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Review Article

IMPACT OF DIFFERENT DRUGS OR MEDICATION ON COVID-19: A REVIEW

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ABSTRACT

SARs CoV-2 was first reported in Wuhan, China and from there it spread to different parts of the world in 2019. Hence, the second name COVID-19 was given to this disease the main organ which was primarily affected by it was lungs and other organs which are affected are liver, kidney, immune system, heart, etc. Interestingly, the COVID-19 shows genetic similarity with the SARs and MERs which were in past responsible for the epidemic. Some studies also shows that the genetic information of COVID-19 to some extent match with the bats SARs virus which according to WHO explained that the potential origins of SARS-CoV-2 was inconclusive because it did not explicitly describe the origin of the virus. Due to the rapid spread of the virus in different parts of the world and non-availability of the treatment options the death toll reached to 6 million. However, due to the advancement in the research and development many medicine and treatment options were devised such as plasma therapy, ivermectin, remdesivir, dexamethasone, and many more. In the article we will thoroughly detail the etiology, clinical characteristics, and most recent novel therapies used to control COVID-19.

Keywords: - SARs-CoV-2, COVID-19, treatment, vaccines, clinical features.

INTRODUCTION

With more than 6 million deaths worldwide as of March 2022, Coronavirus Disease 2019 (COVID-19), the highly contagious viral illness brought on by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), has had a devastating impact on the world's demographics and is emerging as the most significant global health crisis since the influenza pandemic of 1918. SARS-CoV-2 spread quickly throughout the world when the first instances of this primarily respiratory viral illness were initially recorded in Wuhan, Hubei Province, China, in late December 2019. As a result, the World Health Organization (WHO) was forced to declare it a worldwide pandemic on March 11, 2020. Since being deemed a global pandemic, COVID-19 has devastated numerous nations and wreaked havoc on numerous healthcare systems. Due to protracted closures brought on by the pandemic, many people have lost their job, which has had a negative ripple impact on the world economy. SARS-CoV-2 continues to wreak havoc around the world, with many countries experiencing a second or third wave of outbreaks of this viral illness that are primarily attributed to the emergence of mutant variants of the virus. Despite significant advancements in clinical research that have improved understanding of SARS-CoV-2 and the management of COVID-19, limiting the ongoing spread of this virus and its variants has become a matter of increasing concern.

SARS-CoV-2, like other RNA viruses, is susceptible to genetic evolution with the emergence of mutations over time, resulting in mutant forms that may have distinct properties from its ancestral strains. This is true even when SARS-CoV-2 adapts to its new human hosts. Several SARS-CoV-2 variations have been identified throughout this epidemic, however only a small number of these are regarded as variants of concern (VOCs) by the WHO due to their effects on public health around the world.

The emergence of these new SARS-CoV-2 variants poses a threat to undo the significant progress made so far in containing the spread of this viral illness, despite the unprecedented speed of vaccine development against the prevention of COVID-19 and robust global mass vaccination campaigns, including vaccine boosters.[1]

Thus, the goal of this review article is to thoroughly detail the etiology, clinical characteristics, and most recent novel therapies used to control COVID-19.

Etiology

SARS-CoV-2 is a brand-new betaCoV that is related to the Middle East Respiratory Syndrome Coronavirus (MERS-CoV) and the severe acute respiratory syndrome coronavirus (SARS-CoV), both of which have been linked to epidemics with fatality rates of up to 35% and 10%, respectively.[2] It is round or elliptic in shape, frequently pleomorphic, and ranges in diameter from 60 to 140 nm. It is susceptible to heat and UV light like other CoVs. Although a high temperature slows the replication of any viral species, this is the case. The SARS-CoV-2 inactivation temperature is currently the subject of investigation. 90% of SARS-CoV-2 is rendered inactive on a stainless-steel surface kept at an air temperature of 54.5°C (130 °F) for around 36 minutes. At 54.5 °C, the virus had a half-life of 10.8 3.0 min and took 35.4 9.0 min to lose 90% of its infectivity.[3]

After visiting Wuhan, a cluster patient developed atypical pneumonia. Genomic analysis revealed that the novel HCoV

showed 89% nucleotide identity with the bat SARS-like-CoVZXC21 and 82% with the human SARS-CoV. As a result, the International Committee on Taxonomy of Viruses scientists gave it the name SARS-CoV-2. The SARS-CoV-2 single-stranded RNA genome has 29891 nucleotides, which can be translated into 9860 amino acids.

Despite the fact that SARS-origin CoV-2's is currently unknown, zoonotic transmission from an animal is widely hypothesized to be its source. Genomic studies imply that a strain seen in bats is where SARS-CoV-2 most likely came from. High similarity (96%) between the human SARS-CoV-2 and the betaCoV RaTG13 of bats was found when the human SARS-CoV-2 sequence was compared to known animal coronaviruses (*Rhinolophus affinis*).[4] It has been proposed that SARS-CoV-2 spread from bats through intermediate hosts like pangolins and minks before reaching people, just like SARS and MERS did.[5, 6]

However, it did note that SARS-CoV-2 circulated as early as December 2019. A recent report by the WHO explaining the potential origins of SARS-CoV-2 was inconclusive because it did not explicitly describe the origin of the virus. This study looked into a number of potential theories for the virus's origin, including the possibility that it originated in an animal, spread to an intermediary host, and then entered humans.

SARs CoV-2 variants

As was already established, SARS-CoV-2 is prone to genetic evolution, leading to a variety of variations that might differ from its ancestral strains in some ways. In a situation when there is a global pandemic, periodic genomic sequencing of viral samples is crucial because it aids in the discovery of any new genetic variations of SARS-CoV-2. Notably, the globally dominant D614G variation, which was linked to greater transmissibility but lacked the capacity to produce severe illness, emerged early in the genetic evolution.[7] Interestingly, SARS-CoV-2 has several variants, some of which are considered variants of concern (VOCs) because of their potential to increase transmissibility or virulence, reduce neutralisation by antibodies acquired through natural infection or vaccination, and be more difficult to detect, or lessen the effectiveness of treatments or vaccines.

Variants of concern (VOC) of SARs CoV-2 are:

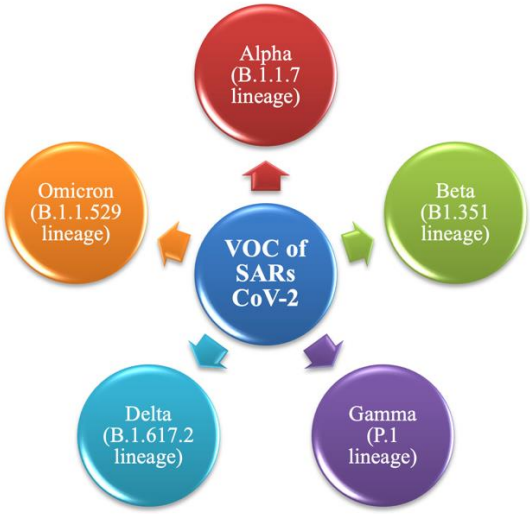

Figure 1: Different variant of concern of SARs CoV-2

Alpha (B.1.1.7 lineage)

- On the basis of whole-genome sequencing of samples from patients who tested positive for SARS-CoV-2, a new SARS-CoV-2 variant of concern, B.1.1.7 lineage, also known as Alpha variant or GRY (previously GR/501Y.V1), was discovered in the UK in late December 2020.[8,9]
- The B.1.1.7 variation was found by genome sequencing as well as in a commonly used commercial test distinguished by the absence of the S gene (S-gene target failure, SGTF) PCR samples. The viral genome of the B.1.1.7 variant carries 17 mutations. Of these, the spike (S) protein has eight mutations (69-70 deletion, 144 deletions, N501Y, A570D, P681H, T716I, S982A, and D1118H). The spike protein's affinity for ACE 2 receptors is increased in N501Y, which facilitates viral attachment and subsequent entry into host cells. [10,11,12]

Beta (B1.351 lineage)

- Another SARS-CoV-2 form is B.1.351, often known as the Beta variant or GH501Y. The second wave of COVID-19 infections, caused by V2 with numerous spike mutations, was first discovered in South Africa in October 2020.[13]
- The spike protein of the B.1.351 variant has nine alterations, nine of which are found in the RBD and improve the binding affinity for ACE receptors: L18F, D80A, D215G, R246I, K417N, E484K, N501Y, and A701V.[14,15]
- The US received a SARS-CoV-2 501Y.V2 (B.1.351 lineage) report at the end of January 2021.

Gamma (P.1 lineage)

- The P.1 version, sometimes referred to as the Gamma variant or GR/501Y.V3, is the third variant of concern. It was discovered in Brazil in December 2020 and was first discovered in the US in January 2021. [16]
- Notably, this variation may be less neutralizable by post-vaccination sera, convalescent sera, and monoclonal antibody treatments. [17]

Delta (B.1.617.2 lineage)

- The fourth variety of concern, B.1.617.2, also known as the Delta variant, was discovered for the first time in India in December 2020 and was in charge of the deadly second wave of COVID-19 infections in India in April 2021. This variation was discovered for the first time in the US in March 2021.

Omicron (B.1.1.529 lineage)

- A rise in COVID-19 cases led to the discovery of the fifth variant of concern B.1.1.529, commonly known as the Omicron variant by the WHO, in South Africa on November 23, 2021.[18]
- Omicron was rapidly identified as a VOC as a result of more than 30 modifications to the virus' spike protein and the dramatic increase in cases seen in South Africa. [19]

SARS-CoV-2 Variants of Interest (VOIs)

VOIs are characterized as genetic variants with particular genetic markers that have been linked to alterations that may result in changes that increase transmissibility or virulence, reduce the ability of antibodies acquired through natural infection or vaccination to neutralize the organism, allow the organism to evade detection, or reduce the efficacy of therapeutics or vaccinations. Eight variations of interest (VOIs) have been identified by WHO since the start of the pandemic, including Epsilon (B.1.427 and B.1.429), Zeta (P.2), Eta (B.1.525), Theta (P.3), Iota (B.1.526), Kappa (B.1.617.1), Lambda (C.37), and Mu (B.1.621).

Clinical characterization

The majority of patients will experience symptoms within 11.5 days of infection, while the median incubation time for SARS-CoV-2 is thought to be 5.1 days. [20]

The clinical spectrum of COVID-19 ranges from asymptomatic or paucisymptomatic forms to clinical disease defined by multiple organ failure, septic shock, and acute respiratory failure necessitating mechanical ventilation. 17.9% to 33.3% of infected people are predicted to experience no symptoms.[21,22]

A sore throat, anosmia, dysgeusia, anorexia, nausea, malaise, myalgias, and diarrhoea are less frequent symptoms of symptomatic patients than are fever, cough, and shortness of breath. According to Stokes et al., of the 373,883 verified symptomatic COVID-19 cases in the US, 70% of them had a fever, cough, or shortness of breath. Additionally, 36% of them reported having myalgia, and 34% had headaches. Laboratory abnormalities were observed to include lymphopenia (47.6%), high C-reactive protein levels (65.9%), raised cardiac enzymes (49.4%), and abnormal liver function tests (26.4%) in a significant meta-analysis of 8697 patients with COVID-19 in China. Leukopenia (23.5%), high D-dimer (20.4%), elevated erythrocyte sedimentation rate (20.4%), leukocytosis (9.9%), elevated procalcitonin (16.7%), and impaired renal function (10.9%) were among the other laboratory abnormalities. According to a meta-analysis of 212 published studies involving 281,461 people from 11 countries/regions and 212 published studies, patients infected with COVID-19 had a death rate of about 6% and a severe illness course in about 23% of cases.[23]

The high neutrophil-to-lymphocyte ratio (NLR), derived NLR ratio (d-NLR), platelet-to-lymphocyte ratio, and WBC-to-neutrophil ratio are all signs of an inflammatory storm brought on by cytokines.[24]

Depending on the level of sickness that is currently being treated, which takes into account clinical symptoms, aberrant lab and radiography results, hemodynamics, and organ function. COVID-19 is divided into five different categories according to criteria released by the National Institutes of Health (NIH).

- **Asymptomatic infections: -** people who tested positive for SARS-CoV-2 but did not exhibit any COVID-19-like clinical signs.
- **Mild illness: -** those who exhibit any COVID-19 symptoms, such as a fever, cough, sore throat, malaise, headache, muscle pain, nausea, vomiting, diarrhoea, anosmia, or dysgeusia, but not abnormal chest imaging or shortness of breath.
- **Moderate illness: -** Those who have oxygen saturation (SpO2) level under 94% on room air and either clinical signs of lower respiratory tract disease or radiologic proof of it.
- **Severe illness: -** individuals with (SpO2) 94% on room air, (PaO2/FiO2) 300 with marked tachypnea and respiratory frequency >30 breaths/min, or those with lung infiltrates >50%.
- **Critical illness: -** those who suffer from multiple organ dysfunction, septic shock, or severe respiratory failure. Acute respiratory distress syndrome (ARDS), which typically develops around a week after symptoms start, can cause patients with severe COVID-19 disease to become dangerously ill.

Despite the fact that COVID-19, the disease brought on by SARS-CoV-2, mostly affects the respiratory system, given the various organ dysfunction it is connected with, COVID-19 might be regarded as a systemic viral infection.The different organs which are affected by COVID-19 infection are kidney, cardiac, hematologic (lymphopenia), gastrointestinal, liver, endocrines, neurologic and cutaneous manifestations.

Treatment of COVID-19

Early in the pandemic, there was a lack of knowledge about COVID-19 and its therapeutic care, which made it urgent to use experimental therapeutics and drug repurposing to lessen the severity of this novel viral infection. Since then, tremendous advancements have been made as a consequence of the tireless efforts of clinical researchers around the world. These advancements have improved our understanding of COVID-19 and its management as well as sped up the discovery of novel medicines and vaccines. Currently, a range of therapeutic options are available, including antiviral medications (such as molnupiravir, paxlovid, and remdesivir), anti-SARS-CoV-2 monoclonal antibodies (such as bamlanivimab/etesevimab, casirivimab/imdevimab), anti-inflammatory medications (such as dexamethasone), and immunomodulators agents (such as baricitin).

Antiviral Therapies

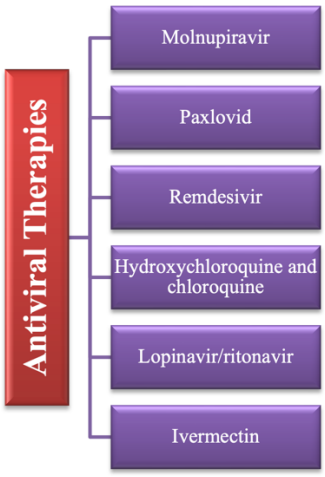

Figure 2: Different anti-viral used for the treatment of SARs CoV-2.

Molnupiravir: Originally developed as a potential antiviral treatment for influenza, alphaviruses including Eastern, Western, and Venezuelan equine encephalitic viruses, it is a directly acting broad-spectrum oral antiviral drug working on the RdRp enzyme. Molnupiravir was found to significantly lower the risk of hospitalisation and death in mild COVID-19 disease based on a meta-analysis of available phase 1-3 studies. A phase 3 double-blind, randomised placebo-controlled trial found that early treatment with molnupiravir decreased the risk of hospitalisation or death in at risk unvaccinated adults with mild-to-moderate, laboratory-confirmed Covid-19. [25]

Paxlovid: (Nirmatrelvir and ritonavir in combination) It is an oral combination medication of two antiviral agents that, according to an interim analysis of phase 2-3 data (reported via press release) involving 1219 patients, found that, when started within three days of symptom onset, paxlovid had an 89% lower risk of COVID-19-related hospital admission or all-cause mortality than the placebo group. To confirm the observed efficacy, more research is being done.[26]

Remdesivir: It is a broad-spectrum antiviral drug that has previously shown antiviral activity against SARS-CoV-2 *in vitro*. [27]

The U.S. Food and Drug Administration approved remdesivir over placebo in three randomized, controlled clinical trials because it sped up recovery for adults hospitalized with mild-to-severe COVID-19. Remdesivir has been given the green light by the Food and Drug Administration (FDA) for use in treating COVID-19 in hospitalized adults and pediatric patients (over the age of 12 and weighing at least 40 kilograms).However, the WHO SOLIDARITY Trial, which involved 11,330 inpatients with COVID-19 and was carried out in 405 hospitals across 40 countries, found that remdesivir had little to no effect on overall mortality, the initiation of mechanical ventilation, and length of hospital stay. A recently published randomized double-blind placebo-controlled trial also found an 87% lower risk of hospitalization or death. [28]

Hydroxychloroquine and chloroquine: Initially during the pandemic, hydroxychloroquine and chloroquine were suggested as COVID-19 antiviral therapies. The clinical status or overall mortality of hospitalized patients treated with hydroxychloroquine with or without azithromycin did not improve when compared to placebo, according to data from randomized control studies.[29]

The use of hydroxychloroquine as post exposure prophylaxis did not prevent COVID-19 symptoms or SARS-CoV-2 infection, according to data from randomized control studies.

Lopinavir/ritonavir: During the early stages of the pandemic, lopinavir/ritonavir, an FDA-approved combination drug for the treatment of HIV, was suggested as an antiviral treatment for COVID-19. Lopinavir/Ritonavir is not currently indicated for the treatment of COVID-19 in hospitalized and non-hospitalized patients, according to data from a randomized control trial that found no benefit with lopinavir-ritonavir treatment compared to standard of care in patients hospitalized with severe COVID-19.

Ivermectin: It is an FDA-approved anti-parasitic drug used to treat COVID-19 because an *in vitro* study showed that it inhibited the replication of SARS-CoV-2. A single-center double-blind, randomized control trial involving 476 adult patients with mild COVID-19 illness who were randomized to receive ivermectin 300 mcg/kg body weight for five days or placebo did not significantly improve or resolve symptoms.

Products with Anti-SARS-CoV-2 Neutralizing Antibodies

Uncertainty exists over the length of time that COVID-19 survivors' neutralizing antibodies against SARS-CoV-2 remain active. Nevertheless, substantial research is being done in ongoing clinical studies to determine their potential significance as therapeutic agents in the treatment of COVID-19.

Convalescent plasma: During the SARS, MERS, and Ebola epidemics, convalescent plasma therapy was assessed; however, there were no randomized control trials to support its efficacy. Convalescent plasma treatment was approved by the FDA under an EUA for patients with severe, life-threatening COVID-19. Data from numerous studies investigating the use of convalescent plasma in life-threatening COVID-19 have produced conflicting outcomes, despite the fact that it first seemed promising. According to a retrospective study based on a U.S. national registry, there was a lower risk of death in patients who received a transfusion of convalescent plasma with higher anti-SARS-CoV-2 IgG antibody levels than patients who received a transfusion of convalescent plasma with low antibody levels among patients hospitalized with COVID-19 who were not on mechanical ventilation. Data from three small, randomized control studies revealed no appreciable differences between convalescent plasma therapy and standard therapy in terms of clinical improvement or overall mortality. According to an *in vitro* investigation, compared to the B.1.1.7 variant, which was not more resistant to neutralization, the B.1.351 variant displayed noticeably higher resistance to neutralization by convalescent plasma taken from patients who had previously contracted the original SARS-CoV-2 strains.[30-33]

REGN-COV: When given prophylactically or therapeutically to non-human primates, the antibody cocktail known as REGN-COV2 (casirivimab and imdevimab), which targets the RBD on the SARS-CoV-2 spike protein, has been demonstrated to reduce the viral load *in vivo* and prevent virus-induced clinical sequelae.[34]

Results from an interim analysis of 275 non-hospitalized COVID-19 patients from an ongoing double-blinded trial who were randomized to receive placebo, 2.4 g of REGN-COV2 (casirivimab 1,200 mg and imdevimab 1,200 mg), or 8 g of REGN-COV2 (casirivimab 2,400 mg and imdevimab 2,400 mg) showed that the REGN-COV2 antibody cocktail decreased viral load in comparison to This interim analysis also established the cocktail antibody's safety profile, which was similar to the placebo group's.[35] REGN-COV (casirivimab/imdevimab) showed a 70% reduction in hospitalization or death in non-hospitalized COVID-19 patients, according to preliminary data from a Phase 3 trial. According to a recent preprint paper by Wilhelm et al., their *in-vitro* testing revealed that the SARS-CoV-2 Omicron variant was resistant to casirivimab and imdevimab.

Bamlanivimab and Etesevimab: Two effective anti-spike neutralising monoclonal antibodies are bamlanivimab and etesevimab. An anti-neutralizing monoclonal antibody called bamlanivimab was created from convalescent plasma from a COVID-19 patient. It targets the RBD of the SARS-CoV-2 spike protein, just like REGN-COV2, and research has shown that it can neutralize the virus and lessen viral replication in non-human primates. Etesevimab neutralizes resistant variants with alterations in the epitope bound by bamlanivimab, according to *in vitro* tests, and binds to a different epitope than bamlanivimab. Data from the Phase 3 phase of BLAZE-1 are not yet available, however early findings suggest that the treatment significantly decreased the chance of hospitalization and mortality by 87%. Available *in vitro* evidence on bamlanivimab/impact etesevimab's on the newly discovered SARS-CoV-2 variants of concern (B.1.1.7; B.1.351) demonstrates retained activity.[36]

Sotrovimab: A powerful anti-spike neutralising monoclonal antibody, sotrovimab (VIR-7831), has been shown to have action against all four VOCs—Alpha (B.1.1.7), Beta (B.1.351), Gamma (P1), and Delta—*in vitro* (B.1.617.2). Results from a preplanned interim analysis (not yet peer-reviewed) of the multicenter, double-blind, placebo-controlled Phase 3 COMET-ICE trial by Gupta et al. that assessed the clinical efficacy and safety of sotrovimab showed that one dose of sotrovimab (500 mg) decreased the risk of hospitalisation or death by 85% in high-risk non-hospitalized patients with mild to moderate COVID-19 compared with placebo.

Immunomodulatory Agents

Corticosteroids: Severe COVID-19 is linked to inflammation-related lung injury triggered by cytokine release characterized by an increase in inflammatory markers. The effectiveness of glucocorticoids in COVID-19 patients was not adequately

documented in the early stages of the epidemic. The Randomized Evaluation of Covid-19 Therapy (RECOVERY) study, which involved hospitalized patients with clinically suspected or laboratory-confirmed SARS-CoV-2 who were randomly assigned to receive dexamethasone (n = 2104) or usual care (n = 4321), demonstrated that the use of dexamethasone resulted in lower 28-day mortality in patients who were on invasive mechanical ventilation or oxygen support but not in patients who were not receiving any respiratory support.[37] Therefore, currently dexamethasone was prescribed alone or with other drugs.

Interferon-β-1a: SARS-CoV-2 inhibits the generation of interferons, cytokines that are crucial in establishing an immunological response to a viral infection.[38] IFN- 1a hasn't helped in the past with acute respiratory distress syndrome (ARDS), though.[39] The use of inhaled IFN- 1a had higher odds of clinical improvement and recovery compared to placebo, according to the findings of a small randomised, double-blind, placebo-controlled experiment.[40] Interferon -1a's effectiveness against the four SARS-CoV-2 VOCs Alpha (B.1.1.7), Beta (B.1.351), Gamma (P1), and Delta is not known, however (B.1.617.2). This medication is not advised to treat COVID-19 infection due to the scant and insufficient data regarding this agent's use and the relative possibility for harm.

Interleukin (IL)-1 Antagonists: An interleukin-1 receptor antagonist called Anakinra has been given FDA approval to treat rheumatoid arthritis. Its off-label use in severe COVID-19 was evaluated in a small case-control study trial using the justification that the synthesis of cytokines, such as interleukin (I.L.)-1, is what causes severe COVID-19. Anakinra decreased the requirement for invasive mechanical ventilation and mortality in patients with severe COVID-19, according to this research, which included 52 patients who received the drug and 44 patients who received standard therapy.[41] Interleukin-1 receptor antagonists' effectiveness against the three newest SARS-CoV-2 strains is unknown (B.1.1.7; B.1.351, and P.1). It is not currently advised to use this medication to treat COVID-19 infection due to the limited data about it based solely on case studies.

Anti-IL-6 receptor Monoclonal Antibodies: The pro-inflammatory cytokine interleukin-6 (IL-6) is thought to be the main cause of the COVID-19-related hyperinflammatory condition. Based on case reports that demonstrated promising results in patients with severe COVID-19, targeting this cytokine with an IL-6 receptor inhibitor may help to reduce inflammation.[42,43]

Tocilizumab: - Anti-interleukin-6 receptor alpha monoclonal antibody tocilizumab has been approved for the treatment of a number of rheumatological conditions. The information on the use of this agent is contradictory. Tocilizumab did not significantly improve clinical status or reduce 28-day mortality as compared to placebo, according to a randomized control trial comprising 438 hospitalized patients with severe COVID-19 pneumonia, of whom 294 were randomly assigned to receive the drug and 144 to a placebo.[44] The use of tocilizumab was not effective in lowering the rate of intubation or mortality, according to the findings of a second randomized, double-blind, placebo-controlled trial comprising 243 patients with verified severe COVID-19.[45]

Two sizable randomized controlled trials—REMAP-CAP and RECOVERY—showed a mortality advantage in patients displaying fast respiratory decompensation (not yet published). [46]

Sarilumab and Siltuximab: Tocilizumab may potentially have a similar impact on the hyper-inflammatory state connected to COVID-19 as do the IL-6 receptor antagonist sarilumab and siltuximab. There are no clinical trials supporting the use of siltuximab in severe COVID-19 that are currently known to have been published. On the other hand, a 60-day randomized, double-blind, placebo-controlled international phase 3 trial with 431 patients did not detect any appreciable reduction in the death rate or clinical condition.[47] Ongoing research on the therapeutic effectiveness and safety of sarilumab in adult COVID-19 hospitalized patients is another randomized, double-blind, placebo-controlled study (NCT04315298).

JAK Inhibitors

Baricitinib: Patients with moderate to moderately active rheumatoid arthritis (RA) are currently prescribed baricitinib, an oral selective inhibitor of Janus kinase (JAK) 1 and JAK 2. Based on its inhibitory action on SARS-CoV-2 endocytosis *in vitro* and on the intracellular signaling pathway of cytokines that generate the late-onset hyper-inflammatory state that culminates in severe disease, baricitinib was thought to be a possible treatment for COVID-19.[48,49] It is a promising treatment medication against all stages of COVID-19 due to this dual inhibitory action. The 2-week mortality rate and clinical symptoms significantly improved in the baricitinib arm compared to the control arm in a multicenter observational, retrospective study of 113 hospitalized patients with COVID-19 pneumonia who received baricitinib in combination with lopinavir/ritonavir (baricitinib arm, n=113) or hydroxychloroquine and lopinavir (control arm, n=78). Additionally, different studies also suggest that the baricitinib not only reduce the recovery time but also improve and enhance clinical condition of the patient admitted in the hospital. Baricitinib was approved for the combinational use with remdesivir by FDA. However, There is insufficient information on the use of baricitinib with dexamethasone, and there have been no studies evaluating the effectiveness of baricitinib alone or in combination with remdesivir in treating SARS-CoV-2 variants.

Ruxolitinib: Another oral selective JAK 1 and 2 inhibitor, roxolitinib is prescribed for steroid-resistant GVHD, polycythemia vera, and myeloproliferative diseases. It has been proposed to have an inhibitory effect on the intracellular signaling pathway of cytokines, similar to baricitinib, making it a possible COVID-19 therapy. There was no statistically significant difference between the standard of care and the small prospective multicenter randomized controlled phase 2 study results, which evaluated the effectiveness and safety of ruxolitinib. However, the majority of the patients showed a considerable decrease in their chest C.T. and a quicker recovery from lymphopenia.[50] The effectiveness and safety of ruxolitinib in treating individuals with severe COVID-19 are being studied in a significant randomised, double-blind, multicenter trial (NCT04362137).

Tofacitinib: Another oral JAK 1 and JAK3 selective inhibitor, tofacitinib is prescribed for moderate to severe rheumatoid arthritis, psoriatic arthritis, and moderate to severe ulcerative colitis. It was assumed that its administration could lessen the viral inflammation-mediated lung harm in individuals with severe COVID-19 due to its inhibitory effect on the inflammatory cascade. Tofacitinib was associated with a lower risk of respiratory failure or death, according to the findings of a small randomized controlled trial that assessed the efficacy and included 289 patients who were randomly assigned to receive the drug or a placebo.[51]

Bruton's tyrosine kinase inhibitors: Acalabrutinib, ibrutinib, and rilzabrutinib are called as Bruton's tyrosine kinase inhibitors, which control macrophage signalling and activation and are currently FDA-approved for various hematologic malignancies.

It is hypothesized that the immunological response characterized by hyper-inflammation in severe COVID-19 results in macrophage activation. Acalabrutinib was given to 19 hospitalized patients with severe COVID-19, and the outcomes of a short off-label research showed that BTK inhibition may have clinical advantages.[52] Clinical trials are being conducted to confirm the effectiveness of these medications in treating severe COVID-19 sickness.

Recent discovery of medicine and vaccine in India

2-DG drug: A repurposed medication, 2-deoxy-Dglucose, has been proposed as an adjunct therapy against COVID -19 in cooperation with Dr.laboratories Reddy's (DRL), Hyderabad, the DRDO (Defense Research and Development Organization) laboratory, and Institute of Nuclear Medicine and Allied Sciences (INMAS) (India). This medication, a glucose mimic, has the power to revolutionise medical practise. According to studies, infected cells contain more glut receptors on their surface than healthy cells. Infected cells rapidly absorb the medication, which builds up there.[53,54] The viral glycoprotein's glycosylation is altered by the 2-DG medication, preventing the virus from creating energy, replicating, and infecting human cells. Additionally, it lessens the requirement for extra oxygen. The viral glycoprotein's glycosylation is altered by the 2-DG medication, preventing the virus from creating energy, replicating, and infecting human cells. Additionally, it lessens the requirement for extra oxygen. The medicinal uses of this chemical against cancer are also well established. This drug belongs to the class of antivirals. When it accumulates in infected cells, it stifles the metabolism of glucose and halts the creation of energy. As a result, it lessens the newly created SARS-CoV-2 virus's ability to spread by blocking anabolic processes necessary for viral growth.[55]

Covaxin: It uses an RNA-based SARS-CoV-2 viral particle that is completely infectious and enclosed in a protein capsid that has been altered to prevent viral replication. Evidence of better humoral and cell-mediated immune responses in Covaxin recipients was one of the most crucial findings from the phase I/II studies. Even though CD4 + and CD8 + T cell responses were only seen in a small subset of patients in the phase I investigation, the phase II trial significantly enhanced the cell-mediated immune response. Increases in CD4 +, CD45RO +, and CD27 + T cells, which enhance the antigen recall memory response, are signs that covaxin increased T cell memory. Agonist for TLR 7/8 is present in the adjuvant chemical Covaxin. Antiviral cytokines such IL-2, IL-4, IL-6, IL-10, IL-17, TNF-, and IFN were also released on days 7 and 14, which may have contributed to an increase in the activation of APC like DCs and macrophages.The production of early-IFN I, which facilitates viral clearance and the production of pro-inflammatory cytokines, has also been connected to TLR recognition in the innate cell population.[56]

Covishield: After vaccination, there was a significant rise in B cell activation, proliferation, and anti-IgA and anti-IgG antibodies to the SARS-CoV-2 virus. Serum from vaccine recipients had S proteins that were simple to identify. Instead of Th2 cytokines, CD4 + T cells mostly produced Th1 cytokines (IFN-, IL-2, and TNF-/-) (IL-5 and IL-13). Importantly, it is demonstrated utilising a variety of methods that ChAdOx1 nCoV-19 vaccination mostly elicits a Th1 response. Paracetamol was found to decrease reactogenicity and tolerance, making ChAdOx1 nCoV-19 safe, tolerant, and immunogenic. This vaccine can induce cellular and humoral responses after a single dose, and a booster shot can produce neutralizing antibody titers.A powerful antibody and cell-mediated immune response is elicited by this vaccine, which is based on highly immunogenic technology and offers long-term protection.[56]

CONCLUSION

Six million people died worldwide as a result of the SARs CoV-2 epidemic. The respiratory system is the main organ that this virus affects, but other organs like the liver, kidney, heart, and immune system are all adversely impacted and contribute to complications and death in infected individuals. Over time, a number of already-approved medications, including hydroxychloroquine, chloroquine, ivermectin, remdesivir, and corticosteroids like dexamethasone, as well as many additional treatments, were approved to treat COVID-19 infections due to advancements in research and the approval process. These medications have shown to be helpful in some circumstances, and in other circumstances plasma therapy and oxygen therapy were also necessary. Recently, 2-DG medication for the treatment of COVID-19 was developed by DRDO and Dr. Reddy labs in partnership in India.

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