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REVIEW

Perspectives on Repurposed Drugs Based on Globally Accepted Therapeutic Guidelines to Combat SARS-CoV-2 Infection

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Abstract: A beta coronavirus was identified in Wuhan, China, in December 2019 and was named severe acute respiratory syndrome coronavirus-2. It spread globally at a rapid rate and killed innumerable people. The SARS-CoV-2 infection, also called coronavirus disease 2019, was declared a pandemic by WHO on March 11, 2020. The increasing number of SARS-CoV-2 related deaths is due to a number of reasons. A few antiviral, antimicrobial, and immune-based drugs have been repurposed for treatment as well as improvement of patient prognosis. These drugs are currently being studied in clinical trials conducted by the World Health Organization (WHO), National Institutes of Health (NIH), and other global health organizations to identify the agents that produce maximum positive patient outcomes and reduction in mortality rate. The aim of this article is to discuss the safety and efficacy of the repurposed drugs in SARS-CoV-2 infection based on currently available clinical evidence and to emphasize the importance of caution required whilst employing the international therapeutic guidelines. Also highlighted in this article are certain specific comorbid conditions, that either involve treatment with the repurposed drugs or have a direct impact of the virus in patients owing to their vulnerability.

Keywords: MERS, SARS-CoV-2, acute respiratory distress syndrome, cytokine storm syndrome, therapeutic guidelines, COVID-19

Background

Coronaviruses are a large family of viruses that predominantly reside in and circulate amongst animals. They can be categorized into *alpha, beta, gamma,* and *delta* subtypes, which together belong to the *Coronaviridae* family and *Nidovirales* order. The *alpha* and *beta* coronaviruses have the ability to transfer between animals and humans. These include the ones that induce common cold, along with MERS and SARS coronaviruses that cause Middle East Respiratory Syndrome and Severe Acute Respiratory Syndrome, respectively.[1] The coronaviruses are enveloped, containing non-segmented, positive polarized, single stranded RNA. They derive the name "Coronavirus" from a common feature shared by all of these viruses – the Spike (S) protein projecting out of the viral envelope, providing a crown like appearance under the electron microscope.[1] The SARS coronavirus (SARS-CoV) that caused a serious acute viral respiratory infection was first reported from Asia in February 2003. More than 8,000 people contracted the infection with 774 deaths. SARS spread exponentially to 26 countries before it

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was controlled within about 4 months. No SARS cases have been reported since 2004.[2,3] Likewise, the MERS coronavirus (MERS-CoV) that induced a similar respiratory disease was first documented in September 2012 in Saudi Arabia, and has since spread to 27 countries, as per the World Health Organization reports.[2] Those infected with MERS-CoV developed similar symptoms to SARS, which included cough, shortness of breath, and fever.[2,3] The World Health Organization has confirmed 2,519 cases of MERS and 866 deaths since its inception till date.[1–3]

In December 2019, an unexplained etiological pneumonia was identified in Wuhan, China, and was reported to the WHO Country Office. Subsequently, it led to the identification of a novel *beta* coronavirus (SARS-CoV-2) in January 2020 as the cause of the outbreak in Wuhan.[4] The infection later came to be known as coronavirus disease 2019 (COVID-19) and spread globally at a rapid rate. WHO announced it as a global pandemic on March 11, 2020.[4,5] Within the first 3 months of its emergence, nearly 1 million people were afflicted and 50,000 had died.[2,4–7] The SARS-CoV-2 causes respiratory symptoms similar to the SARS and MERS coronaviruses. The majority of the infected patients experienced mild-to-moderate respiratory symptoms such as dry cough, fever, fatigue, and malaise, and they recovered with general symptomatic therapy and did not require intensive care. However, geriatric patients (age >60 years) and those with underlying medical conditions like cardiovascular and renal diseases, diabetes, chronic respiratory disorders, cancer, hepatic syndromes, and the immunocompromised were found to be more vulnerable to developing serious life-threatening symptoms due to their weaker immune systems.[7] As per the latest WHO report dated July 22, 2020, the worldwide number of COVID-19 cases had crossed 14 million, with over 600,000 deaths.[8] The virus has a normal incubation period of 14 days from the time of exposure. However, most patients tend of develop symptoms within 4–5 days following exposure.[9–11] Breathing failure from acute respiratory distress syndrome (ARDS) is the main cause of mortality in patients with COVID-19.[11] Yet, recent evidence suggest that an immune reaction called "Cytokine Storm Syndrome" contributes as a secondary cause of death in a subgroup of patients with severe SARS-CoV-2 infection by inducing multiple organ failure, including fulminant myocarditis, leading to severe myocardial damage and circulatory failure.[11–14] Increased production of rapid response inflammatory cytokines such as Interleukin-6, Interleukin-1β, and Tumor Necrosis Factor (TNF) leads to the "cytokine storm" which in turn induces vascular hyperpermeability, inflammation of tissues leading to multi-organ failure, and ultimately death. Hence, there is a growing need to suppress the high cytokine concentrations in COVID-19 patients who have other comorbid conditions and have developed an advanced form of the infection.[12,14–16] Moreover, studies have shown that some of the COVID-19 patients with a poor prognosis have had high values in their D-dimer results. The possible reason for this would be the subsidiary activation of the coagulation pathway as a result of the immune response, which leads to the development of microthrombosis and disseminated intravascular coagulation.[15–21]

Guidelines for Management

The main objective of this article is to bring attention to the currently available therapeutic guidelines for management of COVID-19, with a special focus on treatments involving the drug classes that have been repurposed to treat the infection. Therapeutic guidelines provided by the majority of the international health organizations, including WHO and NIH, shed light on Antithrombotic Therapy, Immune Based Therapy, and specific Antiviral and Anti-Malarial drugs that have been hypothesized to produce promising results in COVID-19 patients.[9,20,22]

Antithrombotic Therapy

As discussed earlier, there is a strong association between COVID-19 and thrombotic events resulting from inflammation and activation of coagulation pathways. This results in a prothrombotic state, thereby leading to an increase in the concentration of fibrin and fibrin degradation products, fibrinogen, and D-dimers in COVID-19 patients.[15–21] The NIH as well as WHO recommends the use of anticoagulants such as LMWH (enoxaparin) or unfractionated heparin in hospitalized COVID-19 patients as prophylaxis to prevent thromboembolic events, unless contraindicated.[9,20] For cases with contraindications, the use of mechanical prophylaxis such as intermittent pneumatic compression devices is recommended.[20]

Immune-Based Therapy

Sufficient data is not available concerning the use of immunomodulators such as interleukin-1 (eg, Anakinra) and interleukin-6 (eg, tocilizumab, sarilumab) inhibitors, interferons, blood derived products such as convalescent plasma therapy, mesenchymal stem cells (MSCs), or SARS-CoV-2

specific immunoglobulins.[9,20,22] Interferons (α and β), a family of signaling proteins that are produced and released by host cells in response to viral activity, have been suggested as a potential treatment for COVID-19 due to their *in-vivo* and *in-vitro* antiviral characteristics.[9,20,22–24,26,27] However, it was clearly evident from prior studies related to infections caused by other coronaviruses (SARS and MERS) that there were no significant positive outcomes in the patients. Furthermore, the risk of adverse events and toxicity caused by interferons far outweighs its benefit.[20,23–27] Therefore, the WHO as well as NIH recommend against the use of these therapeutic agents for the treatment of SARS-CoV-2 infection.[9,20] Similarly, the use of Janus Kinase Inhibitors such as Baricitinib are also not recommended as per the therapeutic guidelines provided by WHO and NIH due to the enhanced immunosuppressive action of these drugs.[9,20] JAK inhibitors exert their anti-inflammatory effects by inhibiting the JAK signal transducer and activation of the transcription pathway. This helps in ameliorating inflammatory immune responses in autoimmune conditions such as rheumatoid arthritis and interferonopathies.[28,29] However, as there are not any clinical data available on the efficacy of JAK inhibitors in COVID-19 patients, and also due to the fact that extended use of these drugs poses a threat of superinfection as a result of immunosuppression, the use of these is strongly not recommended.[20]

Other Antimicrobial and Antiviral Therapy

The WHO strongly recommends against the use of Remdesivir – the investigational antiviral drug, as well as others including Lopinavir, ritonavir, Umifenovir, and Favipiravir as treatment or prophylaxis of COVID-19. The same is applicable for the antimalarial drugs: chloroquine and hydroxychloroquine due to the inadequacy of available clinical data on their efficacy against the SARS-CoV-2 virus.[20] As per the remarks on WHO interim clinical management guidelines, the current scientific literature on the above-mentioned drugs is largely observational in nature and there have been very few clinical trials done to study the effectiveness of these agents in COVID-19 patients.[20] Also, the adverse effects induced by these agents outweigh the possibility of benefit.[23–27,30–32] A recent update on the WHO website dated June 17, 2020, stated that the hydroxychloroquine (HCQ) phase of the Solidarity Trial to identify an effective treatment for COVID-19 has been discontinued based on clinical data from the Solidarity Trial as well as other clinical trials conducted worldwide including the UK's Recovery Trial, France's Discovery Trial, and a Cochrane review of other HCQ related evidence. The data suggested that comparing to standard of care therapy, there was no significant reduction in the mortality rate of hospitalized patients with SARS-CoV-2 infection when treated with HCQ.[33,34] However, the preliminary clinical data from the randomized control trial, called the Adaptive COVID-19 Treatment Trial (ACTT), that was initiated on February 21, 2020 with 1,063 patients and sponsored by the National Institute of Allergy and Infectious Diseases (NIAID), suggested that patients receiving Remdesivir had a 31% faster recovery period than those receiving placebo.[35] Based on this data, the NIH recommends the use of the drug in hospitalized COVID-19 patients with severe disease and extreme lung damage. The drug is currently available under the emergency use authorization of the FDA for specifically hospitalized adults and children with severe COVID-19 infection.[9]

Considerations in Special Comorbid Conditions

Although there are many comorbidities that could exacerbate the clinical condition of COVID-19 patients, this article focuses primarily on a few specific conditions that either involve treatment with the repurposed drugs discussed above or have a direct impact of the virus in patients owing to their vulnerability. These include hepatic disorders, genetic heart diseases, rheumatic autoimmune diseases, chronic kidney diseases, diabetes, and obesity.

Hepatic Disorders

The SARS-CoV-2 virus has a 82% resemblance to the genetic sequence of SARS-CoV virus and hepatic impairment has been reported in up to 60% of SARS patients.[37] Moreover, the SARS-CoV-2 virus uses the angiotensin converting enzyme 2 (ACE 2) receptor to bind and get internalized into its target cells. These receptors are abundantly present on the epithelial cells of hepatic and biliary systems. Hence, patients with SARS-CoV-2 infection are at increased risk of developing liver complications, especially those who have preexisting liver problems.[38,39] The latest report from the European Association for the Study of the Liver (EASL) and European Society of Clinical Microbiology and Infectious Diseases (ESCMID) provides guidelines on the safety of the above discussed repurposed

investigational drugs on COVID-19 patients with preexisting liver conditions or transplantations.[40] Patients who undergo liver transplantations are most likely to develop severe infection due to the immunosuppressive agents. The same is applicable for patients with liver carcinomas and undergoing radiation/chemotherapy. It is crucial to consider the drug–drug interactions between the COVID-19 investigational medications and those that are already being used to treat the patient's preexisting condition.[36,38,40] The EASL-ESCMID position paper recommends that COVID-19 patients with liver disease and risk factors for development of severe infection must be started on an early antiviral therapy program or enrolled in clinical trials at various COVID-19 specific healthcare centers.[40] This recommendation is based on the fact that early initiation of antiviral treatment has shortened the course of other viral infections such as influenza. Thus, it might be beneficial in patients suffering from SARS-CoV -2 infection as well. Nevertheless, appropriate dose adjustments are required based on the functioning capacity of the liver, identified from the patient's Child-Pugh score. It is also imperative to carefully monitor for adverse events and toxicities.[38,40]

Genetic Heart Diseases

It is discernible that genetic heart diseases are relatively rare amongst populations and SARS-CoV-2 is a newly discovered virus. Hence, scientific data about the best clinical practice in this area is limited. Nevertheless, the Cardiac Society of Australia and New Zealand (CSANZ) has provided a few recommendations in their recent consensus statement to effectively manage COVID-19 patients with genetic heart diseases. As per this statement, patients with congenital structural cardiac problems are recommended to continue their cardiovascular drugs such as beta blockers, Angiotensin Converting Enzyme Inhibitors (ACEIs), Angiotensin Receptor Blockers (ARBs), Calcium Channel Blockers (CCBs), etc.[41] There have been conflicting opinions about the safety of ACEIs and ARBs in SARS-CoV-2 patients due to the binding site of the virus on ACE 2 receptors that are found on the cell membranes of renal tissue as well as the epithelial cells of the GI tract and lungs. A few preclinical studies have demonstrated that prolonged use of ACEIs/ARBs upregulates the expression of ACE 2 receptor, thereby causing healthcare professionals combating the infection and leading research scientists to question the possibility of these drugs posing a threat of exacerbating the SARS-CoV-2 infection.[39,42–47] However, as these concerns are largely theoretical in nature and there are not any relevant clinical trials or other sufficient evidence to substantiate this, international organizations focusing on cardiovascular medicine recommend the continuation of the patients' regular cardiac medications.[41–46] Moreover, a recent cohort study showed that the use of ACEIs/ARBs has been associated with significantly improved survival rates amongst hospitalized hypertensive patients with SARS-CoV-2 infection.[47] It is also imperative to consult a specialist cardiologist in genetic heart diseases prior to initiating atypical-repurposed drugs discussed above or enrolling in clinical trials involving these drugs in patients coinfected with SARS-CoV-2 infection.[41]

Rheumatic Autoimmune Diseases

The American College of Rheumatology Guidelines recommend continuing the use of regular antirheumatic drugs in COVID-19 patients suffering from preexisting rheumatic conditions. This includes the use of ACEI/ARB for scleroderma renal crisis or SLE, due to the protective effects of these drugs on the kidneys.[48–51] As for NSAIDs, it was recommended in the guidelines to use them with caution in newly diagnosed rheumatic disorders; nonetheless stop if patients develop severe SARS-CoV-2 infection due to the poor prognosis resulting from the cardiac, kidney, and liver injury that have been associated to COVID-19 as severe manifestations of the infection.[38,40,41,48,49,52] In the case of Glucocorticoid therapy, there has been conflicting evidence in favor of their use in COVID-19 patients. Emerging data indicate that their anti-inflammatory properties could potentially minimize the impact of SARS-CoV-2 infection, especially in its late stages which is characterized by cytokine storm and hyperinflammation.[48,53,54] However, these are very limited data to support the use of glucocorticoids in SARS-CoV-2 infected patients given the risk of glucocorticoid induced immunosuppression, leading to opportunistic infections. Moreover, the plethora of evidence available in support of the detrimental effects of glucocorticoids contradict the limited evidence in support of their beneficial effects. Hence, the guidelines recommend continuing standard of care treatment using the lowest effective doses of glucocorticoids drugs and avoiding sudden termination of therapy in patients with underlying rheumatic disease. However, it was also acknowledged by the guidelines panel that higher doses may be required in cases of serious, life-threatening situations with vital organ damage

even after exposure to SARS-CoV-2.[48] Moreover, an update from the UK's Recovery Trial has demonstrated that Dexamethasone, a synthetic glucocorticoid agent, could save the lives of critically ill patients with SARS-CoV-2 infection. Treatment with the agent showed about one-third reduction in mortality for patients on ventilators whilst for those requiring only oxygen the mortality rate was reduced by about one-fifth.[55]

The panel recommends continuation/initiation of Conventional Synthetic disease-modifying antirheumatic drugs (csDMARDs) when required regardless of whether the patient has been exposed to SARS–CoV-2 infection or not. This recommendation was formed based on the fact that risk of severe infection with these drugs is considerably lower, especially when administered as monotherapy.[48,56,57] Nevertheless, caution must be exercised due to the known adverse effects of these drugs such as diarrhea and other gastrointestinal manifestations, hepatitis, cytopenia, and cardiotoxicity which could be misinterpreted with symptoms of SARS-CoV-2 infection.[48] Likewise, due to lack of sufficient randomized controlled trials data to support sustained use, the panel recommended that all immunomodulators, immunosuppressants, and JAK inhibitors be temporarily withheld or discontinued in the light of reported or suspected SARS-CoV-2 infection.[48]

Chronic Kidney Diseases

The NICE COVID-19 rapid guideline for CKD recommends the continuation of regular medications including ACEI/ARB, diuretics, and immunosuppressants in patients underlying kidney disease exhibiting symptoms of SARS-CoV-2 infection. Dose reduction and therapeutic dose monitoring have been recommended by the Renal Association Guidance for patients on immunosuppressants, corticosteroids, and anti-cancer drugs such as cyclophosphamide.[58,59] This is particularly applicable for patients on the "Induction" phase. Immunosuppressive medications should be assessed on a case-by-case basis, balancing the risk of insufficient therapy or acute relapse against the risk of SARS-CoV-2 infection affecting a particular patient.[59] Abrupt cessation of corticosteroid maintenance therapy is deemed detrimental to patients with autoimmune kidney disease due to risk of relapses and thereby not recommended. In patients under maintenance regimens with biologics such as LA-Rituximab, delayed time interval between infusions is recommended, if the risk of disease flare is less and the likelihood of severe manifestations of SARS-CoV-2 infection is more.[59] Non-Steroidal Anti-inflammatory Drugs (NSAIDs) are to be avoided in patients with both acute as well as chronic kidney diseases. Patients exhibiting flu symptoms are to be treated with acetaminophen (paracetamol). As for patients preparing for renal transplant, the procedure or immunosuppression must not be initiated unless the SARS-CoV-2 nasopharyngeal swab test result is negative.[60] Lastly, dialysis following transplantation must be done in a COVID-19 secure area after having taken precautionary safety measures.[58–60]

Diabetes and Obesity

Based on recent evidence, it is known that both diabetes and obesity are related to severe complications in SARS-CoV-2 infection.[61] Epidemiological findings from regions severely affected by SARS-CoV-2, along with CDC reports have shown that the risk of mortality due to COVID-19 is approximately 50% greater in diabetic patients.[61,62] Likewise, hospitalized COVID-19 patients who were overweight or obese with a body mass index (BMI) of greater than 25 kg/m^2 were at increased risk of requiring mechanical ventilation.[63] There is a strong association between insulin resistance and visceral adipose tissue (VAT) that are abundantly present in obese patients. The adipocytes secreted most of the inflammatory and coagulopathic molecules including TNF-α and interleukin-6, relating to the SARS-CoV-2 induced cytokine storm.[63–65] Evidence suggests that Type-2 diabetic patients had increased levels of TNF-α.[63,66] Moreover, individuals with both the comorbidities had lower levels of Interleukin-10 (IL-10), which is a protective anti-inflammatory cytokine.[63,67] Hence, obese patients with Type 2 diabetes mellitus are at a significantly increased risk of developing a severe form of SARS-CoV-2 infection.[63,68,69]

A few retrospective observational studies have suggested the use of Metformin, the first line therapeutic agent for Type-2 diabetes mellitus, to mitigate the impact of SARS-CoV-2 infection in diabetic and obese patients. It was found that metformin decreased the levels of IL-6, TNF-α, and increased the levels of IL-10.[63,70] Over the years, metformin has been used for treatment of various diseases apart from type-2 diabetes. It is used as an off-label medication for weight loss in the USA.[68,71] Furthermore, findings from a retrospective cohort study demonstrated that early administration of metformin is associated with substantially lower mortality in geriatric patients with pneumonia.[68,72] Since elderly patients are at increased risk of mortality due to SARS-CoV-2, it would be appropriate to consider incorporation of metformin as an adjuvant agent

for treatment of the infection.[68,73] Other beneficial effects of metformin in minimizing the impact of SARS-CoV-2 include reduced macrophage cytokine synthesis, increased insulin sensitivity, and activation of AMP-activated protein kinase (AMPK).[63,68,70,71] Lastly, metformin has also been hypothesized to possess a viral inhibitory capability through increasing insulin sensitivity.[68,74] Therefore, it is plausible to consider metformin as an effective therapeutic agent for management of COVID-19 in obese, diabetic, and geriatric patients. However, there is a need for further research into this topic and, due to the lack of sufficient data from clinical trials, the efficacy of Metformin in SARS-CoV-2 remains to be validated.

Conclusion

At present, limited clinical data is available to substantiate the beneficial effects of repurposed drugs on SARS-CoV-2 patients. The clinical guidelines highlighted above have been made to provide optimal care during the prevailing pandemic situation. Hence, due to the evolving nature of literature as a result of ongoing research to identify the best possible therapeutic agents to combat the infection, frontline health professionals are recommended to keep a close watch for recent updates to the guidelines based on clinical trial results. Furthermore, when patients with serious underlying comorbid conditions contract SARS-CoV-2 infection, it is imperative that the specialist physician involved in the treatment of their underlying condition is also included in the healthcare team treating the infection. This is particularly important for making crucial decisions such as enrolment of patients in clinical trials involving repurposed drugs, initiating the drugs as pre-/post-exposure prophylaxis, and dose alterations as necessitated by standard of care therapeutic guidelines for the patients' underlying disease.

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