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A review on the toxic effects of medicines used in corona virus disease 2019 (Covid-19) treatment

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ABSTRACT

Objectives: The novel coronavirus disease 2019 pandemic is affecting all around the world, particularly healthcare systems. The most critical problem for the COVID-19 infection as an emerging acute respiratory disease is the lack of effective methods to control and treat the disease. To date, there is no specific therapeutic agent approved by the FDA, so treatment options are limited. There are more than 4034 interventional studies in progress listed in clinicaltrials.org (Access date: 21.12.2021). This number was 900 approximately in December 2020. These intensive studies, which have increased fourfold, are to find a safe and effective treatment method. Since absolute therapy has not been standardized globally, the treatment approach varies from country to country and even from hospital to hospital. In addition to the vaccine studies that have been finalized and the vaccines are available for use, additional studies are underway for existing drugs that can prevent this disease or improve outcomes for COVID patients. The potential toxicity of the drugs chosen for the treatment is one of the more critical limiting factors. Although the side effects of previously approved medicines are known, studies are needed to determine the side effect profiles for newly approved products such as remdesivir.

In this review, we gathered the adverse and toxic effects of medications used against COVID-19 treatment according to the COVID guideline published by the Scientific Advisory Board of the Ministry of Health of Turkey.

Keywords: Coronavirus disease 2019 (COVID-19), SARS-CoV-2; medicines, remdesivir, anakinra, tocilizumab, favipiravir, hydroxychloroquine, convalescent plasma, toxic effects, adverse effects

The coronavirus disease, named severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) latter that occurred in Wuhan, China in late December 2019, has spread rapidly to almost the whole world. [1] COVID-19 outbreak has spread to Turkey on March 2020, while the World Health Organization (WHO) declared the COVID-19 pandemic. As soon as the disease began to appear in Turkey, the Scientific Advisory Board was established, and they published an actively updated guideline for treatment of patients across the country. In the first edition of the guideline, the recommendations were focused on controlling the possible coinfections and cytokine storm management. According to increasing evidence about the endothelial invasion of the virus and the increased thromboembolic effects of the disease, anti-aggregate, and anticoagulant drugs were included in the treatment program. [2]

The medications for COVID treatment are limited, and clinical studies are not enough. The phase trials have not reached the optimum level; this state brings us a dilemma, to use or not to use these medications.

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The last example of this situation is Remdesivir, a nucleoside analog pro-drug. Wang et al., conducted a randomized, double-blind, placebo-controlled multicenter trial from China, for evaluating the efficiency of Remdesivir. [3] They stated that no clinical improvement was achieved with Remdesivir treatment and stopped the trial because of the adverse effects. On the other hand, FDA approved Remdesivir for COVID treatment. [4] By the way, there is an urgent need for more phase trials and clinical outcomes for all medicines using for the COVID treatment.

According to the Turkish Scientific Advisory Board, COVID guideline, hydroxychloroquine, oseltamivir, favipiravir, lopinavir/ritonavir, azithromycin, tocilizumab, and low molecular weighted heparins are used frequently. The toxic profile of medications used in COVID treatment should not be ignored. Since these drugs are on the market with different indications for years, there are enough data for the safety profiles. Particularly, adverse, and toxic effects of hydroxychloroquine and chloroquine are well known. Although remdesivir, favipiravir, and tocilizumab are relatively new agents, their toxicity and side effects are also well known not as much as hydroxychloroquine and chloroquine.

A broad-spectrum antibiotic azithromycin is not indicated for the viral infections, and there are not well-controlled, prospective, randomized clinical trials for proving its therapeutic effect in COVID-19. Despite the side effects, convalescent plasma therapy (CPT) is also used in the treatment of severe cases. It is known as classic adoptive immunotherapy, and there are many reports where the CP has successfully been used for the treatment of infectious diseases and other coronavirus outbreaks. In this study, we reviewed the databases and literature to consolidate information about the medications and therapeutics used for COVID treatment.

METHODS

We reviewed the literature using ScienceDirect, UptoDate, Clinicalkey, and Google Scholar search engine with the search terms included COVID treatment, pharmacological treatment of COVID, and toxicity of medications used for COVID treatment. We excluded preprint articles and included case reports. Other articles regarding the review of citation references have also been identified.

Medications used in COVID

Hydroxychloroquine and chloroquine

Quinine derivatives are using since the 1950s for malaria. They have been used for some autoimmune disorders by their immunosuppressive properties. They are also in WHO's Essential Drug List, and their side effects are well known due to their usage for 70 years. A 4-aminoquinoline derivative, hydroxychloroquine, a less toxic molecule from chloroquine, is synthesized by beta hydroxylation of chloroquine. [5]

Colson et al., stated that chloroquine might be effective for COVID based on their in vitro study. They said chloroquine has multiple activities for blocking viral replication, fusion, and uncoating and has a broad antiviral spectrum. It seems to be cost-effective already. By the way, in their opinion, chloroquine could be o good treatment option for the COVID. [6, 7]

The hydroxychloroquine and chloroquine treatment included in the Turkish COVID guideline since the beginning of the pandemic. The guideline recommended hydroxychloroquine treatment 400 mg bid for the first day and 200 mg bid for the following four days maximum of ten days. [2] In addition to the antiviral effects of chloroquine, it inhibits some biochemicals causing cytokine storms like IL-6 and TNF and thought to have positive effects for cytokine storm 8. But in the current treatment protocol, hydroxychloroquine and chloroquine are not recommended for first-line treatment. But, because of the past treatment approach of the Turkish Scientific Advisory Board, we've included adverse effects of these medicines.

Favipiravir

Favipiravir (T-705) is a pro-drug of a purine nucleotide, favipiravir-ribofuranosyl-5′-triphosphate. After metabolization, the active agent inhibits the RNA polymerase. Favipiravir has some preclinical outcomes for Ebola and influenza treatment 9. Favipiravir treatment is not recommended as the first line of treatment and is reserved for the severe COVID pneumonia. According to the Turkish COVID guideline, favipiravir treatment is started with 1600 mg bid for the first day and continue 600 mg bid for the following four days. [2]

Favipiravir treatment for COVID is evaluated on Phase III PRESECO study. This study has important results for understanding the efficacy of favipiravir for mild to moderate COVID patients. The data from this randomized clinical study has shown no significant effect on treatment. [10] There's not a different approach for favipiravir in Turkish Treatment Protocol

and continues to be used routinely in treatment based on guideline

Tocilizumab

Tocilizumab is a humanized monoclonal antibody that inhibits the IL-6 receptor. FDA approved it for the treatment of severe rheumatoid arthritis. When TNF-blockers have failed or contraindicated for the treatment, tocilizumab may be a good alternative. In addition to rheumatoid arthritis, tocilizumab is approved for cytokine syndrome caused by chimeric antigen receptor (CAR) T cell treatment. [11] Although there is not enough data for COVID treatment, tocilizumab thought to be beneficial for the management of the cytokine storm as an adjunctive agent. The Scientific Advisory Board advises tocilizumab treatment, particularly in patients who develop macrophage activation syndrome (MAS) with 8 mg/kg dose (up to 800 mg/kg). Depending on the severity of the patient's symptoms, 400 mg/kg or 800 mg/kg can be given intravenously as the first dose. In the case of giving the first dose as 400 mg/kg, based on clinical and laboratory responses, 200-400 mg dose may also be given within 12-24 hours. [2]

Remdesivir

Remdesivir is a nucleotide analog antiviral medicine approved for COVID-19 treatment based on preclinical studies. It's a prodrug has a broad antiviral spectrum against RNA viruses. This effect comes from inhibiting viral RNA dependent RNA polymerase and mitochondrial RNA polymerase weakly. [12] Although, remdesivir treatment is not recommended in Turkish Guideline briefly, it's been used in clinical practice.

Anakinra

Anakinra is a non-glycosylated human interleukin-1 receptor antagonist that uses for cytokine storm in COVID treatment. Before this repurposing, it has been used for rheumatoid arthritis and other inflammatory diseases.

In a systematic review that compiled by Kyriazopoulou et al., 2021, it's stated that anakinra seems to be an alternative for hospitalized COVID-19 patients at the presence of hyper inflammation. [13]

In another meta-analysis conducted by concluded that anakinra treatment could be effective for patients requiring a mechanical ventilator. [14] In opposite to some positive results, because of insufficient evidence, NIH does not recommend using Anakinra in COVID-19 treatment. On the other hand examined 20 cases and 20 control groups .[15] The results of the study expressed that anakinra treatment was not effective for tocilizumab-resistant severe COVID-19 patients.

Anakinra uses in COVID-19 related macrophage activated syndrome when there is not enough response to glucocorticoid treatment. The administration dosage is 100 mg subcutaneous once or twice a day or 200 mg intravenously three times a day. The dosage could be increased up to 200 mg every 6 hours. [2]

Lopinavir/ritonavir

Lopinavir/ritonavir is an antiviral combination is used for the HIV treatment in adult and pediatric patients. Both medicines are protease inhibitors, and lopinavir concentration is higher than ritonavir in that combination. [16] There is no scientific evidence to use for COVID treatment, but this combination has been used for SARS and MERS treatment. Although limited available studies that associated reduced mortality and intubation rates with uncertain outcomes. [9] The Scientific Advisory Board recommends Lopinavir/ritonavir combination treatment for just pregnant and children. [2]

Azithromycin

Azithromycin is a macrolide antibiotic that semisynthetic form of erythromycin. It shows a good antibacterial effect on gram-positive and gram-negative organisms. It's a bacteriostatic agent that inhibiting protein synthesis by binding the 50S ribosomal subunit. [17] It is used for the treatment of various bacterial infections, as well as in some inflammatory diseases for its immunomodulatory properties. [18, 19, 20] The usage of azithromycin in COVID treatment is reserved just for hospitalized patients, especially in ICU, due to its possible cardiotoxic effects. [2]

Convalescent plasma

Convalescent plasma (CP) is a biologic product from immune people who had an infectious disease. CP therapy (CPT), classic adoptive immunotherapy, has been applied for the treatment of many infectious diseases. It provides passive immunity by giving neutralizing antibodies to the patient. [21] It has been using for patients with various viral infections, such as SARS, pandemic influenza and severe Ebola virus infection. [22, 23, 24] Shen et al. conducted a trial to determine the effects of CPT for five critically ill COVID and ARDS patients. [25] Despite a limited sample size and study design, they stated that CPT might be useful for critically ill patients. Zhou et al., reported that

early convalescent plasma therapy for influenza and SARS-CoV infection is associated with reduction in viral load and mortality. [26] In Turkey, CPT is applying in many hospitals by gathering plasmas from recovered COVID patients. The Ministry of Health of Turkey publishes a guideline describing all the steps for applying Convalescent Plasma Therapy. [27]

Adverse and Toxic Effects of COVID-19 Therapeutics

Effects of hydroxychloroquine and chloroquine

Chloroquine (CQ) and hydroxychloroquine (HCQ) are in clinical use for several years, so both molecules have a well-established safety profile. [28] They are known as well tolerated molecules in general, but they are also extremely toxic in overdose. Some studies draw attention to serious adverse effects that may occur, even during short courses of treatment. The difference in mechanisms of action both of medicines is not fully understood but hydroxychloroquine reported as less toxic. [29] CQ and HCQ's therapeutic index is narrow so effective dose and toxic dose close to each other. HCQ is administered oral route and metabolized in the liver to three different metabolites by conjugation and alkylation. [30]

Cardiologic side effects of quinine derivatives are known. These medicines can cause ventricular arrhythmias, QT prolongation, torsades de pointes, which may pose a particular risk to critically ill persons. Because of this side effect, HCQ/CQ must be used with caution in patients with congenital long QT syndrome, AV block, heart failure, MI, stroke. [30, 31, 32] Patients using medicines that increase the QT interval must also be considered.

CLQ/HCQ cardiotoxicity includes dysrhythmia, depressive cardiac contraction, and conduction related to hypokalemia due to potassium shift. These cardiologic risks increase with the use of azithromycin. [33] HCQ and azithromycin use together only for inpatients in Turkey because of cardiotoxic side effects.

Antimalarial dependent retinal damage is a toxic effect that can be seen in patients that have ocular diseases. Some of these side effects are vision loss and difficulties, scotomata, and impairment in color perception. In some cases that given HCQ for lung cancer treatment, retinal toxicity was observed within 1-2 years of the treatment. It is suggested to screen patients receiving HCQ for retinal damage [34, 35, 36, 37] In Turkey, HCQ is given to all patients at the beginning of the symptoms, so clinicians must be aware of this side effect for the next two years.

CQ/HCQ metabolized in the liver and eliminated by the kidney, so kidney and/or liver failure may increase these drugs' plasma concentrations. [38] Glucose-6-phosphate dehydrogenase deficiency is a contraindication for HCQ treatment because of increased hemolysis risk. HCQ should not be used in the treatment of breastfeeding, pregnant women, and patients allergic to CQ or HCQ. [22] More than 5 grams of chloroquine dose is associated with ventricular arrhythmias and mortality due to hypokalemia. [39]

Effects of Favipiravir

Favipiravir is available as a pro-drug and in in vivo transformed into its active form, Favipiravir- by cellular enzymes. The active form of Favipiravir inhibits the RNA-dependent RNA polymerase (RdRp) of the influenza virus effectively. This specific mechanism of inhibiting influenza virus RdRp specifically involved in DNA synthesis makes it a good option for the treatment of influenza virus infections. [40, 41] Although Favipiravir does not have the specifications of nucleoside analogs that can give rise to mitochondrial toxicity, its possible harmful effects on that organelle could not be excluded entirely. Its potential toxic effects for mitochondria could not be excluded entirely, as it may act as a useful substrate for human mitochondrial RNA polymerase. [42, 43] Jin et al. pointed out that during clinical studies there are severe cases of toxicity associated with ribonucleoside analogs. [42] They assumed that the active metabolites of toxic ribonucleoside analogs, the triphosphate forms, mistakenly target human mitochondrial RNA polymerase thereby inhibit the mitochondrial RNA transcription and protein synthesis. Some researchers have suggested that pro-drug moiety released from ribonucleoside analogs may cause toxicity. In general, they reported that Favipiravir did not have a typical mitochondrial toxic nucleoside profile in their experiments, but the potential toxic effect on the mitochondria should not be ignored as it is a useful substrate such as 6-methylpurine. [42]

On the other hand, many other factors need to be considered to assess the clinical toleration of the use of polymerase inhibitors for their safety. Clinical data for the favipiravir toxicity is limited, but deductions from reported toxicity of other nucleoside analogs can be used. As with all medicines, one disadvantage of Favipiravir is its low solubility in an aqueous medium, which reduces its in vitro efficacy. [44] It has been reported that metabolic acidosis may occur usually after one month or more of treatment in therapeutic dose. Also, this situation has been observed with acute over-

dose. Nagata et al. indicated that favipiravir has a risk for teratogenicity and embryotoxicity in humans. [45]

Effects of Tocilizumab

Tocilizumab (TCZ) is a monoclonal antibody that inhibits the interleukin-6 receptor. According to experimental and clinical studies, while liver toxicity is less common, an increase in lipids parameters and a decrease in neutrophils and skin infections are more common in groups given TCZ. Morrison et al., stated that clinicians should consider monitoring COVID patients using TCZ for hypertriglyceridemia and acute pancreatitis, as described for rheumatoid arthritis patients using TCZ chronically. [46]

Capra et al. did not observe any side effects in their study that aims to evaluate if tocilizumab reduces mortality in patients with COVID-19 related pneumonia. [47] The known important complications of tocilizumab are intestinal perforations or bacterial infections. But in this study, these adverse effects have not been observed.

Tocilizumab can cause hyperbilirubinemia in rheumatoid arthritis patients because it may inhibit uridine diphosphate glucuronosyltransferase 1A1(UGT1A1)-mediated glucuronidation. This increase is thought to be related to the anti-inflammatory effects associated with UGT1A1 polymorphism. Hepatoxicity related to tocilizumab therapy seems low. Macrophage activation syndrome occurs in approximately 7% of juvenile idiopathic arthritis patients. [48]

Infection is an important risk for tocilizumab, like all immunotherapeutics. The occurrence of infection of tocilizumab is researched, and the infection rates of combination therapy (tocilizumab+methotrexate) slightly higher than monotherapy (just methotrexate) regimens. Nasopharyngitis and upper respiratory infections are commonly reported (5%-8%). The risk of severe infections is increasing with the dose. Cellulitis, pneumonia, diverticulitis, gastroenteritis, and herpes zoster were the most common infections reported. [49]

Hypersensitivity is a risk factor, so it should be used carefully for patients with neutropenia (<500 cells/μL) or thrombocytopenia (<50000/μL). Headache, hypertension, increased AST, infusion-related reactions are common side effects of tocilizumab. [9]

Effects of Lopinavir / Ritonavir

Lopinavir / ritonavir treatment for COVID is an obligatory off-label antiviral therapy because of an emergency. The effectiveness of this combination for COVID has been studied in vitro, and clinical implementation was started through acceptable EC50 value. Although there are some favorable outcomes, more clinical evidence is needed . Besides the treatment efficiency, side effects and toxicities must be considered. Yao et al. conducted a trial compromising 199 severe COVID patients. They stated that lopinavir-ritonavir treatment was not associated with clinical improvement. In this trial, the most common side effects are gastrointestinal side effects like nausea, vomiting, and diarrhea. [50] Respiratory failure, acute kidney injury, and secondary infections were also observed in some clinical studies. [51]

The common side of the antiretroviral therapy is the hepatic toxicity, particularly the hepatitis C virus (HCV) infected people. After the treatment of 120 HIV-infected patients (52% HCV-infected) with Lopinavir (LPV), a possible association with severe liver toxicity incidence and LPV plasma levels has been evaluated. [52] According to this study, the incidence of severe liver toxicity was reported as 1.7% in 3rd months, and the cumulative incidence at 12th months was 4%. The development of severe liver toxicity was associated with HCV coinfection, but not with LPV plasma levels. Acute overdose of protease inhibitors is rare, but over 50 g of lopinavir-ritonavir overdose was generally well tolerated and additionally administered. Ritonavir is a very potent CYP3A4, and this effect can cause dangerous drug-drug interactions. [53]

Lopinavir/ritonavir combination must be applied carefully to the patients with hemolytic anemia because of ribavirin. The changes in complete blood count must be monitored closely, and if hemolytic anemia symptom occurs, treatment cessation or dose changes should be considered. One of common adverse effect of ribavirin is bradycardia. [54]

Effects of Azithromycin

Azithromycin, a macrolide antibiotic that is a derivative of erythromycin. Erythromycin is a well-documented molecule that causes hepatotoxicity. Although azithromycin has a very safe side effect profile, cases related to hepatotoxicity due to azithromycin have been reported. In these cases, azithromycin triggered hepatotoxicity associated with oral or intravenous (IV) administration. In the IV administration of azithromycin, an acute increase in AST and ALT levels was observed. [55] Temporary increases in liver enzymes especially transaminases have also been reported in 1.5% of patients. Liver damage due to azithromycin

occurs 1-3 weeks after the onset of azithromycin and is predominantly hepatocellular. While most patients recover completely, severe skin reactions, chronic injuries, and serious complications leading to death or liver transplantation may occur. [56] Azithromycin is generally well-tolerated, but relatively common side effects (1-5% of patients) include gastrointestinal discomfort, headache, and dizziness.

Research points out that azithromycin therapy may cause cardiotoxicity, and its most important side effects include cardiovascular arrhythmias and hearing loss. On the other hand, macrolide resistance is also a problem like interactions with commonly prescribed drugs. [18] Critical adverse effects include QT prolongation and torsades de pointes, resulting in death. In 2012, the FDA issued a warning using drugs that consider the risk of fatal heart rhythm with a long QT interval and may prolong the QT interval with a history of arrhythmias or uncompensated heart failure.

According to a recent meta-analysis of the unfavorable clinical outcomes for the individual and society, long-term azithromycin treatment in patients with chronic lung diseases has increased resistant bacteria risk of macrolide 2.7 times .[57]

Azithromycin is considered safe for pregnant women, and the pregnancy category is known as the drug B1. However, it can cause diarrhea in babies who are breastfed.

Lane et al., reported that the addition of azithromycin to hydroxychloroquine treatment in COVID could potentially cause heart failure and cardiovascular mortality due to synergistic effects on QT length. Caution should be taken if such a combination is used for the management of COVID. [58]

Effects of Convalescent Plasma

The convalescent plasma treatment that has been used for the many kinds of viral infections is not a new approach. Randomized clinical studies are needed to determine the appropriate dose and treatment duration of this treatment method, whose specific effects are known. Recently, Chen et al., and Zhang et al., stated that patient with viral infection immunity plasma can be used in treatment without serious adverse effects. [59, 60] However, safety and efficacy studies should be conducted to determine treatment efficacy for COVID patients. Ahn et al., state that plasma taken from patients with COVID immunity can be an effective treatment option without serious side effects. [61] Convalescent plasma therapy with systemic corticosteroids can reduce excessive inflammatory response and viral load. Moreover, because of the lack of information about the basic biology of SARS-CoV-2, including the variability of the virus and mutations, locally collected plasma can better reflect the virus circulating in the population and be a viable treatment option. In a meta-analysis using convalescent plasma therapy resulted decreasing viral load and mortality. There's not significant adverse effect also in this study. [62]

Besides all these positive effects, plasma transfusion can also cause some side effects. The most common adverse reactions of CP treatment are tremors, fever, anaphylactic reactions, acute lung injury associated with transfusion, circulatory overload, and hemolysis, etc. [23, 24] Meanwhile, the risk of the human immunodeficiency virus (HIV), hepatitis B virus, hepatitis C virus, and syphilis infections should not be ignored. Transfusion-related circulatory overload (TACO) is now recognized as the most common serious side effect of transfusions. CP will result in a direct infusion of a significant amount of complementary protein and clotting factors not found in purified immunoglobulin preparations. [63] For this reason, this treatment approach is recommended as a last resort to increase the survival rate of severe COVID patients. Therapeutic indications need to be further investigated in randomized clinical trials to improve the optimal dose and duration for the treatment of blood products in COVID-19. [26]

It is stated that adverse reactions of convalescent plasma were not increased compared to controls in ESCMID Guideline. Beside some studies reported higher rates of serious adverse events or a small number of infusion-related adverse events. [64]

Effects of Remdesivir

Veklury, the commercial form of Remdesivir for injection, included some side effects on data sheet. There are some clinical outcomes on its safety profile before usage on COVID. In a study for Ebola treatment, one patient developed fatal cardiac arrest because of loading dose administration of remdesivir. But this fatal effect was attributed on Ebola disease, not usage of remdesivir. In another open level study on severe COVID patients, acute respiratory distress syndrome was observed. Atrial fibrillation and hypotension, hypersensitivity reactions, vomiting and nausea, elevated hepatic enzymes, hematological adverse effects, metabolic side effects were reported some clinical studies. [12]

Drug-drug interactions were also reported for chloroquine and hydroxychloroquine co-usage with rem-

desivir. The data based on in vitro experiments Show that HCQ and CQ may be inhibited antiviral activity of remdesivir.

Adverse event reporting from the ACTT-14 trial and the paper by Yeming Wang and colleagues 8 indicate that there is a low risk of remdesivir causing harm, but knowing whether it has any additive effect in combination with corticosteroids is crucial. [65]

In another cohort study, kidney transplanted patients evaluated for renal safety of remdesivir. The treatment did not cease because of side effects. There is no significant hepatotoxic and nephrotoxic side effects of remdesivir. [66]

There's an interesting study about toxicity evaluation of pharmaceutical forms of remdesivir. The injectable form of remdesivir is thought more nephrotoxic than lyophilized form because of an additive-sulfobutylether-β-cyclodextrin. In this study, a number of 1000 patient evaluated for comparing dosage forms toxic effects. It's concluded that injectable form of remdesivir has no disadvantages comparing to lyophilized form. [67]

In conclusion, remdesivir's safety profile is not completed. It should be known that remdesivir treatment could be cause of multiple organs injuries. [68]

Effects of Anakinra

Because of used in rheumatological disease many years, Anakinra's side effects are known compared to other repurposed medicines. One of the major adverse effects is injection site reactions. Besides that, upper respiratory tract infection, headache, diarrhea, abdominal pain is another side effect. [69] In terms of drug-drug interactions, etanercept and anakinra co-usage caused some serious infections.It's not recommended anakinra and etanercept combinations. [70]

Although Anakinra's side effects in rheumatological diseases are well known, it is thought that the side effect profile will change with the disease when used in COVID treatment. For this reason, Anakinra treatment particular in COVID should be considered. In a meta-analysis, hepatic enzymes and thromboembolic reactions were evaluated. There's not statistically significant relation with these markers and Anakinra treatment. [71]

CONCLUSION

While the studies related to updating for vaccines for coronavirus variants are accelerating in many countries, additional studies are ongoing for existing drugs that can prevent this disease or improve outcomes for patients with COVID. For the treatment of COVID, the assignation of old drugs for use as antiviral treatment is an essential strategy because of controlling the disease in the most immediate way. For some of these candidate drugs, knowledge on safety profile, side effects, posology, and drug interactions are well known. [72] On the other hand, there are limited evidence-based research, so clinicians must be aware of these toxicities during the treatment procedures. It is essential to report adverse effects on pharmacovigilance systems for informing health authorities and clinicians. COVID is a new disease for all countries, so the information .and data about the treatment are changing every day. In this dynamic situation, all parts of the healthcare system must upgrade its treatment applications.

Conflict of Interest

The authors have declared no conflicts of interest in this article.

Abbreviations

CAR: chimeric antigen receptor; CP, convalescent plasma; CPT, convalescent plasma therapy; CQ: chloroquine; HCQ: hydroxychloroquine; ICU: intensive care unit; MAS: macrophage activation syndrome; RdRp, RNA-dependent RNA polymerase; TACO: Transfusion-related circulatory overload; TCZ, Tocilizumab; UGT1A1, uridine diphosphate glucuronosyltransferase1A1-mediated glucuronidation

Authors' Contribution

Study Conception: AÖ,; GT,; NK,; Study Design: AÖ,; GT,; NK,; Supervision: AÖ,; GT,; NK,; Data Collection and/or Processing: AÖ,; GT,; NK,; Statistical Analysis and/or Data Interpretation: AÖ,; GT,; NK,; Literature Review: AÖ,; GT,; NK,; Manuscript Preparation: AÖ,; GT,; NK and Critical Review: AÖ,; GT,;NK.

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