New Discovered Molecules of COVID-19

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SARS-CoV-2 antiviral monoclonal antibody cytokine blockers

1. Introduction

Novel coronavirus disease 2019 (COVID-19), also known as severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), has become a grave issue in today's world [1]. Initially, SARS-CoV-2 infection was limited to the Republic of China, but with time, its infection spread across the entire globe. Although the peak of COVID-19 is on the decline after a long time, still cases of infection are increasing due to the emergence of new strains, resulting in changes in symptoms and treatment strategies [2]. A grave challenge with COVID-19 is the continuous mutation of SARS-CoV-2 virus leading to several variants (B.1.1.7, B.1.351, P.1, B.1.617.2, B.1.1.529 etc.) spread all over the world [3]. To control the situation, drug regulatory agencies (such as the United States Food and drug Administration (USFDA) and the European Medicines Agency (EMA)) have given emergency use approval (EUA) to several novel molecules and pre-existing drugs for controlling the pandemic.

2. New Discovered Molecules

New molecules/drugs are discovered by humans for the therapeutic management of new diseases or to address existing health challenges. New molecules/drugs require extensive clinical investigations, followed by approval from drug regulatory agencies for marketing. Several new molecules have been discovered to combat SARS-CoV-2. The newly discovered molecules have been tested in silico via molecular docking studies to assess their interaction with the target receptor on SARS-CoV-2. These new molecules are either antivirals or immunomodulators [4][5]. It has been observed in different studies that these molecules can block SARS-CoV-2 in their conventional way. For example, molnupiravir blocks RNA-dependent RNA polymerase (RdRp) to stop the replication of SARS-CoV-2. Novel MAbs (both alone and in combination) have also been investigated in clinical trials. Drug regulatory authorities have approved several new drugs via the EUA route. Some of these new drugs or molecules are now available commercially for the treatment of COVID-19.

On the other hand, research on new drugs, both monotherapy and combination therapy, is also ongoing. In 2021, the World Health Organization (WHO) recommended EUA to two new drugs, baricitinib and sotrovimab, and later, full approval was granted in 2022 [6].

2.1. Molnupiravir

2.1.1. General Description

Molnupiravir (EIDD-2801/MK-4482) is a ribonucleoside prodrug of N-hydroxycytidine [4][7][8]. It was developed by Drug Innovation Ventures at Emory University and later procured by Ridgeback Biotherapeutics in collaboration with Merck, US. It is a prescription antiviral drug and is available as pills, inhaled powder, liquid, and intravenous solutions.

2.1.2. Mechanism of Action

This novel antiviral agent blocks RdRp of the SARS-CoV-2 virus to inhibit the viral genome transcription and replication [5][9][10][11][12]. It was reported that molnupiravir becomes cleaved in plasma and forms β-D-N4-hydroxycytidine (NHC). NHC is then distributed and metabolized into NHC triphosphate in the cytoplasm of the liver cells, which acts as the substrate of RdRp. NHC causes mutation in the viral RNA with the help of RdRp and changes the genome sequence, leading to the inhibition of genome transcription and replication for SARS-CoV-2.

2.1.3. Clinical Trial, Route of Administration, Dose, and Dosage Form

In preclinical trials, molnupiravir showed effect on the blocking replication of SARS-CoV-2 in mice models [13]. It was found safe and efficacious in ferrets at 2.3 and 7 mg/kg of body weight when administered BID orally [10]. In a different study, the administration of molnupiravir in a Syrian hamster showed blocking of the viral replication of SARS-CoV-2 [14].

The phase 1 randomized, double-blind, and placebo controlled trial (NCT04392219), in 130 adult human volunteers divided into four groups, for molnupiravir was conducted by the developer, Ridgeback Biotherapeutics, at the Covance Leeds Clinical Research Unit, UK [5][15][16][17]. The first group received a single oral-dose capsules of 50 to 1600 mg in fasted state, the second group was administered two oral-dose capsules of 200 mg in fed or fasted state, and the third group received twice daily an oral-dose capsule of the drug or placebo. It was observed that molnupiravir was more tolerable than placebo, and adverse events were also lesser than placebo. Phase 2 (NCT04405570) randomized, double-blind, and placebo-controlled clinical trial, in 204 adults and older adults divided into four groups, was conducted by Ridgeback and Merck at different locations in the US [5][15][16][18]. The groups were administered with a 200, 400, or 800 mg BID oral capsule for 5 days. Placebo was taken as oral capsule BID for 5 days. Viral replication was observed in 1.9% participants treated with molnupiravir and 16.5% participants who received placebo. Moreover, 400 and 800 mg BID doses were found effective in reducing viral replication with no significant adverse effects. In another phase 2/3 randomized, double-blind, and placebo-controlled trial (NCT04575597), in 1850 adults and older adults at 200, 400, or 800 mg BID oral dose and placebo

every 12 h for 5 days, was conducted by Merck at 173 different locations in the US, Brazil, Chile, Argentina, Canada, Colombia, Egypt, France, Germany, Mexico, and so on [7][8][19]. It was observed that molnupiravir was effective in reducing death, 6.8% (95% CI) for the drug and 9.7% (95% CI) for the placebo, in hospitalized patients. Adverse events were alleviated with the drug (30.4%) when compared with the placebo (33%). Unfortunately, this trial was terminated by the data safety monitoring board (DSMB) probably because of the doubtful beneficial data of the drug as compared with the placebo.

2.1.4. Regulatory Approval and Marketing Authorization

Molnupiravir was approved by the United Kingdom Medicines and Healthcare Products Regulatory Agency (MHRA) in November 2021. MSD (Merck Sharp & Dohme) markets this drug as 200 mg hard capsules in the UK as Lagevrio® [20][21]. EMA (November 2021) gave EUA to it and recommends its administration to patients who do not need supplemental oxygen [22]. EUA was also granted by USFDA (December 2021) for molnupiravir [23]. Sun Pharma, Cipla and Torrent market it as Molxvir®, Cipmolnu®, and Molnutor®, respectively, in India after obtaining DCGI (Drug Controller General of India) approval [24][25][26].

2.2. Paxlovid™

2.2.1. General Description

Paxlovid™ is a combination of two drugs, nirmatrelvir and ritonavir, developed by Pfizer [27]. It is a protease inhibitor, which is intended for oral administration.

2.2.2. Mechanism of Action

Nirmatrelvir blocks the SARS-CoV-23-CL protease in the proteolysis phase, leading to the inhibition of the replication of the virus. It is administered with a lower dose of ritonavir, which is a strong CYP3A4 inhibitor and HIV protease inhibitor [28]. Therefore, this combination results in the synergistic inhibition of SARS-CoV-2 viral protease [27].

2.2.3. Clinical Trial, Route of Administration, Dose, and Dosage Form

The phase 1 open-label, randomized, single-dose, and crossover clinical trial (NCT05263921) for Paxlovid™ was conducted in 12 adults (divided in different groups) [29]. In some groups, participants were administered oral commercial tablets in fasted state, whereas in other groups, participants received oral powder. Nirmatrelvir (150 mg)/ritonavir (100 mg) in combination was orally administered in fasted state with water, with applesauce, or with vanilla pudding to the participants. An EPIC-HR (evaluation of protease inhibition for COVID-19 in high-risk patients) study, EPIC-SR (evaluation of protease inhibition for COVID-19 in standard-risk patients) study, and EPIC-PEP (evaluation of protease inhibition for COVID-19 in postexposure prophylaxis) studies have been conducted to assess the clinical benefits of Paxlovid™ [27]. The EPIC-HR study (NCT04960202) was a phase 2/3 randomized and quadruple-blinded trial, conducted across Europe, Africa, North and South America, and Asia in 2246 adults and older adults, was divided into different studies; that is, in that trial, the participants were given the

drug combination and placebo through the oral route as a tablet and/or capsule. According to the interim analysis result of Pfizer, the drug combination showed about 89% risk of hospitalization, and chances of death were decreased when compared with the placebo group. Adverse events were less with the drug combination rather than in the placebo, that is, 1.7% and 6.6%, respectively. Final analysis showed that the therapeutic efficacy was maintained in 1379 patients with a percentage point difference of −5.81 (95% CI, −7.78 to −3.84; $p < 0.001$) [30].

2.2.4. Regulatory Approval and Marketing Authorization

Paxlovid™ received its EUA from EMA in December 2021 [31], and EUA from USFDA was obtained in December 2021 [27]. In India, Torrent Pharma and Aurobindo Pharma have been licensed to commercialize this product [32].

2.3. Baricitinib

2.3.1. General Description

Baricitinib is an orally active immunomodulator, anti-inflammatory, and anticancer agent [33][34].

2.3.2. Mechanism of Action

Baricitinib selectively blocks JAK 1/2 and activates the JAK-STAT (signal transducers and activators of transcription) signaling pathway. It also inhibits numb-associated kinase (NAK) family enzymes, which include BMP-2-inducible kinase (BIKE), serine/threonine-protein kinase 16 (STK16), adaptor-associated kinase 1 (AAK1), and cyclin G-associated kinase (GAK). This results in the blocking of the AP-2 scaffolding protein, which is responsible for the entry and propagation of SARS-CoV-2 [35]. On the other hand, baricitinib also acts as anticytokines and reduces the inflammatory markers of COVID-19 disease, which includes C-reactive protein (CRP), IL-6, and ferritin.

2.3.3. Clinical Trial, Route of Administration, Dose, and Dosage Form

Eli Lilly conducted and completed the phase 3 (NCT04421027) trial, a randomized, double-blinded, and parallel-assigned study (COV-BARRIER), on baricitinib in 1525 adults and older adults at 96 different locations in the US, Argentina, Republic of Korea, Brazil, Mexico, Germany, India, Japan, Italy, Russian Federation, Puerto Rico, Spain, and UK to estimate the therapeutic efficacy of baricitinib in hospitalized COVID-19 patients [36]. Participants were administered 4 mg baricitinib once daily through the oral route against the standard of care. As a result, the chance of mortality was found to be reduced by 38.2%, and one death was found averted per 20 participants. It was also observed that in the baricitinib-treated group, the mortality was 10% in 60 days ($n = 79$; 95% CI; $p = 0.0050$), and in the placebo group, it was 15% ($n = 116$; 95% CI; $p = 0.0050$). Serious adverse events were seen to be slightly lower in the case of the baricitinib-treated group than in the placebo group, that is, 15% and 18%, respectively.

2.3.4. Regulatory Approval and Marketing Authorization

Recently, Eli Lilly received EUA from USFDA (October 2022) for their product Olumiant® (Baricitinib) [37]. EMA has started (in 2021) and is continuing the evaluation of Olumiant® (baricitinib) in the treatment of COVID-19 [38].

2.4. Wharton's Jelly Mesenchymal Stem Cells (WJ-MSC)

2.4.1. General Description

WJ is a gelatinous tissue found in the umbilical cord. It contains myofibroblast-like stromal cells [39]. MSCs are stromal cells, having the capability of self-renewal and multilineage proliferation [40]. MSCs are isolated from the umbilical cord, bone marrow, endometrial polyps, and so on. However, WJ is considered to be the pivotal source of MSCs [41]. MSCs are also considered medicinal signaling cells, which are therapeutically effective stomatal cells. They can be classified in different types of cells, including myocytes, osteoblasts, chondrocytes, and adipocytes. MSCs are found in the cord cells, amniotic fluid adipose tissue, bone marrow, and molar cells. It had proved its effectiveness previously for the treatment of autoimmune diseases, such as Crohn's disease, systemic lupus erythematosus (SLE), multiple sclerosis, osteoarthritis, and graft versus host disease [42]. Apart from this, it also has immunomodulatory effects and antimicrobial effects. WJ-MSCs are obtained from the cord tissue of newborns and cultured to intensity for MSCs. Then these are placed in saline solution (25 mL) containing 0.5% human serum albumin [43][44].

2.4.2. Mechanism of Action

WJ-MSC curbs mitogen-induced T-cell responses rather than other MSCs. Along with this, WJ-MSC blocks the multiplication of mitogen-activated $CD3^+$, $CD4^+$, and $CD8^+$ T cells [45][46][47]. Apart from peripheral blood mononuclear cells (PBMC) and interferon-γ (IFN_γ), WJ-MSC can also mediate T_{reg} cells (regulatory T cells). This helps in the polarization procedure of monocytes/macrophages toward an anti-inflammatory phenotype (type 2) and blocks the separation into the phenotype (type 1) and DCs. More specifically, the MSC-secreted interleukin 1 receptor antagonist (IL1-RA) helps in the polarization procedure of macrophages toward phenotype (type 2). Along with these, proinflammatory Th1 is switched to anti-inflammatory Th2 cells, and the profiles of cytokines are modified. It enhances IL-4 secretion by Th2 cells, increases the production of T_{reg}, and blocks the multiplication, stimulation, and cytotoxicity of natural killer cells (NK cells). It directly blocks the multiplication of alloreactive $CD4^+$ and $CD8^+$ T cells in the absence of other immune cells, which are stimulated by the SC-derived galectin-1. Effector $CD4^+$ T cells can be easily converted to $Foxp3^+$ T_{regs} by B_{regs} (regulatory B cells), which produce IL-10. Along with T cells, it also blocks the multiplication of B cells and T-cell-secreted IFN_γ. In this way, the upregulation of genes involved in the process of phagocytosis in macrophages is increased along with the downregulation of inflammatory cytokines via macrophages.

2.4.3. Clinical Trial, Route of Administration, Dose, and Dosage Form

Assistance Publique–Hôpitaux de Paris had already completed a phase 1/2, randomized, triple-blinded, and parallel-assigned clinical trial (NCT04333368) in 47 adults and older adults [48]. The intervention was administered through the central venous line for 1 h by tubing and at a dose of 1 mg/kg. The placebo group was given 0.9%

NaCl through the IV infusion route. The difference in ratio of partial pressure of oxygen to fractional inspired oxygen (PaO_2/FiO_2) was not significant between the intervention and placebo group (95% CI) [49]. Adverse events were observed in 28.6% participants from the intervention group and 25% patients from the placebo group. Efficacy of WJ-MSC was also evaluated for the treatment of COVID-19 related acute respiratory distress syndrome (ARDS) [50]. However, sponsors did not disclose results for this clinical trial (NCT04625738).

2.4.4. Regulatory Approval and Marketing Authorization

WJ-MSC is not approved by USFDA and EMA so far for use against COVID-19.

2.5. Convalescent Plasma (CP)

2.5.1. General Description

CP is the plasma that is collected from patients who have survived from any viral disease [51]. CP contains antibodies against a virus. COVID-19 survivors have antibodies against SARS-CoV-2 in their blood, and these antibodies have the potential to treat COVID-19 patients. Collecting CP from patients surviving from COVID-19 infection and administering it to patients suffering from this infection may boost the immunity of COVID-19 patients. Although CP therapy is not approved yet, USFDA proclaimed that CP therapy can be used for the treatment of critically ill COVID-19 patients.

2.5.2. Mechanism of Action

In COVID-19 patients, some issues were observed, such as infiltration of inflammatory cells and cytokine storm in the alveoli of the lungs, which further produces ARDS [52][53]. Moreover, the amount of lymphocytes and cytokine levels are also reduced; on the other hand, the levels of IL-6, TNF-α, IL-10, colony-stimulating factor, and granulocyte macrophage are enhanced significantly. CP administration in COVID-19 patients enhances the lymphocyte amount and oxygen saturation and restores liver function. Therefore, CP therapy can boost immunogenicity and reduce the inflammation of lungs. However, this therapy also treats different hemorrhagic fevers induced by Ebola, influenza A (H5N1), SARS, Middle East respiratory syndrome (MERS), and other viruses [54].

2.5.3. Clinical Trial, Route of Administration, Dose, and Dosage Form

An open-label study (NCT04321421) was conducted by Foundation IRCCS San Matteo Hospital in collaboration with Ospedale Carlo Poma Asst Mantova, Ospedale Maggiore Lodi, and Ospedale Asst Cremona in 49 adults and older adults having moderate to severe ARDS, which was lasting <10 days, at Catherine Klersy, Italy [55]. Participants were administered 250–300 mL CP three times over 5 days through IV infusion. However, in this study, the developers were uncertain whether CP was beneficial against COVID-19 or not [56][57]. A different study was conducted by Mayo Clinic (NCT04338360) in adults and older adults at four places in the US, namely, Arizona, Florida, Minnesota, and Wisconsin [58]. Serious adverse events were significantly reduced (<1%), and the mortality

rate, up to 30 days of study, was 25.2% (95% CI) [59]. The study was successful, and the developers obtained marketing approval.

2.5.4. Regulatory Approval and Marketing Authorization

Though USFDA has not approved CP therapy as yet, an IND application for it proclaims that CP can be used effectively in emergency cases and in critically ill patients [60].

2.6. Sarilumab

2.6.1. General Description

Sarilumab is a potent MAb (IgG_1) that inhibits IL-6 receptors [61][62]. It is approved by FDA and EMA for the treatment of rheumatoid arthritis through SC administration. In COVID-19 infection, this agent is thought to be a potent agent because of the evidence of its in vitro and in vivo therapeutic efficacy.

2.6.2. Mechanism of Action

IL-6 is considered to be the pleiotropic cytokine that is responsible for the stimulation of T cells and B cells [61][62][63][64][65]. It is noteworthy that hepatocytes are also stimulated by IL-6 and CRP, which secrete fibrinogen and serum amyloid A (SAA). IL-6 also plays a pivotal role in the process of pathological inflammation. Sarilumab binds to the IL-6 receptor (both soluble IL-6 receptor, namely, sIL-6Rα, and membrane-bound IL-6 receptor, namely, mIL-6Rα). It blocks the gp130 and signal transducer and signaling transcription protein 3 (STAT3) pathway and cis- and trans-signaling pathways (though in vitro). Complexes of IL-6 and mIL-6Rα inducing trans-signaling pathways are also inhibited in those respective cells, which express specifically gp130 and mIL-6Rα.

2.6.3. Clinical Trial, Route of Administration, Dose, and Dosage Form

A randomized, double-blind, and placebo-controlled phase 2/3 clinical trial (NCT04315298) was conducted at 62 locations in the US by Regeneron Pharmaceuticals in collaboration with Sanofi in 1912 adult or older adult patients having confirmed COVID-19 infection and hospitalized with pneumonia or multisystem organ dysfunctions [66]. The trial was supported by USFDA and the Biomedical Advanced Research and Development Authority (BARDA) [67][68]. In the phase 2 clinical trial, the first two experimental groups were administered 200 and 400 mg of sarilumab through the IV route [69]. The next four groups were divided into three cohorts, which received 200 mg (Cohort 1), 400 mg (Cohort 1), 800 mg (Cohort 2), and 800 mg (Cohort 3) of the drug through the IV route. It was observed (especially in phase 3) that the percentage of improvement was 43.2% for the interventional group and 35.5% for the placebo group. Another phase 3, randomized, quadruple-blinded, parallel-mode (NCT04327388) trial, by Sanofi in collaboration with Regeneron Pharmaceuticals, in 420 adults or older adults was conducted at 47 different locations in Brazil, Argentina, Chile, Canada, Germany, France, Japan, Israel, Russian Federation, Italy, and Spain [70]. The participants were divided into three groups, of which the first experimental group was administered a single dose of 200 mg sarilumab through IV injection once a day on the first day. The second group was administered a single dose of 400 mg of sarilumab through IV injection once a day. The comparator group was

provided placebo through IV injection once a day on the first day. However, no significant difference in therapeutic activity was observed between groups receiving 200 mg sarilumab (*n* = 159 (38%)), 400 mg sarilumab (*n* = 173 (42%)), and the placebo (*n* = 84 (24%)) [71]. Adverse events were 70% with 400 mg sarilumab, 65% with 200 mg sarilumab, and 65% in the placebo group.

2.7. Tocilizumab

2.7.1. General Description

Tocilizumab is a recombinant MAb that contains human and murine components [72][73]. Antigen-binding domains of the murine antihuman IL-6R antibody are grafted to human IgG_1 scaffolding. It is effective against inflammation and autoimmune diseases by blocking IL-6R. This MAb is thought to be a potential agent to combat against COVID-19. Tocilizumab is already available in the market as Actemra® and ACTPen™. Actemra® is single-dose manual injection of tocilizumab, and ACTPen™ is a single-dose autoinjector containing tocilizumab [74][75]. Actemra® and ACTPen™ can be administered via the subcutaneous and IV infusion route. Hoffmann-La Roche marketed these products for the treatment of arthritis [76].

2.7.2. Mechanism of Action

Like sarilumab, tocilizumab competitively blocks IL-6R receptors, both sIL-6R and mIL-6R, resulting in the inhibition of signal transduction, leading to the reduction in inflammation [72]. B cells and T cells generate IL-6, which is a proinflammatory cytokine and helps in the formation of an antibody and differentiation of cytotoxic T cells and is responsible for the stimulation of hepatocytes, CRP, fibrinogen, and SAA secretion along with the diminishing of the differentiation of T_{reg} cells. It is conventionally used for the treatment of rheumatoid arthritis, systemic juvenile idiopathic arthritis, giant cell arteritis, polyarticular juvenile idiopathic arthritis, cytokine release syndrome, and so on.

2.7.3. Clinical Trial, Route of Administration, Dose, and Dosage Form

Another phase 3, randomized, double-blinded, parallel-mode, and multicenter clinical trial (NCT04320615) was conducted by Hoffmann-La Roche in 452 adult or older adult patients at 62 different locations in the U.S., Canada, Denmark, Germany, France, Italy, Netherlands, Spain, and UK [77]. Participants were administered 8 mg/kg of this drug (maximum up to 800 mg each dose), and one more dose was only administered in case of worse condition or lack of improvement through IV infusion. It was observed that 24.5% of the participants from the interventional group and 25% of the participants from the placebo group died by the 60th day [78]. Adverse events were seen in 24.1% of the participants (interventional group) and 29.4% of the participants (placebo group). Result indicates that no beneficial outcomes were obtained in this research.

2.7.4. Regulatory Approval and Marketing Authorization

Actemra® (tocilizumab), manufactured by Genentech (member of the Roche Group) is approved by USFDA in December 2022 for severe COVID-19 patients [79].

2.8. Bevacizumab

2.8.1. General Description

Like tocilizumab, bevacizumab is also a humanized IgG_1 MAb that has the ability to bind with vascular endothelial growth factor A (VEGF), resulting in the apoptosis of tumor cells [80]. It is conventionally used for the treatment of various types of cancers, such as cervical cancer, colorectal cancer, non-small cell lung cancer, fallopian tube cancer, ovarian cancer, peritoneal cancer, and renal cell carcinoma. It is already a FDA-approved agent for the treatment of cancer [81][82]. Currently, it is being evaluated for its potential efficacy against COVID-19 infection for which many clinical trials are being continued. Bevacizumab is already available in the market as Avastin®, Mvasi®, and Zirabev®. Avastin® injections are used for the treatment of diseases such as colorectal cancer and non-small cell lung cancer [80][81].

2.8.2. Mechanism of Action

Bevacizumab binds to VEGF, a well-known proangiogenic growth factor expressed by tumor cells, and blocks VEGF receptors of lung tissues, leading to an increase in vascular permeability [81][82][83]. Therefore, oxygen perfusion and anti-inflammatory effects increase.

2.8.3. Clinical Trial, Route of Administration, Dose and Dosage Form

Another phase 2 open-label trial (NCT04275414), in 27 adults or older adults having confirmed COVID-19 infection, was conducted by Qilu Hospital of Shandong University in collaboration with Renmin Hospital of Wuhan University and Moriggia-Pelascini Gravedona Hospital, Gravedona, Italy [84]. Patients were administered with 500 mg of bevacizumab along with 100 mL normal saline through IV drip for a minimum of 90 min and onwards. Body temperature was normalized in 93% patients and improvement in PaO_2/FiO_2 ratios was observed in 92% patients who received both bevacizumab and the standard of care [83].

2.8.4. Regulatory Approval and Marketing Authorization

Till date, bevacizumab is not approved for the treatment of COVID-19.

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