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Adverse drug reaction of Re-purposing drugs in the management of Covid-19- A current updated review

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Abstract

The majority of the drugs used to treat covid-19 are repurposed drugs, and the preponderance of them functions through immune modulation mechanisms. Most of these treatments have not been demonstrated to be beneficial in a robust manner, but since we had no other alternatives, we began repurposing existing drugs. Relevant articles with experimental studies conducted in-silico, in-vitro, in-vivo, clinical trials in humans, case reports, and news archives were selected for the review. Number of drugs such as remdesivir, favipiravir, ribavirin, lopinavir, ritonavir, darunavir, arbidol, chloroquine, hydroxychloroquine, tocilizumab and interferons has shown inhibitory effects against the SARS-CoV2 invitro as well as in clinical conditions. When adverse drug reactions (ADRs) occur, they add another layer of intricacy to the care of COVID19 patients. Because they are repurposed medications, there is already a body of knowledge about how to cope with their adverse effects. In this study, we want to provide assistance on ADRs, including drug hypersensitivity responses and allergies which are produced by medications presently used to treat COVID-19.

Keywords: Adverse Drug Reactions, COVID-19, Repurposing drugs

Introduction

In 2020, World health organization stated the COVID-19 outbreak as a global pandemic as reported cases reach 200,000 people, with over 8,000 people died due to the complications related to COVID-19 in more than 160 countries. The number of confirmed cases surges every day, exerting a wide variety of symptoms in the infected persons. SARS-CoV-2 has now spread to more than 213 countries worldwide [1]. The cost of the new drug

development process amounts to more than a billion dollars extending for a period of 10–15 years [2]. With the success rate of only 2.01% [3]. Considering the time and cost required for coming up with new therapies, probing the existing antiviral and other drugs against SARS-CoV2 is cost-effective. In recent times, repurposing of available drugs for the management of several disease conditions is increasingly becoming a popular strategy as it uses de-risked compounds with known pharmacokinetic, pharmacodynamics profiles which can directly enter phase III or IV clinical trial making the drug development process potentially a low-cost and relatively rapid [4]. Number of drugs such as remdesivir, favipiravir, ribavirin, lopinavir, ritonavir, darunavir, arbidol, chloroquine, hydroxychloroquine, tocilizumab and interferons has shown inhibitory effects against the SARS-CoV2 invitro as well as in clinical conditions. Although the majority of infections are self-limiting, approximately 15% of infected adults develop severe pneumonia that presupposes supplemental oxygen treatment, and an additional 5% progress to critical illness with hypoxemic respiratory failure, acute respiratory distress syndrome, and multiorgan failure that necessitates ventilator support, often for several weeks. At least half the patients with coronavirus illness who required invasive mechanical ventilation died in hospital, placing pressure on health-care systems, notably in Intensive Care Units (ICUs), which have been swamped by severe cases in numerous impacted nations.

Although numerous approved drugs and research treatments have demonstrated antiviral activity against SARS-CoV-2 in vitro, there are currently no antiviral therapies with proven efficacy in treating critically ailing COVID-19 patients. Immunomodulatory and antiviral drugs are the most widely reused for covid-19, which comes with Adverse Drug Reactions (ADRs), complicating patient management. There is already a foundation of knowledge in dealing with their ADRs.

In this review, we want to provide insight in selecting an appropriate drug based on its documented adverse drug reactions [5].

Materials and methods

A detailed literature search was conducted in the electronic databases such as Medline, PubMed, SCOPUS, Cochrane Library, Google Scholar, Clinical Trials Registry India (CTRI) and clinicaltrials.org. The search strategy combined the Medical Subject Heading (MESH) terms and non-MESH terms of Repurposing drugs, Covid-19 drugs, ADR on Covid-19 treatment to find the suitable publication. References of all the identified original research articles were also checked for any additional literature. Two of the authors (SU, KS) independently reviewed the title/abstract obtained by the search strategy and selected the studies which were relevant to the current review. The full-text screening was carried out by two independent reviewers and any disagreements were resolved through mutual discussion or by discussing with another co-researcher of the team.

Reported adverse drug reaction on re-purposing drugs in Covid-19 patients

Hydroxychloroquine

The French Pharmacovigilance Network notified all cardiac adverse drug reactions connected with "off-label" use of hydroxychloroquine (HCQ) in COVID-19 to the National Institute for Health and Care Excellence's (NICE) Regional Center of Pharmacovigilance in March 2020. The cardiac safety of these medications in COVID-19 should be investigated because they are known to promote cardiac ADRs, particularly QTc interval widening on the ECG and

arrhythmia [6, 7]. In one month, 120 reports of cardiac adverse drug reactions were received, with 103 of them linked to hydroxychloroquine alone (86%). There were 8 abrupt, inexplicable, or aborted deaths (7%), 8 ventricular arrhythmias (7%), 90 reports of extended QTc (75%), the majority of which were "serious" (64%), 20 reports of serious conduction problems (17%), and 5 reports of other cardiac causes (4%). Other cardiac issues were observed in four HCQ-related alerts (3.3 percent of total) [8]. There is currently no solid or persuasive data on the efficiency of hydroxychloroquine in the treatment of covid-19. Nonetheless, their safety remains a concern due to their proclivity to extend the QT interval on the ECG [9]. Brazilian research comparing two doses of HCQ-associated with AZI was prematurely discontinued due to cardiac safety concerns [10]. Sodium and calcium channel blockade also generates HCQ-induced conduction blocks [11,12]. As HCQ inhibits the ether-a-go-go related gene (hERG) potassium channel, which resembles the crucial potassium current IKr leading to arrhythmias [13].

Macrolides

Macrolide labels warn of the potential of QTc prolongation [14, 15, 16]. A substantial increase in cardiovascular mortality in individuals with cardiac comorbidities has been reported [17]. Azithromycin is claimed to inhibit IKr to a lower extent than erythromycin or clarithromycin, but all three lengthen the QT interval experimentally and practically. Fever exacerbates drug-induced IKr blockage and an elevation in interleukin-6, as noted in COVID-19 infection has been proposed as a route for QT prolongation linked with inflammation [18,19,20]. Azithromycin efficiency in the treatment of COVID-19 has yet to be documented in a solid or succinct manner [9]. Month-long research found 120 adverse medication responses, 60% of which were linked to azithromycin usage [8].

NSAIDs

Non-Steroidal Anti-Inflammatory Drugs (NSAIDs) have been among the most widely employed fever medications. Nonselective cyclooxygenase (COX) inhibitors, such as ibuprofen, aspirin (acetylsalicylate), diclofenac, and naproxen, are examples of NSAIDs. Questions have been voiced that NSAIDs may be linked to an increased risk of adverse reactions when administered in individuals with acute viral respiratory infections, especially COVID-19. A narrative review in a news article revealed that consumption of NSAIDs such as ibuprofen and corticosteroids should be bypassed in cases of acute respiratory infection because these drugs entangle to ACE-2 and exacerbate the condition, and it was also not advised to bring temperature down in Covid-19 patients due to its renowned cardiac and GI side effects. As a result, certain studies by NICE and TMG advocate acetaminophen above it as an antipyretic [21]. WHO conducted a comprehensive study utilising databases and revealed that there is currently no evidence of serious adverse events, acute health care usage, long-term survival, or quality of life in patients with Covid-19 as a response of NSAID use? Ibuprofen, have been linked to the advancement of pulmonary illness in nonpregnant individuals. In bacterial lung infections, this association has been observed. Experimental evidence suggests that NSAIDs impair neutrophil function, delaying bacterial clearance and inflammation resolution [22].

Aspirin as prophylaxis

There is concern about the safety of pregnant women taking aspirin for the prevention of preeclampsia and fetal growth restriction. The dispute might have led to

misunderstandings among healthcare professionals and pregnant women, resulting in the discontinuation of preventive low dose aspirin treatment. There is currently no evidence on the relationship between the risk of Covid-19 advancement and the use of low dose aspirin [23] . Preeclampsia affects 2–8% of pregnancies globally and is one of the major contributing factors of maternal and perinatal death and morbidity [24].

Tocilizumab and Infliximab

Tocilizumab has already been investigated for potential risk factors in RA patients because of its activity on the CYP450 enzyme. Patients receiving TCZ and consuming background corticosteroids had a greater risk of severe infections than those not receiving background corticosteroids. Tocilizumab has been linked to serious drug-induced liver impairment, including acute liver failure, hepatitis, and jaundice. Between 2 weeks and more than 5 years after starting Tocilizumab, serious liver damage occurred. Abnormalities in the blood Following therapy with tocilizumab 8 mg/kg in conjunction with MTX is found, neutrophil and platelet counts was also found to be decreased [25]. Tocilizumab has also been linked to neurological manifestations like headache, dizziness, numbness, hematological (leukopenia, neutropenia), and metabolic side effects (hyper lipidemia) [26]. According to the study, infliximab has also been connected to neurological embodiments such as (headache, dizziness), vasculitis, gastrointestinal (abdominal pain, Diarrhoea), nephropathy, cytopenia, acute infusion reactions, fever, malignancies, HAHA, serum sickness, interstitial pneumonia, and the potential to cause hepatic injury [26].

Remdesivir

The most reported ADRs for remdesivir represented liver dysfunction, kidney injury, cardiovascular adverse effects (hypotension, atrial fibrillation, deep-vein thrombosis), gastrointestinal adverse effects (diarrhea) [27].

Favipiravir

Favipiravir, which has been licensed for the treatment of influenza in Japan and China, has been linked to birth abnormalities and liver damage. Glenmark (an Indian pharmaceutical manufacturer) stated that the medicine can be used in Covid-19 patients with comorbid diseases like as diabetes and heart disease, but it should not be given to individuals with severe renal and liver damage, or pregnant or lactating women. The medicine should also be considered with caution in individuals who have a history of aberrant uric acid metabolism or who have gout, according to the manufacturer [28].

Lopinavir/ritonavir

A retrospective review of 217 COVID-19 patients revealed that the prevalence of ADRs was 37.8 %, with drug-induced gastrointestinal symptoms dominating the list (23.0 %). The most frequent gastro intestinal ADRs include diarrhea, nausea, vomiting, and abdominal pain. In clinical studies, hypertriglyceridemia and hypercholesterolemia were the most frequently identified laboratory abnormalities in lopinavir/ritonavir recipients and may be the rationale for treatment cessation in certain individuals [29]. Total cholesterol and triglyceride levels surged during the first month after initiating medication and were rather steady thereafter [20]. Lopinavir and ritonavir were also linked to neurological side effects such as headache, hepatotoxicity [3,30].

Convalescent plasma (CP)

The use of CP is an interim approach to treatment until availability of hyper immunoglobulin, drug therapies, and vaccines. It is Known to cause allergic reactions, transfusion-associated circulatory overload (TACO), and transfusion-associated acute lung injury (TRALI) as with

any plasma or blood transfusion. All studies that assessed adverse events have reported no or minimal adverse events. Only 7 transfusion-associated circulatory overload (TACO), 11 transfusion-related lung injury (TRALI), and 3 severe allergic. Overall, among a total of 20,749 patients reported with safety data, the incidence of adverse events related to CP transfusion was less than 0.8%, comparable or even lower than the incidence of adverse events related to plasma transfusions in other clinical settings [31].

Drugs in the treatment of type 2 infection (ARDS) of COVID-19 pneumonia

Drugs such as dexamethasone, baricitinib, sarilumab, interferon beta 1B, and intravenous immunoglobulins, have the potential to trigger thromboembolic events by expanding d-dimer levels four times higher than the Upper limit normal among in-patients, as demonstrated in numerous studies [32,33,34].

Colchicine

The previous gout medication is now being examined for a different purpose and is currently being tested. colchicine seems to be well tolerated at therapeutic doses. In a systematic review of colchicine with respect to safety diarrhea and gastrointestinal adverse events were commonly observed. However, the rate of hepatic, sensory, muscular, infectious or hematological toxicities, or death was not augmented [35].

Anakinra

This medication inhibits IL-1, the most prominent pro cytokine that begins the inflammatory cascade via integrin expression in leucocytes and endothelial cells [36]. Serious infections, liver damage, thrombocytopenia, and neutropenia are also possible side effects (it is not recommended to begin therapy with count (less than 1.5109/L) [37].

Anikinra has also been implicated to hematopoiesis, Hypertransaminasemia, upper respiratory tract infections, and Nasopharyngitis [26].

Pirfenidone

It is an anti-fibrotic and anti-inflammatory medicine that is taken orally that's used to treat idiopathic pulmonary fibrosis. GI and skin ailments are more prevalent in persons taking this medicine; however, they can be avoided by adjusting the dose. Monitoring the liver function is critical while pirfenidone therapy [38]. Elevations in aspartate transaminase (AST) and alanine transaminase (ALT) levels to more than three times the upper limit of normal (ULN) occurred in 3.2 percent of phase III studies, which were handled with dosage adjustments or termination [39].

Ivermectin

Adverse effects of ivermectin may include dizziness, pruritis, nausea, or diarrhea. Neurological adverse effects have been reported with the use of ivermectin for the treatment of onchocerciasis and other parasitic diseases. The FDA first issued a warning in April 2020 that ivermectin intended for use in animals should not be used to treat COVID-19 in humans [40].

Corticosteroid

It suppresses lung inflammation but can also inhibit immune responses and pathogen clearance if used early. In COVID-19, inflammation persists after viral clearance. Pulmonary histology performed in cases of SARS and MERS infections reveal inflammation and diffuse alveolar damage, with a report suggestive of hem phagocytosis [41].

Fluvoxamine

Fluvoxamine is a cytochrome P450 (CYP) 2D6 substrate and a potent inhibitor of CYP1A2 and CYP2C19 and a moderate inhibitor of CYP2C9, CYP2D6, and CYP3A4.

Gastrointestinal effects (e.g., diarrhea, indigestion), neurologic effects (e.g., asthenia, insomnia, somnolence, anxiety, headache), and rarely suicidal ideation [42].

Conclusion

When others are looking for a solution to this epidemic, the efficacy (benefit) of the treatment takes precedence above the safety (risks) of the drug. The primary goal of this article is to examine the adverse effects of all medications employed in the treatment of COVID-19 to date. Before concluding that ADR is induced by the suspected medicine, we must first comprehend the changed mechanism of our body when infected with COVID. When it enters our bodies, it naturally produces electrolyte imbalances such as hypomagnesaemia, which may be the cause of the research subject's diarrhea.

It has been proposed that COVID-19 permeates our bodies through binding to ACE-2. As a result, providing AACE-2 inhibitors to an infected person may restrict viral entrance or result in a good outcome. This notion is associated to an increased infection risk in older adults with co-morbidities, particularly those with HTN. People who use ACE-2 inhibitors have ACE-2 deficiency. ACE-2's normal function is vasodilation, inflammation, and fibrosis, which is reversed in deficient people. A comparison of patients currently using ACE inhibitors vs other anti-hypertensive medicines may provide light on this risk. As a corollary, a medicine should be chosen with both safety and efficacy in mind, and safety should oftentimes be prioritized in risk-benefit analysis.

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