https://doi.org/10.31925/farmacia.2022.5.2 **REVIEW**

THE IMPACT OF INFLAMMATION AND DRUG INTERACTIONS ON COVID-19 PHARMACOTHERAPY. A MINI-REVIEW

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Abstract

The pandemic induced by the SARS-CoV-2 virus, named COVID-19, produced in addition to the severity of the symptoms in some of the patients also a series of challenges regarding their treatment. The pathogenesis of the virus is mediated mainly by the structural proteins of the envelope, membrane and nucleocapsid, as well as by the spike glycoprotein that facilitates the entry into cells. It was pointed out, that there is a disorder caused by the inflammatory syndrome that influences the severity of COVID-19 and its unfavourable prognosis. The inflammatory process is responsible for the transient phenoconversion, characterized by the deviation between the function encoded in the genotype and the expression of the phenotype. Systemic inflammation and the immune response are an important element in many acute and chronic diseases, being strongly involved in changing the pharmacokinetics of the drug. Existing medical comorbidities in elderly patients requires multiple drug therapies, making them the most vulnerable group for both drug-drug interactions and disease-drug interactions. In the following, a series of data will be provided on the interactions that occur in the main classes of drugs used so far in COVID-19 therapy.

Rezumat

Pandemia indusă de virusul SARS-CoV-2, denumită COVID-19, a produs pe lângă gravitatea simptomatologiei în cazul unora dintre pacienți și o serie de provocări în ceea ce privește tratamentul acestora. Patogenia virusului este mediată în principal de proteinele structurale ale învelișului, membranei și nucleocapsidelor, precum și de către glicoproteina spike care facilitează intrarea în celule. S-a pus în evidență faptul că există o dereglare produsă de sindromului inflamator care influențeză severitatea COVID-19 și prognosticul nefavorabil al acesteia. Procesul inflamator este responsabil de fenoconversia tranzitorie, caracterizată de devierea de la funcția codificată în genotip și expresia fenotipului. Inflamația sistemică și răspunsul imun reprezintă un element important în multe boli acute și cronice, fiind puternic implicat în modificarea farmacocineticii medicamentului. Comorbiditățile medicale existente la pacienții vârstnici necesită terapii medicamentoase multiple, făcându-i astfel grupul cel mai vulnerabil atât pentru interacțiunile medicament-medicament, cât și pentru boală-medicament. În cele ce urmează vor fi aduse o serie de date privind interacțiunile care apar în cadrul principalelor clase de medicamente utilizate până în prezent în terapia COVID-19.

Keywords: COVID-19 therapy, drugs interactions, systemic inflammation, phenoconversion

Introduction

The pneumonia-induced by the new coronavirus, named COVID-19 by the World Health Organization in February 2020, has spread worldwide rapidly since its appearance, becoming a global pandemic. However, this is not the first outbreak of severe respiratory disease caused by a coronavirus. In the last two decades, coronaviruses have produced two more epidemics, namely severe acute respiratory syndrome (SARS) and Middle East respiratory syndrome (MERS). COVID-19 or SARS-CoV-2 is a pathology that frequently affects the respiratory tract and while most cases develop mild symptoms, some of them can progress rapidly to a more severe stage, leading to hospitalization in intensive care units [28].

This global viral infection has produced increased morbidity and mortality among all populations and in the absence of an adequate and effective antibody test, the diagnosis is currently based on polymerase chain reaction (PCR) test from samples collected from the nasopharyngeal and oropharyngeal region. The clinical spectrum of the disease may present differently in the form of a mild, moderate or severe condition. Most patients are either asymptomatic carriers who, despite having no symptoms, have the potential to be infectious to those they come in contact with, or have a mild flu-like illness that is difficult to differentiate from a

simple upper respiratory tract infection. Moderate and severe cases require non-invasive and invasive ventilation, along with specific pharmacotherapy. Complicated cases may require treatment with immunomodulatory drugs and plasma therapy [29].

Coronaviruses are encapsulated, positive-sense viruses with a single-stranded RNA of 3030 kb. They infect a wide variety of host species and are divided into four genera: α, β, γ and δ based on their genomic structure, mammals being infected only by types α and β. Human coronaviruses, such as 229E and NL63, are responsible for the common cold and diphtheria and belong to the genus α. In contrast, SARS-CoV, Middle East respiratory syndrome coronavirus (MERS-CoV) and SARS-CoV-2 belong to the genus β [49].

The virus is transmitted through respiratory droplets and aerosols from one person to another and once in the body, the virus binds to the receptors of host cells and enters them through endocytosis or fusion at the membrane level. Coronaviruses are made up of four structural proteins, namely: spike proteins, membrane proteins, the envelope and the nucleocapsid proteins. The spike protein (S) is prominent on the viral surface and is the most important structure for the attachment and penetration of the host cell. This protein is composed of two functional subunits (S1 and S2), of which S1 is responsible for binding to the host cell receptor, and the S2 subunit has a role in the fusion of viral and host cell membranes [30].

The pathogenesis of the virus is mediated mainly by the structural proteins of the envelope, membrane and nucleocapsid, as well as by the spike glycoprotein that facilitates entry into cells by binding to receptors for the angiotensin-2 (ACE2) conversion enzyme [49]. Spike glycoproteins are the most immunogenic components with similarities between them and the receptor. The distribution of receptors, especially on the surface of alveolar epithelial type II, cardiac, renal, intestinal and endothelial cells, explains the involvement of these organs in the clinical picture of SARS-CoV-2 infection. Upon entering the cytoplasm of the host cell, the virus will release RNA and replicate resulting in the formation of new viral particles. Subsequently, the cell will disintegrate and spread the viral particles. As the immune system recognises viral antigens, both innate and adaptive immunity is activated, causing the release of large amounts of proinflammatory cytokines and chemokines. For some patients, this activation is extremely intense and severe, so the tendency to thrombosis and multi-organ failure can set in, leading to death [25].

Although the complexity of this disease is not yet fully understood, more and more evidence indicates that is a disorder caused by the inflammatory syndrome that influences the severity of COVID-19 and its unfavourable prognosis [29].

Thus, in cases where that exaggerated immune response occurs, an overproduction of pro-inflammatory mediators will occur, which will later lead to the installation of an acute respiratory distress syndrome, disseminated intravascular coagulation and multiple organ failure [7], as has been described above.

The influence of the inflammatory process on pharmacotherapy in COVID-19

An important aspect of inflammatory responses in patients with COVID-19 is the suppression of the biological activities of drug metabolising enzymes and transporters [3].

This phenomenon could generate a transient mismatch between their expressions and genotype - phenotype, a phenomenon named phenoconversion. The inflammatory process is responsible for the transient phenoconversion in which there is a deviation between the function encoded in the genotype and the expression of the phenotype [39].

Addressing the potential implications of such phenoconversion events in the management of patients with COVID-19 may be the basis for safer pharmacological interventions.

Inflammation-mediated phenoconversion should be taken in consideration especially in patients with COVID-19 who have comorbidities. In their case there are complex therapeutic regimens that could be influenced by metabolic changes and drug transport. The polymedication of these patients, pharmacokinetically modified by inflammation-mediated phenoconversion, will undergo a change in clinical efficacy and safety.

There are some situations in which there is a greater influence of inflammation-mediated phenoconversion, such as: elderly patients who normally have changes related to physiological conditions (reduced renal and hepatic function); patients with pre-existing kidney and liver disease, impairment also of the alternative metabolic pathway of the drug; reduced functionality of metabolic pathways due to genetic polymorphisms; concomitant use of a drug that is an inhibitor of metabolic enzymes or of the transporter; patients using a drug with a low therapeutic index.

Therefore, it is important to identify patients who are prone to be affected by inflammation-mediated phenoconversion, as well as potentially affected drugs in this situation. They also need to be aware of the potential impact of inflammation-mediated phenoconversion and therefore to monitor more closely the potential side effects of certain medicines and, if necessary, to adjust the dose of the drugs [3].

For many drugs, however, it is difficult to observe in clinical conditions the phenomenon of phenoconversion described above, because they have a high therapeutic index and can also be metabolized in several ways. Another impediment lies in the fact that there are still no guidelines to manage this phenoconversion that can occur between the drug and the inflammatory condition, although such interactions have been highlighted in other pathologies accompanied by marked inflammation.

Chronic inflammation occurs when the antigen is persistent in the body, and the immune system acts continuously against this antigen. This chronic inflammation is associated with changes in the level of drugs that bind the drugs. An important aspect of this marked inflammatory process and which has major implications in pharmacotherapy is the downregulation of various liver and extrahepatic enzymes that metabolize drugs [23].

Inflammation is associated with the presence of cytokines which are a broad class of signalling proteins responsible for maintaining the homeostasis of the immune system. The proinflammatory cytokines interleukin-1 (IL-1), interleukin-6 (IL-6) as well as tumour necrosis factor (TNF-α) are mainly responsible for triggering this acute immune response [11]. The pathogenic mechanisms by which SARS-CoV-2 causes such a fatal syndrome remain largely unknown, but may be similar to those of SARS-CoV [43].

Coronavirus replication probably activates the defence system of host cells, which increases the production of antiviral proteins (interferon) and the subsequent release of various types of proinflammatory cytokines [24]. It has been observed that in patients with severe COVID-19, levels of proinflammatory cytokines, such as interleukins (IL-2, IL-6, IL-7, IL-8, IL-10), tumour necrosis factor (TNF)-α, granulocyte colony-stimulating factor (GCSF), interferon gamma-induced protein (IP)-10, monocyte chemoattractant protein (MCP)-1 and macrophage inflammatory protein (MIP)-1α, have levels increased, suggesting a possible correlation between elevated levels of proinflammatory cytokines and the severity of this condition [3].

In coronavirus infection, these locally synthesized cytokines can circulate through the bloodstream and lead to a systemic effect due to the interaction with cell membrane receptors, vascular endothelial transporters and parenchymal cells in many organs. It is known that inflammation and the immune response are major factors in many acute and chronic diseases and are also involved in influencing the clearance of the drug by changing its transport mechanism and the activity of metabolic enzymes.

Although a number of antimalarial agents (hydroxychloroquine, chloroquine), antivirals (remdesivir, lopinavir-ritonavir, favipiravir), interferons, azithromycin, angiotensin converting enzyme inhibitors (captopril, enalapril), as well as the plasmapheresis, produced clinical positive responses in the early stages of SARS-CoV-2 infection, the vast majority have not been shown to be effective in cytokine storms characteristic of the late stages of the disease [51].

For this reason, in addition, it is necessary not only to prevent viral infection, but the therapies should aim more reducing the intense inflammatory state induced by COVID-19 which in addition to the destructive effects on the body can also influence the kinetics or action of drugs. Thus, attempts have been made to use several immunomodulators and anti-inflammatory drugs, including corticosteroids, IL-1 or IL-6 antagonists, anti-TNF-α agents or Janus kinase inhibitors. Unfortunately, to date, no therapy has been able to completely combat the exacerbated immune response observed in patients with severe COVID-19 [40]. This is probably due in part to the complexity of cytokine interactions and the multiplication of inflammatory pathways, with several molecules being involved in this process, making inhibition of one or more of them insufficient to stop the entire inflammatory syndrome.

Disorders that occur during the inflammatory process can influence the metabolic transformation of drugs. It has been shown that the pro-inflammatory cytokine IL-6 is responsible for increasing the expression of the CYP2B1 isoform, this being possible through an epigenetic mechanism. Thus, those cytokines may indirectly influence the metabolism of hydroxychloroquine, which is of clinical relevance especially for drugs with a narrow therapeutic index [23].

As previously mentioned, the inflammatory response also produces changes in the expression and activity of drug carriers such as ABC (ATP binding cassette) and SLC (solute carrier). Elimination of drugs involves their metabolism using CYP enzymes (cytochrome P450). It is now well known that ABC and SLC carriers play an important role in the elimination of most antiviral drugs and are involved in several drug interactions. Although the role of CYP enzyme systems in the metabolism of drugs used in the treatment of COVID-19 infection as well as drug-drug interaction are well known, some studies require further studies.

Inflammation can also influence the function of the major transporter of drugs, such as P-glycoprotein

(P-gp), by suppressing mRNA expression as well as its biological activity [1].

Changes in transporters may also lead to changes in the pharmacokinetic parameters for certain drugs. Therefore, inflammation could play a key role in both the efficacy and toxicity of the drug. However, although there is a risk of drug interactions, some combinations should not be banned, as they can often be manageable and may even bring a therapeutic benefit [23].

Finally, the potential impact of inflammation on drug therapy in COVID-19 should be considered in conjunction with a number of intrinsic factors: genetics, comorbidities: kidney/liver disease; physiological factors: age, sex, body mass index; extrinsic: medicines, vitamins and supplements or herbal products.

It is important that in addition to the factors listed above, the lifestyle is also taken into account: smoking, exercise or alcohol consumption, which could change the safety and effectiveness of the drug. The coexistence of internal factors (genetic polymorphisms, comorbidity) and external ones (co-medication) can produce complex interactions, such as drug-drug-gene-disease interactions (the condition of overlapping drug-drug interaction, genetic polymorphisms and disease) [41].

Impact of inflammatory condition on hepatic metabolism in COVID-19

Systemic inflammation and the immune response are important elements in many acute and chronic diseases, being strongly involved in changing the pharmacokinetics of the drug. The main contributor to the metabolic biotransformation of most drugs is represented by CYP systems that are widely involved in such disease-drug interactions [19].

The liver is considered to be the main metabolic organ, responsible for the elimination of drugs, where many metabolic reactions take place. Acute and chronic liver damage will of course also influence metabolic mechanisms, eventually leading to poor elimination of drugs [45].

Regardless of the cause, it is considered that the severity of liver disease is correlated with the degree of alteration of metabolism [10]. The exact mechanism of impaired liver function in COVID-19 infection is not fully understood, but it appears that the SARS-CoV-2 virus may cause direct liver damage. Viral hepatotropism can also be attributed to the relatively high expression at this level of the ACE2 receptor, which is the gateway to the cell (in cholangiocytes, rather than in hepatocytes), making them vulnerable to viral attack [17].

This hypothesis is supported by increased circulating serum gamma-glutamyl transferase (GGT) levels in patients with COVID-19. On the other hand, liver abnormalities can also be considered as a side effect after the initiation of specific treatment which is represented by hepatotoxic agents such as antipyretics (acetaminophen), antiviral drugs (oseltamivir and lopinavir), antibiotics and steroids [42].

Although viral antigens have not been detected in the liver, the intense systemic inflammatory reaction caused by SARS-CoV-2 may also be a major cause of multiple dysfunctions in various organs, including the liver, as has been observed to appear also in other respiratory viral infections.

The immune response, with IL-6 at the centre of its network of mediators, is a hallmark of the pathogenesis of COVID-19. Agents that interfere with IL-6 action have led to the recovery of inhibited CYP activity. Thus, it is assumed that the metabolic activity of CYP will inevitably be altered, mostly downregulated, during SARS-CoV-2 infection, which will lead to a pharmacokinetic interaction correlated with the clearance of the administered drugs [8].

In 2020, the antiviral agent remdesivir received authorization to use from FDA (Food and Drug Administration) for the treatment of COVID-19. According to the manufacturer, remdesivir is extensively metabolized by CYP, especially the CYP3A4 isoform [*]. Moreover, other potential candidates for COVID-19 treatment, such as chloroquine and colchicine, are metabolized by the liver, so understanding the basis of such an interaction is essential because it may influence patients' therapeutic / toxic response to the pharmacotherapy used [31].

The inflammatory elements highlighted by the high levels of their mediators in severe cases reach a maximum that leads to the occurrence of the cytokine storm. Together with specific markers for liver damage, such a state of hyperinflammation can trigger significant disorders in the metabolic mechanisms of hepatic cytochrome P450. Under these conditions, the clearance of the drug will be altered, which may lead to an unexpected response both therapeutically and toxically. Moreover, patients with COVID-19 are potentially vulnerable to significant disease-drug interaction and, therefore, appropriate dosing guidelines should be implemented to therapeutically monitor these drugs to ensure optimal clinical outcomes [8].

Drug interactions in vulnerable groups of patients with COVID-19

A number of pharmacokinetic parameters of the drugs used in COVID-19 pharmacotherapy (metabolism, distribution, absorption and elimination) may change during both the disease and the onset of the inflammatory response.

The COVID-19 pandemic has brought to the attention of specialists a number of significant vulnerabilities, especially for the elderly. Not only the direct risk of COVID-19 infection and its potential complications, but also the polymedication, which sometimes proves to be inadequate, may have a contribution [32].

It is known that when several drugs are administered at the same time, the risk of drug interactions increases, but a more complex disease-drug-drug interaction may also occur in COVID-19. The data collected so far suggest that more complicated than usual disease-drug and drug-drug interactions are anticipated in COVID-19 infection. SARS-CoV-2 infection produced, as it affected more and more people, an increasing frequency of hospitalization and hospitalization in the intensive care unit [15].

Acute or chronic diseases involve the frequent addition of drugs to the patient's treatment regimen and therefore increase the risk of drug interactions due to polymedication. Patients in this situation are at an increased risk of prescribing errors with approximately 800,000 medication-related errors that occur each year and which are preventable [32].

CYP enzymes are involved in mediation of clinically relevant drug interactions in several pathological conditions. Such interactions are considered the main reason for reviewing and updating the safety profiles of pharmaceuticals. The interactions between the pathological condition and the drug are frequently observed in inflammatory diseases with drugs whose clearance is predominantly mediated by the CYP system. Such conditions are rheumatoid arthritis, hepatitis, Crohn's disease, acquired immunodeficiency syndrome (AIDS), influenza, congestive heart failure and cancer [8].

Due to the concomitant administration of several drugs in the treatment of COVID-19, the literature refers increasingly to the occurrence of these more complex situations, which pose serious problems for patients prone to such interactions [26].

Moreover, the demographic analysis of patients with COVID-19 revealed that the elderly with comorbidities is the most affected group, which are also potential candidates for the transition to severe stages and the inevitable hospitalization in intensive care units [18]. Drug combinations used to treat COVID-19 may include antibiotics, anticoagulants, systemic corticosteroids, inhalatory therapies, and a number of nutritional supplements. Although some of these therapies have been shown to be beneficial in the treatment of COVID-19, many have not yet fully proved their usefulness. These combinations may increase the risk of medication errors, drug interactions, and administration difficulties due to the large number of drugs involved. The risk will increase with the duration of treatment if the regimen for COVID-19 infection is not reviewed or some medications are not discontinued after the acute episode is over [4].

The selection of COVID-19 therapy should take into account the interaction of drugs used in the treatment of this condition with the treatment of comorbid diseases. Drug interactions can sometimes provide benefits by increasing the effectiveness of the associated drugs, but they also offer disadvantages such as reduced efficacy, side effects and even toxicity.

Thus, the pharmacokinetics of drugs used in these regimens should be treated with the utmost importance, especially in patients with multiple pathologies. Drug metabolism is a very important stage of pharmacokinetics, which can significantly influence the clearance and possibly their efficacy and/or toxicity [21].

Existing medical comorbidities in elderly patients require multiple drug therapies, making them the most vulnerable group for both drug-drug and disease-drug interactions [14]. For this reason, additional precautions are required to determine the optimal dose for these patients.

In the following, a series of data will be provided about the interactions that occur in the main classes of drugs used so far in COVID-19 therapy.

Drug interactions in COVID-19 pharmacotherapy

Antiviral drugs

Remdesivir

Remdesivir is an antiviral drug and a nucleotide prodrug of an adenosine analogue. It binds to viral RNA and inhibits viral replication by prematurely stopping RNA transcription. *In vitro* remdesivir has been shown to work against SARS-CoV-2. This antiviral has broad spectrum activity, being effective against SARS-CoV or MERS-CoV [27, 47].

Intravenous remdesivir has been approved by the Food and Drug Administration (FDA) for the treatment of COVID-19 in both adult and pediatric patients (≥ 12 years of age and weighing ≥ 40 kg). It is used to treat mild to moderate forms of COVID-19 in high-risk patients who have not been hospitalized and given for 3 days (it should be started within 7 days of the onset of symptoms). It can also be used in patients hospitalized with COVID-19 (for a period of 5 days).

In vitro, remdesivir has been shown to be a minor substrate for cytochrome P450 CYP3A4, for organic anion transporter polypeptides (OATP) 1B1 and (OATP) B3 as well as for drug-carrying P-glycoprotein, being an inhibitor [48].

Data from healthy human subjects confirm that remdesivir is extensively metabolized by CYP2C8, CYP2D6 and CYP3A4 [48]. In vitro data indicated that the inflammatory response may reduce mRNA expression of several CYP450 isoenzymes, including CYP1A2, CYP2B6, CYPC9, CYP2C19, CYP2D6 and CYP3A4 and transporters. Therefore, inflammation could influence, at least theoretically, their pharmacokinetics [37]. Thus, it is possible to discover potential drug interactions associated with remdesivir, an example being carbamazepine which could significantly decrease its levels [33].

However, to date, evidence on the safety and efficacy of remdesivir in the treatment of COVID-19 is still limited.

Lopinavir and ritonavir

Lopinavir and ritonavir are anti-HIV protease inhibitors. As for lopinavir, it binds to the site of activity of the HIV protease and prevents the formation of functional proteins necessary for viral pathogenesis. This results in immature viruses that lack infectious capacity. Ritonavir, in turn, inhibits the enzyme CYP3A4, which is responsible for the metabolism of lopinavir in the gut, liver and other tissues [33]. This mechanism will lead to an increase of lopinavir plasma concentrations. In addition, when formulated in combination with lopinavir, ritonavir improves its bioavailability and increases its half-life. Thus, a low dose of ritonavir can be used to increase the activity of other protease inhibitors and reduce side effects.

Lopinavir is also the substrate or inhibitor of various transporters (P-glycoprotein, BCRP (breast cancer resistance protein), OATP1A2, OATP1B1, OATP1B3 and OATP2B1), and CYP3A4 mediates their metabolism [23]. OATPs are membrane influx transporters that regulate the intracellular transport of a number of endogenous compounds and clinically important drugs. Breast cancer resistant protein (BCRP) and P glycoprotein (PGP) are efflux transporters, located at the membrane level, which carry several chemical classes of compounds and act as barriers to tissue permeability, thus regulating tissue exposure of their substrates.

Ritonavir is a potent inhibitor of CYP3A4 and a moderate inhibitor of P glycoprotein, CYP2D6, OTAP1B1 and OTAP1B3 while lopinavir inhibits only CYP3A4 and CYP2D6 isoforms [6].

This combination of lopinavir and ritonavir may interact with many other drug groups and it is very important to take in consideration these interactions in the pharmacotherapy of patients with COVID-19. Thus, ritonavir may influence the metabolism of warfarin differently, reducing it by inhibiting the enzyme CYP3A4 or may increase it by stimulating the enzymes CYP2D9 and CYP1A4. In general, however, it is considered that the need for warfarin will increase 2-3 times. Therefore, INR should be routinely checked during concomitant use of this combination [33].

With antidiabetic agents, the lopinavir/ritonavir combination may also interact in different ways. Thus, the effects of nateglinide will decrease and its concentration must be closely monitored. In contrast, the effects of repaglinide or saxagliptin will increase due to impaired CYP3A4 metabolism. In this situation, the dose should be limited to 2.5 mg/day when co-administered with potent CYP3A4 inhibitors [6]. Because corticosteroids are used in COVID-19 therapy, due to the high-level inflammatory syndrome that sets in, it is also important to monitor their interactions. Budesonide administered nasally and inhalatory, fluticasone nasally and triamcinolone have an increased effect due to impaired liver enzyme metabolism. Concomitant use of corticosteroids with the antiviral combination mentioned above can cause Cushing's syndrome [36].

Although moderate, the interactions between lopinavir/ritonavir and digoxin, theophylline, nifedipine, which lead to increased levels, should also be considered, which requires close monitorization of the patient. When co-administered with nifedipine, there is a major interaction that led to increased calcium blocker levels, which requires careful recommendation of this combination [9].

A special category of patients with COVID-19 infection are oncologic ones, who have a treatment regimen that often includes polymedication in which both antineoplastic and antiviral drugs are found. Some antineoplastic drugs are often substrates for CYP3A4, CYP2B6 and P-glycoprotein. Drugs in this category are: docetaxel, erlotinib, imatinib, irinotecan, vinblastine and vincristine. The use of the above combination should be closely monitored in these patients as it may increase the plasma concentration of antineoplastic agents by inhibiting the metabolism of these liver enzymes [34].

Other interactions that require close monitoring are those that occur between lopinavir / ritonavir and drugs such as antacids, digoxin, theophylline and tramadol.

Ribavarin

Ribavirin is a broad-spectrum antiviral drug that is an analogue of guanosine. It is known to cause interactions with many drugs, but in COVID-19 infection should be followed especially the interaction with vitamin K antagonists such as warfarin when its anticoagulant effect is reduced [38]. In this pathology, patients are under threat of the risk of thrombotic events and anticoagulant drugs may also appear in the treatment regimen.

Although, in recent in vitro studies, ribavirin has been shown to achieve an effective increased

concentration against COVID-19, in patients with ADRS (Acute respiratory distress syndrome) it has produced significant adverse effects [27].

The mechanism of drug interactions produced by ribavarin is still unclear, as it is neither a substrate nor an inhibitor of the hepatic or extrahepatic CYP enzyme system. It is sometimes used in triple combination with nitazoxanide and hydroxychloroquine [23].

Chemotherapic drugs

Chloroquine/hydroxychloroquine

Chloroquine and hydroxychloroquine are two aminoquinolines, used for the prophylaxis and treatment of uncomplicated malaria and rheumatic diseases. During the COVID-19 pandemic, it has been shown that they show activity against COVID-19, which recommends them as a primary therapeutic option for this disease [12].

However, concomitant administration of other drugs with them should be done with caution due to the interactions that may occur. Thus, concomitant administration of chloroquine with paracetamol should be avoided or treated with caution as it may lead to a significant increase in the maximum plasmatic concentration of paracetamol [22]. This can have serious consequences, as its hepatotoxicity is known.

Moderate interactions of chloroquine with other drugs include those with antacids (pharmacokinetic), which will decrease its absorption, recommending a four-hour break between administrations but also with bisoprolol, which will require monitoring of the patient because increased levels of beta-blocker are achieved. A major pharmacokinetic interaction has also been shown with concomitant administration of cimetidine and leading to a prolongation of the chloroquine half-life. In this case, replacement with ranitidine is recommended [9].

Chloroquine is responsible for the reduction of the bioavailability of ampicillin due to the decreasing of the rate of gastric emptying and enhancement of bowel motility.

For hydroxychloroquine a major pharmacokinetic interaction occurs with concomitant administration of rifampicin, manifested by reduced levels of hydroxychloroquine which makes it necessary to increase its dose and monitor the patient closely. Other but moderate pharmacokinetic interactions have been reported with bisoprolol and digoxin, leading to elevated levels. A number of moderate pharmacodynamic interactions with antidiabetics such as glimepiride and metformin may also occur, resulting in improved glycemic control.

Several clinical studies indicate that chloroquine may increase the metformin-induced cell apoptosis and significantly enhance the metformin-induced inhibition of cancer cell proliferation [44]. Concomitant administration of both mefloquine (an antimalarial drug) is contraindicated in both chloroquine and hydroxychloroquine because this combination will prolong the QT interval [9].

CYP and its isoforms could play an important role in the metabolism of hydroxychloroquine and chloroquine. Unfortunately, no details are known about the hepatic metabolism of hydroxychloroquine. Thus, the effects of chloroquine on CYP3A4/5, CYP2C8 and CYP2D6 were extrapolated. Both drugs turn into active metabolites through the dealkylation process produced by CYP isomers [31].

The administration of hydroxychloroquine in the pharmacological management of COVID-19 infection has produced several side effects among people with different CYP genotypes. Thus, the genotyping of the CYP enzyme system becomes extremely important, especially for CYP2D6, which may contribute to the determination of the optimal dose of hydroxychloroquine in personalized medicine.

Ivermectin

Ivermectin is an effective antiparasitic drug, also demonstrating activity against many viruses. Recently, an in vitro study showed that ivermectin is capable to prevent COVID-19 replication [5].

Ivermectin is metabolised to several metabolites by CYP3A4 and is a substrate for P-glycoprotein. Less than 1% of the dose of ivermectin is excreted in untransformed urine. Further in-depth studies would be needed to monitor the factors affecting ivermectin plasmatic concentrations [23].

Tetracyclines

In patients with COVID-19, tetracyclines, although part of the antibiotic group, can be used as a possible treatment option, due to their activity in reducing the level of inflammatory cytokines, such as IL-1b and IL-6 (both increased in COVID -19) [20].

The possibility of using them for the treatment of HIV, West Nile virus and viral encephalitis or also for the prevention of ARDS-induced septic shock has been previously studied [16].

For this reason, tetracyclines have been proposed as an option for the treatment of inflammatory diseases. They could also be selected as a possible treatment option for COVID-19 infection. In a recent study, during treatment with tetracyclines, COVID-19 symptoms decreased to disappear in all patients within ten days. Surprisingly, the characteristic ageusia and anosmia disappeared in the first week of tetracycline treatment. These results make tetracyclines a promising drug for treating the patients with COVID-19 who have mild symptoms [13].

It has been shown that tetracyclines can have an indirect antiviral effect with immunomodulatory, anti-inflammatory and anti-apoptotic / antioxidant

properties. Immuno-modulation inhibits neutrophil chemotaxis and may alter endothelial permeability by matrix metalloproteinases (MPPs): MMP-2 and MMP-9. Tetracyclines can also reduce the synthesis of proinflammatory cytokines (TNFα, IL1β) as well as the release of macrophage neutrophils that are known to infiltrate patients with COVID-19 into the alveoli of the lungs. It has been observed that doxycycline is able to reduce proinflammatory cytokines (IL-6, IL-1, IL-8 and TNF-α), which is of great clinical relevance especially in viral infections with a prominent inflammatory reaction [30, 46].

Regarding the metabolism of tetracycline, as the mechanism is not fully known, there is no evidence to interact with different metabolic systems. However, it is known that antiacids decrease its bioavailability due to the insoluble chelates that form, decreasing its absorbability in the gastrointestinal tract.

Azithromycin

Azithromycin is an antibiotic that is part of the macrolide class and is recommended for patients with pneumonia. Azithromycin is thought to have the ability to prevent severe respiratory tract infections because when used orally it is distributed in a variety of tissues but especially in the lungs. Thus, azithromycin has been used to treat patients with COVID-19 in combination with hydroxychloroquine [2].

Regarding the interactions that may occur with pharmacotherapy with other drugs, the prolongation of the QT interval was observed with the concomitant administration of amiodarone. In this case, it is recommended to replace it with another drug.

Azithromycin may reduce the metabolism of cyclosporines and warfarin, so careful monitoring is required during therapy. It has also been noted that the level of tacrolimus (an immunosuppressant used in organ transplants) increases when used with azithromycin, which requires a number of precautions [9].

Monoclonal antibodies

Tocilizumab

Tocilizumab is a recombinant monoclonal antibody used primarily in the treatment of rheumatoid arthritis. Its mechanism of action is based on blocking IL-6 receptors to reduce inflammation. In patients with this condition, T lymphocytes and macrophages generate IL-6, which causes a cytokine storm and generates severe inflammatory responses, mainly in the lungs. Therefore, the use of tocilizumab for the treatment of this condition is justified, being an effective therapeutic treatment [50].

Tocilizumab has no direct inhibitory or inducing effects on the CYP enzyme system but may nevertheless act indirectly by inhibiting IL-6-induced CYP suppression. As mentioned above, it has been shown that increasing IL-6 during inflammation will inhibit the activity of CYP1A2, CYP2C9, CYP2C19 and CYP3A4, leading to increased exposure to substrate drugs. When tocilizumab treatment is initiated, CYP activity is normalized, leading to a reduction in exposure to drugs that, prior to treatment, were altered [23].

Itolizumab

Itolizumab is a recombinant G1 immunoglobulin monoclonal antibody to the CD6 glycoprotein (Cluster of Differentiation 6) - a transmembrane receptor found in T cells that plays an important role in autoimmune diseases. Itolizumab can modulate the activation and proliferation of T lymphocytes by binding to CD6. It was used until now for the treatment of psoriasis.

Itolizumab may reduce the inflammatory cytokines IFN-γ, TNF-α and IL-6, so it may be a treatment option for COVID-19 infection. It has been shown that it reduces IL-6 levels in critically ill patients [35].

As with tocilizumab, itolizumab has not been shown to have direct inhibitory or inducing effects on the CYP system. However, it can reverse cytokine-induced CYP suppression [23].

Conclusions

Despite the declining evolution of COVID-19, there is still no approved drug with significant effects in treatment for patients with COVID-19 without side effects or interactions. Based on the evidence gathered so far, many antiviral and anti-inflammatory drugs have been authorized by the Food and Drug Administration (FDA) to treat patients with COVID-19, although not all possible interactions in their regimen are yet known.

The severity of COVID-19 has been closely linked to the inflammatory state produced by the virus. For this reason, a number of therapeutic strategies are needed to address the process of hyperinflammation and the cytokine storm in addition to preventing and eliminating SARS-CoV-2. This is of utmost importance for patients suffering from other comorbidities or immune disorders. A variety of anti-inflammatory therapies have been used and adapted for the treatment of COVID-19 and some of these are still under clinical evaluation, including low molecular weight drugs, monoclonal antibodies and cell therapies.

Patients suffering from multiple pathologies have a higher risk of side effects, because they often have a much more complex treatment schedule. Polypharmacy may increase the risk of drug interactions and decrease patient compliance. These can expose the patient to the risk of serious side

effects and reduce the safety and effectiveness of treatment.

In order to achieve effective pharmacotherapy in COVID-19, drug-drug or drug-disease interactions should not be ignored. Drugs used in COVID-19 therapy can produce several types of interactions through mechanisms of absorption, distribution, metabolism and elimination. Pharmacists and the medical team treating patients are responsible for preventing the effects of unwanted interactions and improving the quality of life of patients with COVID-19, especially those with comorbidities.

Conflict of interest

The authors declare no conflict of interest.

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