least 72 hours.	Phase III

	on day 1andday 2 followed by TID dose at 600mg for 14 days. Thereafter: 600mg, TID, for a maximum of 14 days.					
Tocilizumab (NCT04345445) [122]	Human monoclonal antibody against IL-6 receptor. **Dose:** Intravenously administered with a concentration of 8 mg/kg (body weight) once, within 60 minutes.	This drug has been used against immune suppression and in RA.	Genentech-hoffmann La Roche	Multiple countries	As per 8-point WHO scale, improvement of more than 2 point is observed.	Phase II
Sarilumab (ID:NCT04327388) [123]	Human monoclonal antibody against IL-6 receptor. **Dose:** Sarilumab Dose 1 given intravenously one time on Day 1	RA	Regeneron-Sanofi	Multiple countries	Patients improvement in oxygenation.	Phase II/ Phase III

Dapagliflo **(ID:NCT04350593)** [124,125]	glucose cotransporter inhibitor. **Dose:** Dapagliflozin 10 mg daily	mia	Luke's Mid America Heart Institute, Astrazeneca	countries	functionality of organs are observed in hospitalized patients at 30th day.	Phase III
Recombinant Human Angiotensin-converting Enzyme 2 (rhACE2) **(ID:NCT04287686)**[126]	It is a monocarboxy-peptidase that metabolizes several peptides, including the degradation of angiotensin II, and contributes to cardiovascular effect. **Dose:** Together with standard treatment0.4 mg/kg IV BID given for 7 days.		Hospital of Guangzhou Medical University	Guangdong China	24-48 hours of Pulmonary imaging showed that progression of the lesions are more than 50% and the patients were managed as severe	Phase II
Clevudine with combination Hydroxychlor	Clevudine is an antiviral drug used against hepatitis B.	Hepatitis B	Bukwang Pharmaceutical		Trial ongoing	Phase II

oquine **(ID:NCT04347915)** [127]	**Dose:** Clevudine 120 mg once daily for 14 days (Hydroxychloroquine 200mg twice daily for 14 days.					
Drug: FT516 **(ID: NCT04363346)** [128]	FT516 is a cryopreserved NK cell product of an iPSC that was transduced with ADAM17 non-cleavable CD16 (Fc receptor). **Dose:** Firstly, FT516 is administered at 9 x107 cells/dose in low concentration Secondly, FT516 is first given at low dose (9 x107 cells/dose) additionally at Day 4 it is provided in medium	Cancer	Masonic Cancer Center, University of Minnesota	Minneapolis, Minnesota, United States.	Trial ongoing	Phase I

	cells/dose) Thirdly, along with the low and medium doses, a higher dose of drug is given at day 7 (9 x 108 cells/dose)					
DAS181 (ID: NCT04324489) [129]	**Dose:** 9mg daily for 10 days		Renmin Hospital of Wuhan University	Wuhan, Hubei, China	Trial ongoing	
Losartan (ID: NCT043 35123) [130]	**Dose:** 25 mg for first 3 days folllowed by 50 mg QD till study completion		University of Kansas Medical Center	Kansas City, United States.	Trial ongoing	Phase I
Ivermectin with Nitazoxanide (ID: NCT04360356) [131–133]	Antiviral drug that affect the viral RNA and DNA replication in a broad spectrum. **Dose:** Ivermectin 200 mcg/kg once orally on		Tanta University		Trial ongoing	Phase II

	Nitazoxanide 500 mg twice daily orally with meal for 6 days					
Transfusion of SARS-CoV-2 Convalescent Plasma. (ID: NCT04372979) [134,135]	Convalescent plasma contains antibody against SARS-CoV-2. **Dose:** Intravenous		Direction Centrale du Service de Santé des Armées	France	Trial ongoing	Phase III
Isotretinoin (ID:NCT0436 1422) [136]	Inhibitors of PLpro, a protein encoded by SARS-CoV2 **Dose:** Orally	used to decrease virema in HIV patients	Tanta University	___	Clinical clearance Change in COVID-19 virus load	Phase III
Colchicine (ID:NCT0437 5202) [137]	Non-selective inhibition of NLRP3, a pathophysiologic component of SARS-CoV **Dose:** 0.5mg every 8	Cardiovascular disease	University of Perugia	Italy	Trial ongoing	Phase II

	orally (Tablet)					
Ruxolitinib (ID: NCT04355793 ,NCT04338958) [138–140]	Treat the cytokine storm and hyperinflammation in COVID-19 patients **Dose:** 5mg orally twice daily	Treat bone marrow disorders like myelofibrosis	Incyte corporation University of Jena	USA	Reduce 25% hyperinflammation caused due to the cytokine storm	Phase II
Sildenafil (ID:NCT04304313) [141]	Relaxes the muscles of the lungs by increasing the potency of nitric oxide gas to widen the blood vessels resulting in more oxygen inhalation **Dose:** 0.1g daily for 14 days, orally	Erectile dysfunction	Tongji hospital	China	Respiratory symptom remission Decrease in fever C-reactive protein recovery	Phase III
Sirolimus (ID: NCT04341675) [142]	mTOR inhibitor, immune suppressor **Dose:**6mg on first Day then 2mg daily for next	Used for preventing organ transplant rejection and	University of Cincinnati	USA	Trail ongoing	Phase II

		eiomyomatosis (LAM)				
Peginterferon Lambda-1a (ID: NCT04331899) [143]	Reduces viral shedding of SARS-CoV-2 **Dose:** One subcutaneous injection of 180 ug	Hepatitis B Virus infection Hepatitis C virus infection	Stanford University	USA	Trial ongoing	Phase II
Rintatolimod and IFN Alpha-2b(ID:NCT04379518) [144]	Rintatolimod is a dsRNA designed to mimic viral infection by activating immune pathways and IFN Alpha-2b activate immune responses and both participate in limiting viral replication and shedding **Dose:** IV rintatolimod for 2.5-3 hours together with IV of recombinant interferon alpha-2b over	Viral infections	Roswell Park Cancer Institute	USA	Trial ongoing	Phase I/ IIa

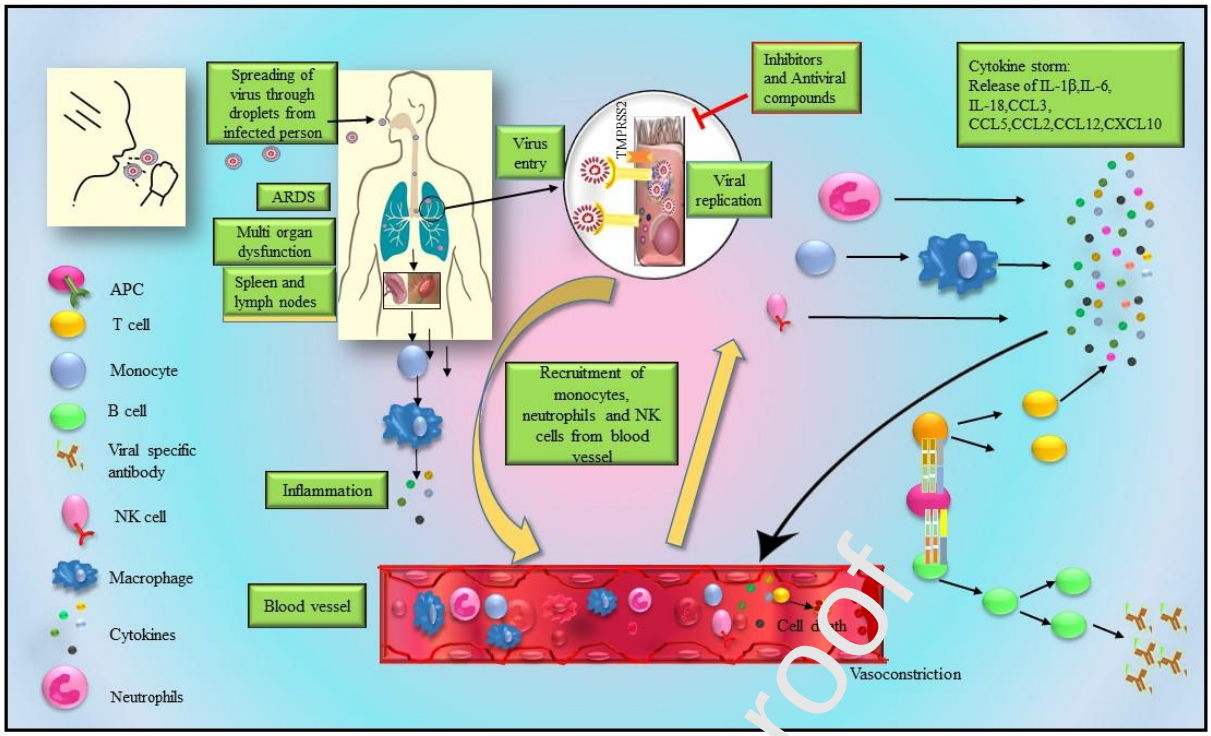
	3, 5, and 8 if there will be the disease progression or no unacceptable toxicity treatment will be followed up at 14th day and 28th day					
L-ascorbic acid (ID: NCT04357782) [145]	Reduce inflammation, ARDS, reduce supplement oxygenation, reduce risk respiratory failure which intubation **Dose:** 50mg/kg IV given every 6 hours for 4 days (16 total doses),	Sepsis	Hunter Holmes Mcguire Veteran Affairs Medical Center	Virginia, USA	Trial ongoing	Phase I/ II
mRNA1273 (ID:NCT04283461) [146,147]	A lipid nanoparticle (LNP) encapsulated with mRNA encoding full length S protein of SARS-CoV-2. **Dose:**10/25/50/100/250		National Institute of Allergy and Infectious Disease (NIAID)		Trial ongoing	Phase I

	.05mL intramuscular injection in deltoid muscle.					
INO-4880 (ID:NCT04336410) [148]	It is a DNA vaccine against whole- length S protein of SARS-CoV-2. **Dose:** intradermal injection of 1.0 mg of INO-4800		Inovio Pharmaceuticals		Trial ongoing	Phase I
ChAdOx1 nCoV-19 COVID-19 (ID:NCT04324606) [149,150]	Adenovirus encoding full-length S protein **Dose:** One dose of 5 x 10^10vp		University of Oxford	UK	Trial ongoing	Phase II
COVID-19 LV- SMENP-DC (ID:NCT04276896) [151]	Lentivirus infected dendritic cells with SMENP minigenes that express COVID-19 antigens and activated CTLs.		Shenzhen Geno-Immune Medical Institute		Trial ongoing	Phase II

SARS-Cov (ID:NCT04368988) [152]	spike (S) protein of SARS-CoV-2					Phase I
BNT162a1, b1, b2, c2 (ID:NCT04368728)[153]	It is a LNP encapsulated mRNA vaccines with mRNA targets for both larger S sequence and RBD. **Dose:**0.5mL intramuscular injection.		BioNTech SE and Pfizer, Inc.		Trial ongoing	Phase I
Recombinant Novel Coronavirus Vaccine (Adenovirus Type 5 Vector) (ID:NCT04313127) [58]	Adenovirus type 5 encoded with full length S protein		CanSino Biologics, Inc.	China	The vaccine is tolerable and immunogenic at 28 days post-vaccination in healthy adults, and rapid specific T-cell responses were noted from day 14 post-vaccination.	Phase I
bacTRL-Spike-1 (ID:NCT0433	Live *Bifidobacteriumlongum*, engineered for the		Symvivo Corporation		Trail ongoing	Phase I

4980) [154	containing synthetic DNA encoding spike protein from SARS-CoV-2.					

ADAM 17, a disintegrin and metalloproteinase 17; CTLs, cytotoxic T lymphocytes; dsRNA, double stranded RNA;IFN, interferon; LAM, lymphangioleiomyomatosis; LNP, lipid nanoparticle; mTOR, mammalian target of rapamycin; NK, natural killer; NLRP 3, NLR family pyrin domain containing 3; PI3K, phosphatidylinositol 3 kinase; RBD, receptor binding domain; RA, rheumatoid arthritis; RdRp, RNA dependent RNA polymerase; S, spike;SARS-CoV-2, severe acute respiratory syndrome coronavirus 2



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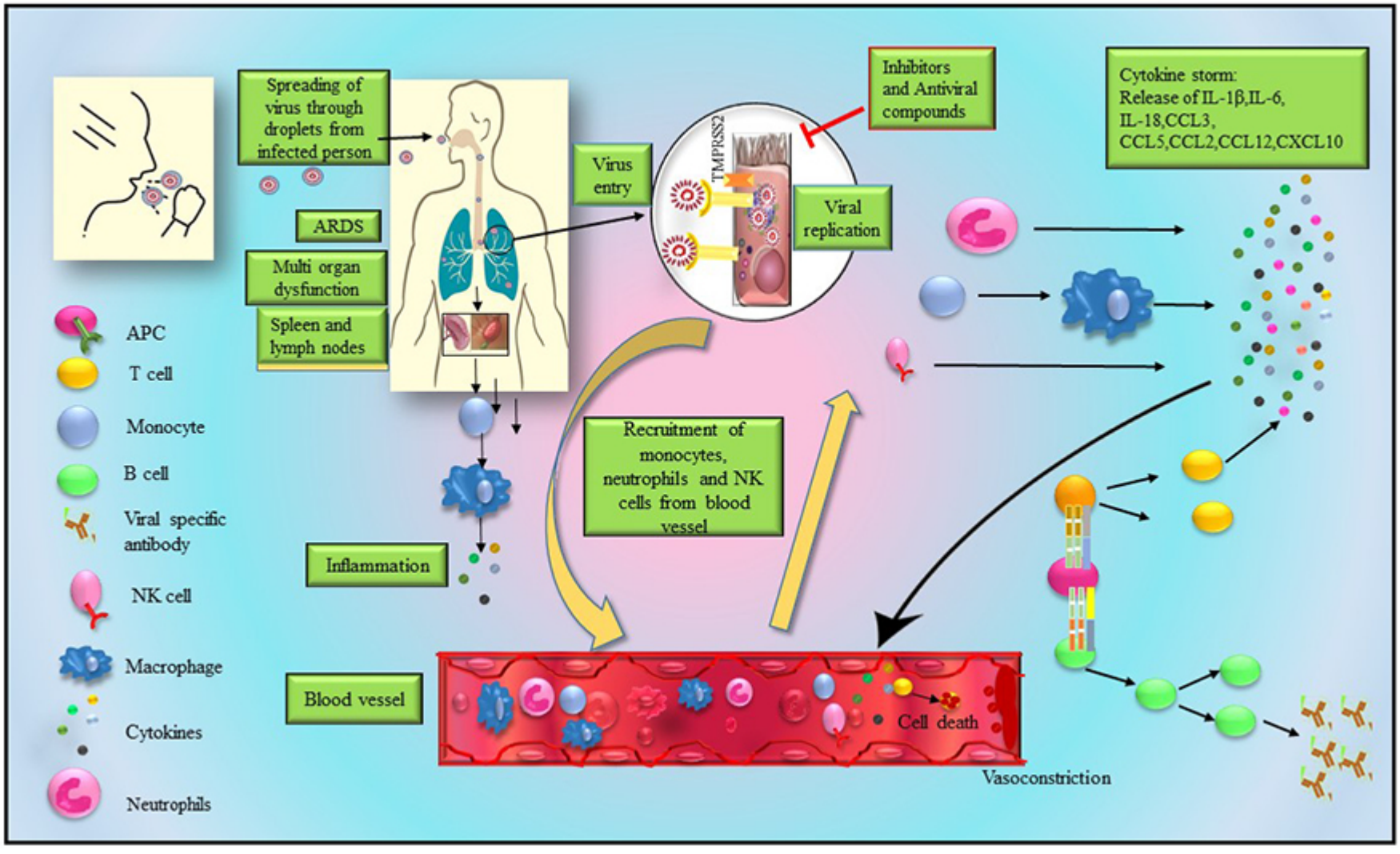
- Mutation accumulation results in new variants of SARS-CoV-2 causing severe pathogenicity.
- SARS-CoV-2 infection the apoptosis of lymphocytes via tissue resident CD169+ macrophages.
- In SARS-CoV-2 infection NK cells shows high level of negative immune check point marker.
- Epitope mapping and stem cell therapy are now also considered as a novel approach for drug development.
- Clinical trials of various repurposed drugs are ongoing for developing potent vaccines



Graphics Abstract

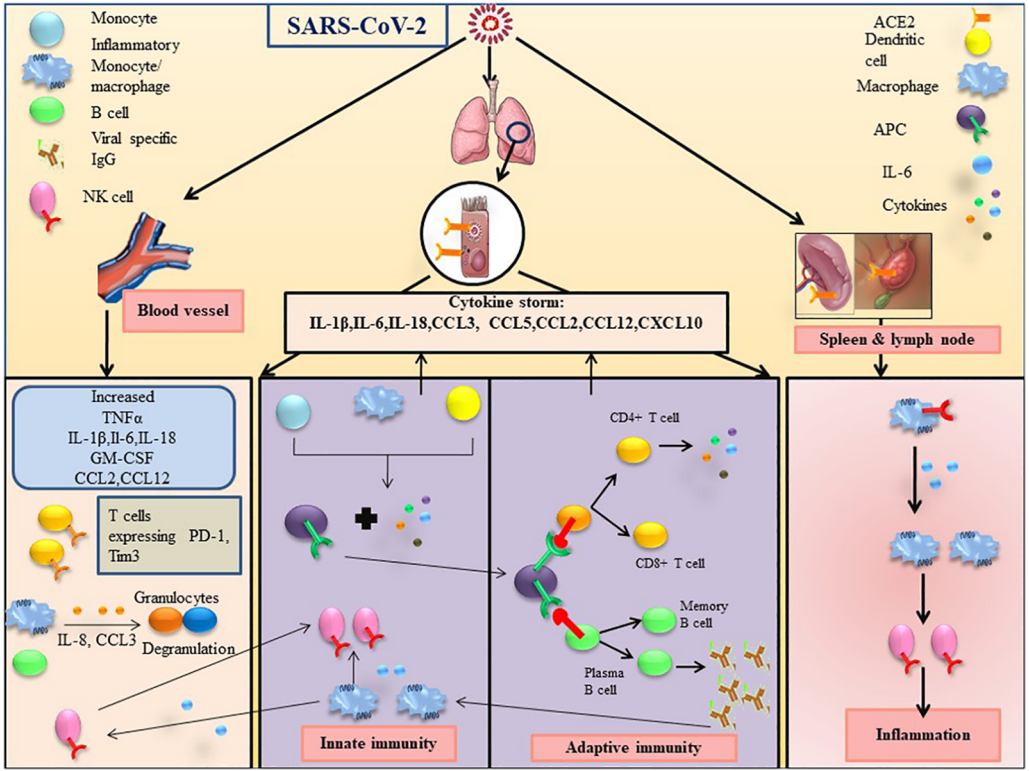

Monocyte
Inflammatory Monocyte/ macrophage
B cell
Viral specific IgG
NK cell
SARS-CoV-2
ACE2
Dendritic cell
Macrophage
APC
IL-6
Cytokines
Blood vessel
Cytokine storm:
IL-1β,IL-6,IL-18,CCL3, CCL5,CCL2,CCL12,CXCL10
Spleen & lymph node
Increased
TNFα
IL-1β,Il-6,IL-18
GM-CSF
CCL2,CCL12
T cells expressing PD-1, Tim3
Granulocytes
IL-8, CCL3
Degranulation
CD4+ T cell
CD8+ T cell
Memory B cell
Plasma B cell
Innate immunity
Adaptive immunity
Inflammation

Figure 1

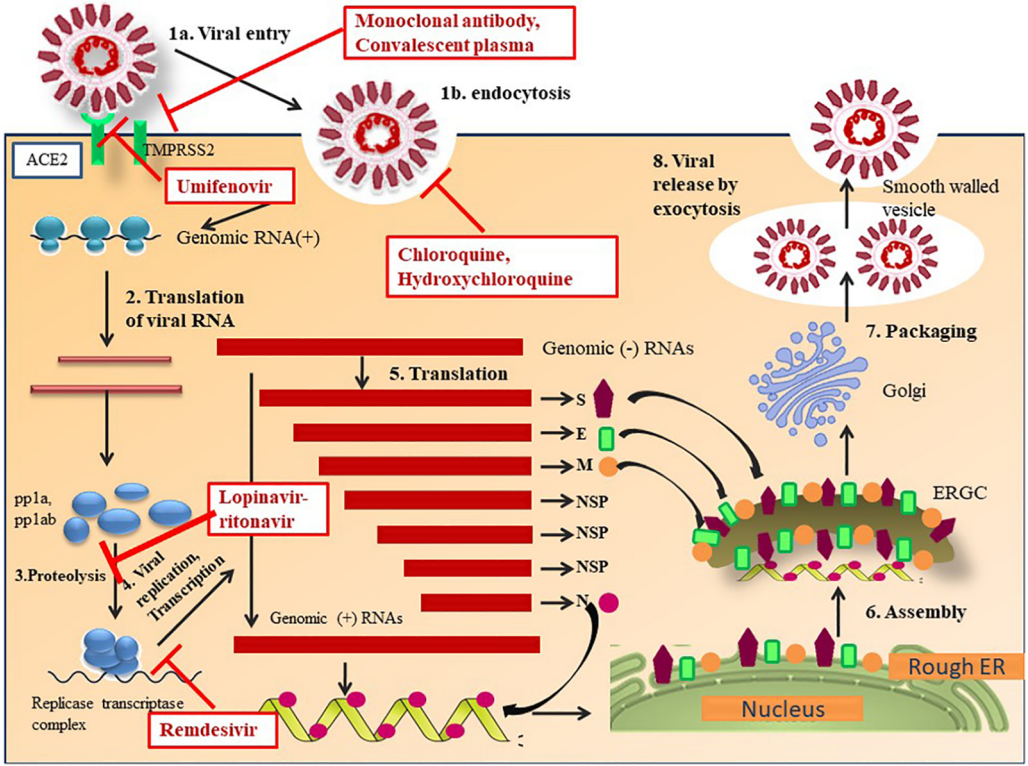

1a. Viral entry
Monoclonal antibody, Convalescent plasma
1b. endocytosis
ACE2
TMPRSS2
Umifenovir
Genomic RNA(+)
Chloroquine, Hydroxychloroquine
2. Translation of viral RNA
pp1a, pp1ab
Lopinavir-ritonavir
3.Proteolysis
4. Viral replication, Transcription
Replicase transcriptase complex
Remdesivir
Genomic (-) RNAs
5. Translation
S
E
M
NSP
NSP
NSP
N
Genomic (+) RNAs
8. Viral release by exocytosis
Smooth walled vesicle
7. Packaging
Golgi
ERGC
6. Assembly
Rough ER
Nucleus

Figure 2