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Review Article

Management Protocols Deviation of COVID-19 in Diabetic Patients. Is it Applicable?

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Abstract

Background: Corona virus 2019 (COVID-19) disease is a globally infectious disease caused by Severe Acute Respiratory Syndrome-Coronavirus-2 that is emerging and rapidly spreading. Diabetes is considered as one of the main contributing factors of high morbidity and mortality rates globally, where, uncontrolled diabetes is associated with macro- and micro-vascular complications affecting patient's health wellbeing and survival. Concerning therapeutic protocols and treatment, several selected repurposed drugs are used in the management of COVID-19 infection as there is no approved effective vaccine till the moment, therefore, concerns might raise about potential drug interactions between drugs used in management of both COVID-19 and diabetes.

Results: About 42.3% of COVID-19 mortalities were diabetic patients, death rates were significantly higher in hospitalized type 2 diabetic patients than non-diabetic ones and were more susceptible to acute respiratory distress syndrome and other life threatening complications. Most antiviral agents are CYP450 inhibitors or inducers or CYP450 substrates, thus, drug interactions might occur with CYP450 substrates as thiazolidinediones, sulfonylureas, and short-acting secretagogues used in the management of diabetes. Besides, chloroquine and hydroxychloroquine cause hypoglycemia and prolonged QTc which should be taken in consideration upon management of diabetic COVID-19 patients.

Conclusion: Diabetic patients are more susceptible to severity and incidence of COVID-19, antidiabetic agents may interact with antiviral drugs and other therapeutic agents used in management of COVID-19, thus, caution should be taken in consideration upon selection of drug treatment to avoid undesirable potential adverse events or lack of therapeutic efficacy.

Keywords: COVID-19; Diabetic Patients; Drug Interactions; CYP3A4; Chloroquine; Hydroxychloroquine

Introduction

Corona virus 2019 disease is caused by Severe Acute Respiratory Syndrome-Coronavirus-2 (SARS-CoV-2), where, COVID-19 has emerged as a rapidly spreading worldwide infectious disease that occurred primarily via large respiratory droplets despite the fact that it is not possible to exclude the possibility of other transmission routes, as the virus was found in the urine and feces of affected patients [1]. The severity of the disease varies from mild self-limiting flu-like disease to severe and sudden pneumonia, respiratory collapse and death, and there are geographical variations in estimates of death rates that are subject to change as more data becomes available.

It is worth mentioning that, according to the World Health Organization's situation report on June 26, 2020, about 9,473,214 confirmed COVID-19 cases worldwide with a death rate of 5.1 percent [2]. Taking into account that the number of unconfirmed and unreported covid-19 cases is likely to be much higher than the cases reported, the actual mortality rate may be less than 1%, similar to that of severe seasonal influenza [3]. Different continentals showed different prevalence percentages for example; Africa showed a 258,752 confirmed cases with a mortality rate of 2.1%, European countries reported a 2,619,753 confirmed cases with a death rate of 7.5%, USA showed a 4,709,927 confirmed cases with a mortality rate of 5.0% till 26th June, 2020 [2]. The understanding of this infec-

tion's epidemiological characteristics evolves on a daily basis as the infection spreads to different regions of the world.

It is well known that COVID-19 is highly transmissible through respiratory secretions from individual to individual, where the virus enters through mucosal membranes of the upper airways and later affects the lungs [4]. COVID-19 is a mild disease in most cases, while some individuals develop severe disease characterized by respiratory compromise (dyspnea; where respiratory rate ≥ 30 breaths per minute; saturation of blood oxygen ≤ 93%; PaO2:FiO2 < 300; and/or more than 50% of lung fields on radiology shows pulmonary infiltrates) [5]. In addition, a small number of patients may develop a critical disease with septic shock, or respiratory or multi-organ failure. Less than 5% of those affected develop serious or critical illnesses [6].

Diabetes is a chronic inflammatory condition that is characterized by multiple abnormalities in the metabolic and vascular system that can affect body response to pathogens [7] as a consequence of an increased synthesis of pro-inflammatory cytokines and glycosylation end products, oxidative stress, in addition to influencing adhesion molecule production, that mediate inflammation of the tissue are encouraged by insulin resistance and hyperglycemia [7,8]. This inflammatory process may compose the underlying mechanism that leads to a greater propensity for infections with worse outcomes in patients with diabetes [7], In addition, decreased T cell reaction, neutrophil dysfunction, and disordered humoral immunity are contributory factors [9].

Diabetes is one of the leading causes of morbidity and mortality throughout the world which is associated with several macro- and micro-vascular complications that ultimately impact the overall patient's survival. Influenza and pneumonia are considered of the common and more serious infections, in particular when it comes to older people with type 2 diabetes mellitus (T2DM) [10]. Despite that, the evidence remains controversial regarding whether diabetes itself indeed increases infection susceptibility and impacts outcomes, or other comorbidities like renal and cardiovascular diseases that are frequently associated with diabetes are the main factors included [7].

Diabetes and unmanaged glycaemic levels have been reported as a major predictor of severity and mortality in infected patients with various viral infections, including influenza A (H1N1), coronavirus and MERS-CoV virus. Reports from China and Italy found that elderly patients with comorbidities such as diabetes had a higher risk of extreme COVID-19 infection and mortality [11].

Many Oral hypoglycemic drugs are metabolized by CYP450 like Sulfonylureas, Short-acting secretagogues [12], thiazolidinediones [13], DPP-4 inhibitors [14], which may interact with different antiviral agents, so in-order to avoid potential drug-drug interactions, fatal adverse events and lack of therapeutic outcomes, special care should be taken in the management of SARS-CoV-2 infected patients, especially those suffering from diabetes and other comorbidities that need chronic therapeutic drug treatment.

The aim of this review was to investigate the correlation between presence of diabetes and other related comorbid conditions and higher incidence of COVID-19 infection and increased death rates. Also, detection of possible drug interactions between repurposed therapeutic agents that are used to treat COVID-19 and those that are used to treat diabetes. Finally, the use of drug alternatives and various modifications to therapeutic regimens for COVID-19 management are options to be used to prevent potential drug interactions and achieve a better therapeutic outcome.

Discussion of different clinical studies

Data from Wuhan, China showed that 42.3% of 26 mortalities due to COVID-19 disease where suffering from diabetes [15]. Another study of 140 COVID-19 patients showed that diabetes was not a contributing factor for serious illnesses [16]. Also, it was reported in about 72,314 patients suffering from COVID-19 that mortality rate increases in diabetic patients [17]. However, another study including 150 patients (from which 68 patients died and 82 patients recovered) in Wuhan indicated that number of co-morbidities is a remarkable predictor of death rates [18], leading to the fact that elderly people with pre-existing disease conditions as diabetes, cardiovascular disorders, cancer, and acute kidney injury, have revealed a higher risk of having more serious COVID-19 cases and a higher risk of mortality. The effect of the global COVID-19 pandemic and type 2 diabetes (T2D) has led to the very serious fact that T2D is the second most prevalent COVID-19 comorbidity [19].

Another cohort study performed on about 7337 COVID-19 cases in Hubei region in China, where, it was reported that the percentage of type 2 diabetes was 13.0%, which was comparable to China's country-wide prevalence (nearly 10.9%) of type 2 diabetes [20].

In one study including about 1590 cases from 575 hospitals in china, it was found that about 399 (25.1%) of them were suffering from comorbidities including; hypertension (n = 269, 16.9%), cardiovascular diseases (n = 59, 3.7%), cerebrovascular diseases (n = 30, 1.9%), diabetes (n = 30, 8.2%), hepatitis B infections (n = 28, 1.8%), COPD (n = 24, 1.5%), chronic kidney diseases (n =

21, 1.3%), malignancy (n = 18, 1.1%) and immunodeficiency (n = 3, 0.2%). Asthma was not diagnosed in any of the cases. Those patients with comorbidities were most probably have dyspnea (41.4% *vs* 17.8%), nausea or vomiting (10.4% *vs* 4.3%), and demonstrate abnormal chest radiograph (29.2% *vs* 15.1%) [21].

Previous studies in literature showed that Patients suffering from Type2 Diabetes reported significantly higher incidences of fatigue (38.0% versus 31.4%) and dyspnea (20.5% versus 15.4%). In addition, comorbidities such as pre-existing elevated blood pressure (53.4% vs 19.7%), coronary heart disease (13.7% vs 3.7%), cerebrovascular disease (5.6% vs 1.5%) and kidney disease (4.9% vs 1.3%) were found to have higher rates in the type 2 diabetes patients compared to the non-diabetic patients. Moreover, the probability of bilateral lung lesion occurrence was higher (88.1% vs 80.4%) in the diabetic patients compared to the non-diabetic ones. A remarkable higher incidence of lymphopenia (44.5% vs 32.6%), and higher ratio of leukocyte elevation (11.3% vs 6.6%) and neutrophil (17.2% vs 9.9%) levels in diabetic patients type 2 compared to the non-diabetic individuals. Besides, laboratory investigations showed an elevated levels of CRP and procalcitonin, while there was a decrease in renal function (creatinine) and an increased coagulation status (D-dimer) were found more frequently in the Type2 Diabetes group than in the non-diabetic group. Additionally, oxygen saturation below 95% occurred many times in the diabetics than non-diabetics (18.8% vs 13.2%) on admission [22].

The previous paragraph may lead us to the fact that the in-hospital mortality rate was greater in patients with pre-existing T2D compared to non-diabetic patients during the 28-day follow-up period starting from hospital admission (7.8% vs 2.7%, $p < 0.001$). In addition, people with type 2 diabetes have been more prone to acute respiratory distress syndrome (ARDS) (16.9% vs 7.2%), acute heart injury (7.3% vs 3.0%), acute kidney injury (3.9% vs 0.8%), septic shock (3.8% vs 1.0%), and disseminated intravascular coagulation (0.5% vs 0.2%) than the non-diabetic group [22].

Drugs used in management of diabetes

Oral hypoglycemic drugs metabolized by CYP450

- **Sulfonylureas:** Tolbutamide, Glyburide, and Glimepiride are a substrate of CYP2C9. The metabolism of sulfonylureas can thus be affected by CYP2C9 inducers and inhibitors. Active or inactive sulfonylurea metabolites are removed through the renal route and so shortness of renal function may decrease the elimination of sulfonylureas [12].
- **Short-acting secretagogues:** Being metabolized by CYP2C9 and CYP3A4, Nateglinide may be affected by strong CYP2C9 inhibitors/inducers, while Repaglinide is metabolized by the CYP3A4 and CYP2C8 iso-enzymes and then exhibits extensive glucuronide conjugation [12]. The combination of strong CYP3A4 inhibitors with short-acting secretagogues has been documented in several reports of severe, prolonged hypoglycemia [23].
- **Thiazolidinediones:** Rosiglitazone is primarily metabolized by CYP2C8 and to a lesser extent by the CYP2C9 route, and pioglitazone for CYP2C8 (39%) and CYP3A4 (17%), as well as many other CYP450 routes [13]. Although, rosiglitazone, and pioglitazone have significant drug-disease interactions, they can cause fluid retention that may lead to peripheral edema or, in some rare cases, pulmonary edema and/or heart failure. This may be mechanistically related to an increase in renal sodium reabsorption, a decrease in systemic vascular resistance or other mechanisms [24].
- **DPP-4 inhibitors:** Saxagliptin is a dipeptidyl peptidase-4 inhibitor approved as a therapy for type 2 diabetes mellitus. Cytochrome P450 enzymes CYP3A4 and CYP3A5 metabolized Saxagliptin and formed 5-hydroxy Saxagliptin (M2) [14]. The US product label for Saxagliptin states the recommended dose of 2.5 mg to be taken once daily upon co-administration with cytochrome P450 3A4/5 inhibitors as atazanavir, indinavir, nelfinavir, ritonavir, saquinavir [25].

Oral hypoglycemic drugs metabolized by NON-CYP450 pathways:

- **DPP-4 inhibitors:** Vildagliptin, highly metabolized through at least 4 metabolic pathways before get excreted, and a major metabolite M20.7 which results from the hydrolysis of cyano group. Metabolites resulted from hydrolysis of amide bond, glucuronidation, or vildagliptin pyrrolidine moiety oxidation (M20.9 and M21.6), make vildagliptin less liable to possible pharmacokinetic interactions with co-medications of P450 inhibitors/inducers [26].
- Regarding Sitagliptin, nearly 79% of Sitagliptin is excreted unchanged in urine with metabolism being a minor pathway of elimination. Following oral administration of labelled Sitagliptin, about 16% was excreted as metabolites [27].
- **SGLT-2 Inhibitors:** Canagliflozin, Dapagliflozin, and Empagliflozin exhibit a minimal hepatic metabolism which is largely via UDP-glucuronylsyltransferase (UGT-1A9 and 2B4 among others) [28].

- **Biguanide:** Metformin is the only biguanide approved for the treatment of type 2 diabetes at present. Due to good clinical efficacy and a low incidence of adverse events, it is recommended as a first-line therapy [29]. Metformin is partially absorbed in the gastrointestinal tract, shows low plasma binding, and is excreted without liver metabolism by renal elimination [30].

Management of COVID-19 and Potential Drug Interactions with hypoglycemic medications

There are no approved vaccines or specific therapeutic drugs that target SARS-CoV-2 up to the date of this review article. Medical practitioners face major challenges in deciding what possible treatment choices are appropriate for the prevention and treatment of severe COVID-19 cases. Until then, specific medicines or vaccines for SARS-CoV-2 repurposed medications have been used in the treatment of patients with COVID-19, and these medications have been approved by the US FDA for other indications [31]. It will be demonstrated and discussed below the most commonly used therapeutic protocols in management of COVID-19 and their possible drug interactions, and proposed therapeutic alternatives.

Co-administration of Chloroquine/Hydroxychloroquine with different therapeutic agents

According to a study findings published in Drug Safety, there appears to be a drug interaction between hydroxychloroquine (HCQ) and metformin leading to death, which identified an indication for the combination of hydroxychloroquine and metformin that could cause serious adverse effects, including suicide than when administered individually. Of the 10771 ICSR which involves Hydroxychloroquine, 52 (ICSR) were recorded as 'fatal results'. The combination of Hydroxychloroquine and metformin was associated with an odd ratio (ROR) of 57.7 (23.9-139.3) compared with Hydroxychloroquine alone. Compared to metformin alone, the combination of hydroxychloroquine and metformin was correlated with a ROR of 6.0 (2.6-13.8) [32].

A warning message was reported regarding the probable lethal toxicity of CQ or HCQ in combination with metformin. The combination of CQ or HCQ and metformin used as probable anticancer agents in mice studies resulted in 30-40 percent mortality. The authors reported an increased autophagosomes number in the heart, liver and kidneys of treated mice with the combination. They did not conclude that their observation was univocal, but the suggestions of the authors concluded that metformin (inhibitor of mitochondrial complex I), and hydroxychloroquine (autophagy inhibitor) were synergistic [33].

The previous findings suggest that the association between metformin and CQ or HCQ increases the risk of death. From the clinical point of view, the results suggest a warning sign for diabetic patients on metformin treatment receiving Hydroxychloroquine, for management of COVID-19.

Moreover, hypoglycaemia is a significant specific safety concern that must be properly considered as a known adverse effect of the treatment of chloroquine/hydroxychloroquine [34]. Reduced intra-cellular insulin degradation, increased glucose transport, increased insulin release and increased insulin sensitivity are the proposed interaction mechanisms for CQ/HCQ [34]. When using CQ or HCQ with other antidiabetic agents, extra caution should be taken and dose reduction may become necessary.

Also, Chloroquine/Hydroxychloroquine may cause prolonged QTc, so electrocardiography should be performed on regular bases before these drugs are administered. Many other drugs are well known to prolong the QTc interval like anti-arrhythmic, anti-depressants, anti-psychotics, antihistaminic, teneligliptin, ondansetron and moxifloxacin, thus co-administration of those drugs with CQ/HCQ must be avoided [35].

It was reported that co-administration of azithromycin and hydroxychloroquine might lead to QTc prolongation and thus it was recommended that ECG should be done if QTc is 450-500 msec. Therefore, Chloroquine and Hydroxychloroquine shouldn't be used concurrently with lopinavir/ritonavir and remdisivir for probability of QTc prolongation [36].

The reported findings suggest to avoid using Chloroquine and Hydroxychloroquine in combinations with lopinavir/ritonavir, and azithromycin in order to avoid anticipated QTc prolongation.

Potential interactions in therapeutic protocols used for treatment of COVID-19 with antidiabetic agents and suggested modifications.

Advantages of some proposed agents in prophylaxis and management of COVID-19

In the following lines some therapeutic and supplemental agents that possess a potential benefit in prophylaxis or management of COVID-19 in case of diabetic patients with minimal or no drug interactions would be investigated.

Therapeutic protocol/doses [37,38,39]	Potential interaction with antidiabetic agents and suggested modifications
Chloroquine phosphate 500 mg BID for 10 days.	Hypoglycemia is a known adverse effect for CQ/HCQ that should be taken in consideration. Potential fatal toxicity of CQ/HCQ when combined with Metformin. We don't recommend the use of CQ/HCQ and metformin together. The use of CQ/HCQ with other antidiabetic agents require careful monitoring and dose adjustment for antidiabetic drugs to avoid hypoglycemia.
Moderate to severe COVID-19: Combination of Lopinavir 400mg and Ritonavir 100 mg administered twice per day or Administration of Chloroquine 500 mg P.O. once daily or Hydroxychloroquine 400mg P.O. daily for 7-10 days.	Lopinavir/Ritonavir are CYP450 Inhibitors [13] and caution should be considered upon administration with Sulfonylureas, Short-acting secretagogues, Thiazolidinediones, and DPP-4 inhibitors (Saxagliptin) to avoid sever hypoglycemia. Investigations is required to estimate the benefit of Favipiravir and Sofosbuvir as alternatives for Lopinavir/Ritonavir to avoid sever hypocalcemia. DPP-4 inhibitors (vildagliptin or Sitagliptin), and SGLT-2 Inhibitors are a safe choice for diabetes management in COVID-19 upon administration of Lopinavir/Ritonavir. IV Vitamin-C can be applied for reduction of Cytokine storm in case of ARDS.
URTI plus positive PCR: Chloroquine phosphate 500 mg BID for 5 days. Oseltamivir 150 mg BID for 5 days.	Hypoglycemia is a known adverse effect for CQ/HCQ that should be taken in consideration. Potential fatal toxicity of CQ/HCQ when combined with Metformin. We don't recommend the use of CQ/HCQ and metformin together. The use of CQ/HCQ with other antidiabetic agents require careful monitoring and dose adjustment for antidiabetic drugs to avoid hypoglycemia.

Table 1

Therapeutic protocol/doses [37-39]	Potential interaction with antidiabetic agents and suggested modifications
COVID-19 Pneumonia: Co-administration of Chloroquine phosphate 500 mg twice daily for 5 days and Darunavir 800 mg/ Cobicistat 150 mg OD for a period of two weeks. Atazanavir 400 mg OD for 2 weeks plus Oseltamivir 150 mg BID for 5 days 600 mg of Chloroquine base followed by 300 mg after 12 h on day1, then 300 mg 2/day per person on days 2-5	Darunavir/Cobicistat are metabolized by CYP450 [40], Atazanavir is CYP450 Inhibitor [25] and caution should be considered upon administration with Sulfonylureas, Short-acting secretagogues, Thiazolidinediones, and DPP-4 inhibitors (Saxagliptin) to avoid sever hypoglycemia. Investigations is required to estimate the benefit of Favipiravir and Sofosbuvir as alternatives for Lopinavir/Ritonavir to avoid sever hypocalcemia. DPP-4 inhibitors (vildagliptin or Sitagliptin), and SGLT-2 Inhibitors are a safe choice for diabetes management in COVID-19 upon administration of Darunavir/Cobicistat and Atazanavir. Tocilizumab may be an effective and safe choice for management instead of using CQ/HCQ.

Mild to moderate COVID-19: Lopinavir/ritonavir plus Chloroquine 500 mg, 2/day or Hydroxychloroquine 200 mg per day for 10 days.	Lopinavir/Ritonavir are CYP450 Inhibitors [12] and caution should be considered upon administration with Sulfonylureas, Short-acting secretagogues, Thiazolidinediones, and DPP-4 inhibitors (Saxagliptin) to avoid sever hypoglycemia. Investigations is required to estimate the benefit of Favipiravir and Sofosbuvir as alternatives for Lopinavir/Ritonavir to avoid sever hypocalcemia. DPP-4 inhibitors (vildagliptin or Sitagliptin), and SGLT-2 Inhibitors are a safe choice for diabetes management in COVID-19 upon administration of Lopinavir/Ritonavir.
Severe or critical COVID-19: Remdesivir plus Chloroquine 500 mg 2/day or Hydroxychloroquine 200 mg per day for 10-20 days	No clinically significant interaction expected form Remdesivir with oral antidiabetics. Hypoglycemia is a known adverse effect for CQ/HCQ that should be taken in consideration. Potential fatal toxicity of CQ/HCQ when combined with Metformin. We don't recommend the use of CQ/HCQ and metformin together. The use of CQ/HCQ with other antidiabetic agents require careful monitoring and dose adjustment for antidiabetic drugs to avoid hypoglycemia. The use of QC/HCQ with remdisivir should be avoided for anticipated QTc prolongation. IV Vitamin-C can be applied for reduction of Cytokine storm in case of ARDS instead of using CQ/HCQ Tocilizumab may be an effective and safe choice for management instead of using CQ/HCQ.
Critical COVID-19: Remdesivir 200 mg loading dose i.v within ½ hour followed by 100 mg OD for 2-10 days (Hydroxychloroquine is second option if Remdesivir is unavailable)	Favipiravir, Oseltamivir may be a second good options in case of Remdesivir is unavailable. No clinically significant interaction expected form Favipiravir, Oseltamivir with oral antidiabetics. IV Vitamin-C can be applied for reduction of Cytokine storm in case of ARDS instead of using CQ/HCQ Tocilizumab may be an effective and safe choice for management instead of using CQ/HCQ.
Mild/moderate/severe COVID-19: Chloroquine 600 mg on day 1, then 300 mg BID for 5 days (lopinavir/ritonavir as second option)	Favipiravir, Oseltamivir, Ribavirin may be a second good options No clinically significant interaction expected form Favipiravir, Oseltamivir with oral antidiabetics. IV Vitamin-C can be applied for reduction of Cytokine storm in case of ARDS instead of using CQ/HCQ Tocilizumab may be an effective and safe choice for management instead of using CQ/HCQ.

Critical COVID-19: Remdesivir for 10 days plus chloroquine for 5 day Hydroxychloroquine 200 mg TID for 10 days.	Hypoglycemia is a known adverse effect for CQ/HCQ that should be taken in consideration. Potential fatal toxicity of CQ/HCQ when combined with Metformin. We don't recommend the use of CQ/HCQ and metformin together. The use of CQ/HCQ with other antidiabetic agents require careful monitoring and dose adjustment for antidiabetic drugs to avoid hypoglycemia. IV Vitamin-C can be applied for reduction of Cytokine storm in case of ARDS instead of using CQ/HCQ Tocilizumab may be an effective and safe choice for management instead of using CQ/HCQ.

Table 2

OD: Once Per Day; BID: Twice Per Day; TID: Thrice Per Day; URTI: Means Upper Respiratory Tract Infection; PCR: Means Polymerase Chain Reaction; i.v: Intravenous.

Zinc nanoparticles have been shown to inhibit the viral load of H1N1, although their impact on COVID-19 is unknown and untested [41]. Co-administration of Zn with standard antiviral therapy, demonstrated in patients with HCV, HIV and SARS-CoV-1, can achieve synergistic effects. Moreover, Zinc helps to protect or stabilize the cell membrane that prevents the entry of virus to the cells and thus prevents viral replication in rhinoviruses, HCV, influenza viruses and decreases the RNA-synthesizing activity of nidoviruses for which SARS-CoV-2 belongs [42].

Vitamin C supplement has some role in the prevention of pneumonia and needs assessment of its impact on COVID-19. Intravenous vitamin C reduces the cytokine storm at the end stage of Covid-19 infection, as mentioned in the literature review, and, like other antioxidants, is an extremely good agent for acute respiratory distress syndrome, in addition to the known safety and efficacy of high doses of IV vitamin C [43].

Probiotics are defined as live micro-organisms that, when given in an appropriate amount allow a health benefit to the host, including the gastrointestinal tract, and stimulate immune response by increasing the production of antibodies. Probiotic studies using strains of Lactobacillus and Bifidobacterium as treatments have shown that probiotic supplementation either decreases the severity or shortens the duration of the infection [44].

Therefore, the use of supplements like Zinc and Vitamin C containing products, and probiotics may add value in prophylaxis of individuals from COVID-19 infection, besides the beneficial effect of intravenous administration of vitamin C in Acute Respiratory Distress Syndrome management without any possible drug interactions.

Sofosbuvir and management of COVID-19

Sofosbuvir is an authorized HCV direct antiviral treatment and is effective against other types of positive-strand RNA viruses. Corona viruses are a family of conserved polymerase positive-strand RNA viruses, so Sofosbuvir is most likely to be effective inhibitor for SARS-CoV-2 RdRp. In a 24-week therapeutic regimen, it is safe and well tolerated at 400 mg daily dose. In addition, the active metabolite of Sofosbuvir shows a high degree of intracellular stability, leading to a suggestion that SARS-CoV-2 infection may also be cured by Sofosbuvir. Also, it was reported that Sofosbuvir does not affect the main cytochromal metabolizing enzymes as cytochrome P450 system [45].

It was reported in a study that the SARS-CoV-2 have the ability to infect brain tissues, destroy neural cells, and altered the process of new synapses creation (synaptogenesis). In the neural precursor cells, cell death was thirty times higher and the astrocytes had a fourfold elevated mortality rate as a result of the virus, but no accumulation of the virus was noted. The results showed that vGLUT1 protein expression could restored in the synapses or neural links when using sofosbuvir, which could reverse the damage caused by the virus [46].

Sofosbuvir advantages represented in no presence of CYP450 interference, besides its possibility to restore neuronal damage

caused by COVID-19 make it a favorable choice in management of coronavirus-19 infection.

Ribavirin in management of COVID-19

Ribavirin is a guanosine analog that works by interfering with RNA and DNA virus replication [47]. The use of ribavirin in COVID-19 management is beneficial for several reasons, such as broad activity towards conventional and novel types of DNA and RNA viruses, multiple direct anti-viral mechanisms, well-known safety and tolerability, affordable and accessible [48].

In-vitro studies have shown that ribavirin is not a CYP450 enzyme substrate [49], meaning that there is minimal drug-drug interaction.

Advantages of administration of Metformin in patients with COVID-19

Data from individuals hospitalized with Covid-19 metformin showed a significant association with reduced mortality in women with obesity or DM type2 in an observational analysis of claims. This finding coincide with that metformin's causes more reduction in TNFα in females compared to males resulting in protection of Covid-19 infection through TNFα effects [50].

Conclusion

From the above reviewed data and according to the findings of clinical studies it can be concluded that most of the resulting pharmacokinetic interactions of the antidiabetic agents with the therapeutic regimens for management of COVID-19 are based on the either induction or inhibition of hepatic CYP450 enzymes while other interactions might be related to Pharmacodynamic interactions.

The aforementioned classes of anti-diabetic drugs appear to be an ideal choice for the administration with COVID-19 therapeutic agents used in COVID-19 diabetic patient management. Moreover, most interactions are related to Thiazolidinediones, Sulfonylureas, and Short-acting secretagogues. On the other side, DPP-4 inhibitor including Saxagliptin and the fatal combination of Metformin and CQ/HCQ.

CYP450 inhibitors/inducers or substrates, such as indinavir, nelfinavir, atazanavir, ritonavir, saquinavir, darunavir/cobicistat, lopinavir/ritonavir, or atazanavir, may exhibit potential drug interactions with sulfonylureas, thiazolidinediones, and short-acting secretagogues when administered for COVID-19 management. For previous antiviral agents with almost no or minimal drug interaction, sofosbuvir, Remdesivir, Oseltamivir, Favipiravir, and Ribavirin are considered as clinically accepted alternatives.

Chloroquine and Hydroxychloroquine use is suggested to be avoided in combinations with lopinavir/ritonavir and remdisivir to avoid anticipated QTc prolongation. Also a potential fatal toxicity was reported when CQ/HCQ combined with Metformin. Hypoglycemia is known adverse effect for CQ/HCQ and should be careful upon its use with oral hypoglycemic agents.

Caution should be taken upon selection of therapeutic protocols in covid-19 management, and necessary therapeutic modifications should be performed for antidiabetic drug if required. Potential drug interactions may result in life threating conditions like sever hypoglycemia or prolonged QTc and cardiovascular complications. Other interactions may affect CYP450 metabolic enzymes leading to altered therapeutic drug levels which in turn lead to toxicity or lack of therapeutic efficacy.

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