REVIEW ARTICLE

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ABSTRACT

This article aims to understand the pharmacological properties of AZT and analyze possible reasons for its use in the treatment of COVID-19 alone or associated with chloroquine (CQ) or hydroxychloroquine (HCQ). For this, a bibliographical research was carried out in the following databases: Scientific Electronic Library Online (SciELO), US National Library of Medicine (PUBMED) and ScienceDirect. In the study, data on the pharmacology of Azithromycin (AZT) were collected, its history, its uses, highlighting the research conducted in 2020 with this drug for the treatment of COVID-19. It should be noted that AZT is an

antibiotic of the macrolide subclass with varied pharmacotherapeutic use, especially in the treatment of bacterial, respiratory, genitourinary and enteric infections. During the SARS-COV-2 pandemic, HCQ-associated AZT was considered for the treatment of the disease due to its in vitro results. There was much debate about the use of the combination of these drugs and even before the results of clinical studies were published, the Ministry of Health has already made recommendations regarding the use of these drugs to treat COVID-19. National and international health organizations were more cautious and highlighted the lack of scientific evidence for this use. The information collected in this review of the literature suggests that the administration of AZT or AZT associated with HCQ or CQ was not effective in the treatment of COVID-19 patients for both mild and moderate or severe cases.

Keywords: Azithromycin, Utilization, COVID-19, Pharmacology.

1. INTRODUCTION

Azithromycin (AZT) is an antibiotic of the macrolide subclass with varied pharmacotherapeutic use, especially in the treatment of bacterial, respiratory, genitourinary and enteric infections. Its chemical name is 9-deoxy-9a-aza-9a-methyl-9a-homoerythromycin A, has a molecular weight of 749.0 and is obtained from the addition of a nitrogen atom in the lactal ring of erythromycin A, distinguishing itself from it by its broader spectrum of action, greater half-life, good oral tolerance and low toxicity (ASTRO, 2015; MATZNELLER et al., 2013).

AZT's main performance is bacteriostatic, that is, it acts to prevent the multiplication of the bacterium. However, some studies indicate that, in addition to antimicrobial activity, macrolides have anti-inflammatory and antiviral properties, being among the immunomodulatory action drugs in various respiratory diseases (JOHNSTON, 2006).

During the Covid-19 pandemic, AZT became the subject of discussions about its use, especially when associated with hydroxychloroquine (HCQ), for the treatment of SARS-CoV-2. AZT gained great prominence after the publication of a French study "*Hydroxychloroquine and azithromycin as a treatment of COVID-19: results of an open-label non-randomized clinical trial*" by Gautret et al., (2020), even with harsh criticism, which included the effect of

zeroing the viral load of patients affected by the disease through the combined use of these drugs. Since then, health institutions started to use these drugs in clinical trials with patients affected by COVID-19, including in Brazil (BRASIL, 2020a).

Decisions in favor of the therapeutic acceptance of AZT for the fight against SARS-CoV-2 were based on in vitro studies such as those of Poschet et al., (2020). Although they have shown good results to reduce viral load, several recent clinical studies have not proven this efficacy, and its use in respiratory diseases such as COVID-19, intending to achieve an immunomodulatory action, is still controversial (CAVALCANTI et al, 2020; ROSENBERG et al, 2020; MAGAGNOLI et al, 2020)

In addition, AZT usually has mild to moderate intensity side effects. However, some studies point to possible cardiovascular effects, since macrolide antibiotics prolong the QT interval, which can cause disorders in cardiac ritmicity (ASTRO, 2015). In addition, this drug may also have hepatotoxic effects, therefore, the use of this drug should be well considered, especially in the treatment of COVID-19 (OLRY et al, 2020). In this sense, the aim of this article was to conduct a descriptive study seeking information about the pharmacological properties of AZT, such as therapeutic use, efficacy and side effects, as well as clarifying the reasons for its use in the treatment and/or prevention of COVID-19 both as a single drug, as in association with CK or HCQ.

2. METHODOLOGY

In order to understand the pharmacological properties of AZT, and to analyze possible reasons for its use in the treatment of Covid-19, a review of health publications was carried out through research in the Scientific Electronic Library Online (SciELO), US National Library of Medicine (PUBMED) and ScienceDirect database. For the search, the following descriptors were used: "Azithromycin", "Utilization" "COVID-19" and "pharmacology" and their respective in Portuguese. The research period was from 1997 to 2021, this time frame was operated due to the fact that this study also aims to understand the already known properties of azithromycin, however, the vast majority of the articles used are from recent periods, since, during the pandemic, many studies on the subject have been carried out since to date the vast majority of the world population has not yet received the vaccine and the

search for effective treatment is still necessary. In addition, language filters were applied to obtain only publications in Portuguese, English and Spanish.

For the construction of the present work, the selection of articles took place in three stages. In the first, 833 publications were selected from the identification of subject descriptors, already mentioned above; in the second, titles and abstracts of the material found and the selection of what was in agreement with the purpose of the work were performed; in the third, a pre-analysis was made, with reading of the selected articles, and 52 references were finally used.

3. DEVELOPMENT

3.1 HISTORY AND THERAPEUTIC EMPLOYMENT

AZT is the first antibiotic of the macrolide subclass, derived from erythromycin, differing from it by the addition of a nitrogen atom in the lactonic ring of erythromycin (ASTRO, 2015). This modification improved the stability in acid medium and tissue penetration and expanded the spectrum of activity and provided a prolonged tissue half-life that allows dose reduction during treatment, being an antibiotic with varied pharmacotherapeutic use, mainly in the treatment of respiratory, enteric and genitourinary bacterial infections (BAKHEIT et al, 2014).

The rapid spread of the disease caused by the new coronavirus called SARS-CoV-2 (acute severe respiratory coronavirus syndrome 2) between countries and communities, resulting from high viral transmissibility, associated with the lack of specific vaccines and antivirals effective for the prevention and treatment of the disease, makes non-pharmacological interventions the most efficient options for the mitigation and control of COVID-19 at the local and global level.

In this context, on March 11, 2020, the World Health Organization (WHO) decreed the COVID-19 pandemic, when the epidemic, which began in China, was already present in more than 100 countries, reaching the level of 1,940,352 deaths worldwide in January 2021 (WHO, 2021).

In view of the increasing number of infected and deaths due to complications of the disease, some medications have been tested, with emphasis on the use of AZT in the treatment of patients, being the target of numerous studies on its use.

In this sense, it is important to mention that the repositioning of old drugs already used for antiviral treatment is a good strategy, because side effects, dosage, interactions with other drugs and the safety profile (GAUTRET et al, 2020) are already known. Thus, some studies have suggested a synergistic effect of the combination of HCQ and AZT, mainly because this macrolide has been shown to be active *in vitro* against Zika and Ebola viruses, in addition to preventing severe respiratory tract infections when administered to patients suffering from viral infection (GAUTRET et al, 2020), as well as a regimen of combining AZT with chloroquine (CQ) has been used in the treatment of malaria in cases of chloroquine resistance, and a synergy of this *in vitro* effect has also been reported (COOK et al, 2006).

AZT acts predominantly as bacteriostatic, preventing the multiplication of the microorganism. However, during the COVID-19 pandemic, it has been the subject of numerous debates and controversies, especially in the hypothesis of its use associated with HCQ due to antiviral effects detected *in vitro* (CAVALCANTI et al., 2020).

Primarily, AZT is indicated for the treatment of lower respiratory tract infections, including bronchitis and pneumonia, skin and soft tissue infections, acute otitis media, upper respiratory tract infections, including sinusitis and pharyngitis/tonsillitis (ASTRO, 2015).

It is also used in mild or moderate typhoid fever due to multibacterial resistant organisms in the treatment or prophylaxis of *Mycobacterium avium-intracellulare* infection in AIDS patients (BAKHEIT et al, 2014), in addition to uncomplicated non-gonococcal urethritis presumably caused by *C. trachomatis* and in the prevention of bacterial endocarditis in patients undergoing dental procedures who are at high risk of endocarditis, pertussis, mycobacterial infections, for patients allergic to β -lactam agents (JOINT FORMULARY COMMITTEE, 2009; MORENO et al, 2009).

In sexually transmitted diseases in men and women, especially during pregnancy, when tetracycline stems are contraindicated, AZT has been used in uncomplicated genital infections due to *Chlamydia trachomatis* and *Neisseria gonorrhoeae*, cancer treatment due to

Haemophilus ducreyi and granuloma inguinal or venereal lymphogranuloma (ASTRO, 2015; BAKHEIT et al, 2014; MORENO et al, 2009). AZT has also been studied for the treatment of other pathologies in addition to its antimicrobial effects, many are still in the study phase, but positive results have been observed in the treatment of gastroparesis and gastrointestinal dissimilarity (RANG and DALE, 2007; SWEETMAN, 2009), late-onset asthma (MOSHIREE et al, 2010), uncomplicated falciparum malaria, when used in combination with artesunate or quinine (CHINI et al, 2012), gingival hyperplasia, when associated with cyclosporine, especially when administered at the beginning of the process (GÓMEZ et al, 1997).

Cystic fibrosis with long-term use of AZT has shown evidence of a reduction in pulmonary function decline and exacerbation rate, probably by stopping the growth biofilm *Pseudomonas aeruginosa* (HURT and BILTON, 2012). In addition, the use of AZT has been investigated in the prevention of ischemic heart disease, based on a suggested link between atherosclerosis and *Chlamydomphila pneumoniae* infection. Although preliminary results from some pilot studies have been promising, long-term studies in large numbers of patients have been frustrating, have not decreased ischemic events, nor have they provided clinical benefit (MORENO et al, 2009; NOEDL et al, 2006). AZT has also been studied for the treatment of COVID - 19, both for its antibiotic effects when patients have bacterial infection, as well as for its possible antiviral effects.

3.2 PHARMACOLOGY

Regarding the pharmacokinetic properties of AZT that include absorption, distribution and elimination. After oral administration in humans, AZT is widely distributed throughout the body, having bioavailability of approximately 37%, and may have its bioavailability reduced by 50% when administered in the form of capsules and after a substantial meal. The time required to reach plasma concentration peaks is 2 to 3 hours (BAKHEIT et al, 2014; MORENO et al, 2009).

AZT has extensive distribution in tissues and high concentrations of medicines within cells (including phagocytes), resulting in much higher concentrations of drugs in tissues or secretions compared to simultaneous serum concentrations. In experimental animal models, higher concentrations of AZT are released during active phagocytosis than by unstimulated

phagocytes, resulting in high concentrations of AZT being released to the sites of infection (BAKHEIT et al, 2014; MORENO et al, 2009; ASTRO, 2015).

When administered orally, AZT is rapidly absorbed and widely distributed throughout the body, with the exception of the brain and cerebrospinal fluid (BAKHEIT et al, 2014; MORENO et al, 2009). AZT levels in tissues is up to 50 times the maximum concentration observed in plasma, according to pharmacokinetic studies in humans. (YANG et al, 2009; ASTRO, 2015)

Macrolides, a class to which AZT belongs, express their activity as antibiotics by binding to RNAr 23S of the ribosomal subunit 50S of microorganisms blocking protein synthesis by inhibiting the transpeptidation/translocation step (ASTRO, 2015; MATZNELLER et al, 2013). The cells are considerably more permeable to the ionized form of the drug, which probably explains the increase in antimicrobial activity in alkaline pH.

Some studies have pointed out that, in addition to their antimicrobial activity to prevent bacterial superinfection, thus attenuating a viral infection caused by SARS COV-2, macrolides have anti-inflammatory and antiviral properties (JOHNSTON, 2006).

In this sense, regarding the mechanism of antiviral action, the recurrent association of AZT with HCQ is observed due to the fact that they act in a similar way, performing the so-called "drug interaction", which, in this case, enhances the effect of drugs in combating COVID-19. Some studies also state the overlap of azt's mode of action in relation to HCQ. Studies claim that these drugs cause pH alteration within intracellular organelles, especially in the Golgi apparatus. Thus, the decrease in endosomal acidification causes an interference in ACE2 receptor glycoylation with s protein s virus SARS COV-2, blocking viral entry and dissemination (POSCHET et al, 2020).

Previous studies have shown AZT's action against viruses causing previous outbreaks such as Ebola and Zika (ANDRIANI et al, 2020; GAUTRET et al, 2020). In addition, this drug demonstrated efficacy in preventing the progression to more severe viral infections of the respiratory tract (BACHARIER et al, 2015; GAUTRET et al, 2020). This results from a positive regulation of interferon (IFN) I and IFN III. (ANDREANI et al, 2020; LI, et al, 2019).

Although in vitro AZT has this potential to reduce the viral load of SARS COV-2, this

characteristic does not remain in practice (GAUTRET et al, 2020; TOURET et al, 2020). Recent studies in patients with COVID-19 indicate that the use of AZT with HCQ did not cause improvement in clinical status (CAVALCANTI et al, 2020). Among these studies are a retrospective cohort study of 1,438 patients hospitalized in metropolitan New York with treatment including AZT in one group, HCQ in another, and the third being medicated by both associated drugs. In the end, it was concluded that none of the alternatives led to statistically significant improvement in the patients' pictures (ROSENBERG et al, 2020).

Another study, this time conducted in different medical centers in Brazil, evaluated 504 patients whose tests confirmed SARS COV-2 infection. In this group, the second was also divided into three groups, the first being control, the second was medicated only with hydroxychloroquine and the latter used the associated hydroxychloroquine therapy with AZT and, again, no improvement in the clinical status of patients with the medication was observed in relation to the placebo group (CAVALCANTI et al, 2020). Finally, a relevant study conducted in different medical centers in the United States showed that, in addition to not causing improvement in the clinical status of patients, AZT and HCQ still had little or almost no relevance in reducing the risk of mechanical ventilation of patients hospitalized with COVID-19 (MAGAGNOLI et al, 2020).

Moreover, this class of drugs is evaluated as immunomodulatory drugs in various respiratory diseases. Research claims that its effects are related to increased secretion of anti-inflammatory cytokines from neutrophil activity by inhibiting their migration to inflammation sites, as well as inhibiting the synthesis and secretion of pro-inflammatory cytokines (GOOD et al, 2012; ZAROGOULIDIS et al, 2012).

In this sense, studies have shown that this immunomodulatory action of AZT and HCQ occurs during cell involvement, more specifically in inhibiting the ICAM1 molecule and developing cytokines such as interleukins (IL) - 6 and IL- 8 of rhinovirus in lung epithelium cells (JANG et al, 2006). In addition, they can inhibit the degranulation of leukocytes, reduce eosinophilic inflammation, activate phagocytosis of macrophages and increase mucociliary transport, decreasing mucus production in vivo and in vitro (BARKER et al, 2015; BEIGELMAN et al, 2009; GOOD et al, 2012; ZAROGOULIDIS et al, 2012). Although there are many studies related to the subject, the indication of AZT to achieve such immunomodulatory actions in response to SARS COV-2 infections is still somewhat controversial (JOHNSTON et al, 2006;

SOUTHERN et al, 2012).

4. POSITIONING OF NATIONAL AND INTERNATIONAL MEDICAL ENTITIES

Uncertainties about the management of patients in the pandemic by SARS-COV-2 during 2020 was certainly a very debated one. The use of several drugs and protocols for the treatment and prophylaxis of COVID-19 was considered and studies were conducted to verify the effectiveness of these therapies. One of the drugs considered was AZT, in many cases associated with HCQ and CQ. Although there was not much evidence in favor of these drugs, this combination was recommended by the Ministry of Health (MH) in May for adult patients with mild to severe cases, emphasizing early administration, that is, in the first days of symptoms (BRASIL, 2020a; UFRGS, 2020).

The Brazilian Medical Association (AMB) published in March 2020 a position on the use of AZT+HCQ/CQ, highlighting the lack of scientific evidence of this conduct, since many of the studies that were being conducted at the time did not have reliable scientific criteria because they were partial, non-randomized or *in vitro* research. In addition, the consideration of medical autonomy is highlighted in this note of the AMB, especially with regard to the conduct of severe and life-threatening cases (AMB, 2020).

The position of the World Health Organization (WHO) on the subject was more cautious, being expressed in the “*Interim Guidance*” in May that the administration of antiviral, immunomodulatory, corticosteroid drugs, among others, should be reserved for clinical research and that the data available to the public. at that time, they were insufficient and of low scientific quality to propose any type of effective treatment for COVID-19. The WHO also points out that many of these drugs, including the combination AZT + HCQ / CQ, have side effects to be considered, so this experimental use can be harmful for some patients (WHO, 2020).

In the second week of June, the MH published a new information note replacing that of May, also advocating early treatment and indicating the use of the AZT+HCQ/CQ combination for, in addition to adults, pediatric patients and pregnant women with mild, moderate or severe cases (BRASIL, 2020b). At the end of June, the Brazilian Society of Infectious Diseases (SBI)

published its position on early drug therapy, highlighting that double-blind and randomized clinical studies showed no benefits of the use of HCQ/CQ, nor azt in critically obese patients (SBI, 2020).

Regarding the use of AZT and other drugs for COVID-19 prophylaxis, this practice is discouraged by the SBI, the Brazilian Society of Pulmonology and Tisiology (SBPT) and the WHO. The SBPT took a stand in late June, warning that there is no scientific evidence to support the use of any medication to prevent the disease from being installed. Moreover, AZT is an antibiotic drug, so there is no indication for its use in viral infections, with the possibility of providing the selection of resistant bacterial strains (SBI, 2020; SBPT, 2020; NIH, 2020a).

Moreover, internationally, other health organizations such as the Pan American Health Organization (PAHO), the Centers for Disease Control and Prevention (CDC), the U.S. National Institute of Health (NIH), claim that there is no drug with scientific proof of efficacy to treat or prevent Infection by SARS-COV-2 (CDC, 2020; NIH, 2020b; PAHO, 2020).

The results of several randomized and double-blind clinical trials were made public throughout 2020 and many of these pointed to the inefficacy of HCQ/CK treatment with or without AZT. The studies “Coalizão I” and “Coalizão II” conducted by Brazilian scientists and published in July and October, respectively, did not observe differences in the clinical evolution of patients in the groups that used a standard treatment, only HCQ/CQ or AZT+HCQ/CQ (CAVALCANTI et al, 2020; FURTADO et al, 2020).

Thus, in late 2020, the SBI released the document “Updates and Recommendations on COVID-19” emphasizing that there are no early treatments for the disease so far and symptomatic medications could be prescribed when needed. Soon after, the SBPT declared support for SBI and its position on infection with SAR-COV-2 (SBI, 2020; SBPT, 2020).

5. POSSIBLE SIDE EFFECTS OF AZT IN THE TREATMENT OF COVID-19

AZT is generally widely tolerated by most patients, with reported adverse reactions being mild to moderate intensity. The most common effects affect the gastrointestinal system, such as anorexia, dyspepsia, nausea and vomiting, flatulence, constipation, among others. There are also reports of headache, drowsiness, dizziness, arthralgia, insomnia, hepatitis,

hypotension, itching, anaphylaxis, anxiety, agitation, tinnitus, transient neutropenia, and thrombocytopenia (ASTRO, 2015).

It is important to highlight that AZT was considered as one of the possible treatments for COVID-19, especially as prophylaxis for secondary bacterial infections. Many clinical studies have been conducted combining the administration of AZT with HCQ or CQ to verify the efficacy of these drugs against COVID-19 infection (SULTANA et al, 2020; ZEQUIN et al, 2020).

Some factors may lead to prolongation of the QT interval, one of which are medications such as AZT, HCQ and CQ (REY et al, 2003; RAY et al, 2012; WU et al, 2020;). AZT has as one of its known side effects some disorders of cardiac rhythm. Palpitations, arrhythmias, ventricular tachycardia and, more rarely, prolongation of the QT and Torsades de Pointes interval (ASTRO, 2015). In addition, both HCQ and CQ are recognized as cardiotoxic drugs, especially in their prolonged use (WHITE, 2007; ZEQUIN et al, 2020). This change in the QT interval in the use of these drugs occurs due to the blockade of the potassium channel hERG, and the combination of AZT+HCQ/CQ can potentiate the inhibition of these channels and lead to arrhythmias (ZEQUIN et al, 2020).

The QT interval on the electrocardiogram comprises all electrical activity of the heart, starting from depolarization to ventricular repolarization. This value oscillates according to heart rate (HR), so it is necessary to correct this measurement according to HR, obtaining the measurement of the corrected QT interval (QTc). The QTc is considered normal when in the ≤ 440 ms for males and ≤ 460 ms for females (WU et al, 2020).

Another point to consider is that SARS-COV-2 infection alone can already cause liver damage, and increase serum levels of some liver enzymes, such as aspartate aminotransferase (AST) and alanine aminotransferase (ALT) (RIDRUEJO and SOZA, 2020; ZHANG et al, 2020;). AZT may also cause an increase in AST and ALT, but it is an acute and transient increase in patients treated for a short period of time. Azt hepatotoxicity can also lead to cholestatic hepatitis within three weeks of use of the drug (OLRY et al, 2020; LIVERTOX, 2017). These adverse effects should be well analyzed when the use of AZT is proposed in the treatment of COVID-19.

6. FINAL CONSIDERATIONS

It is undeniable the importance that AZT has in the treatment of various bacterial diseases that affect the human being. In addition, there are studies being conducted to verify its possible antiviral and immunomodulatory actions, being something still very uncertain. Although this drug has shown promising results *in vitro*, in several clinical studies conducted worldwide AZT, combined or not with HCQ/QC, has not demonstrated efficacy for the treatment of mild to severe cases, nor as prophylaxis of COVID-19. While the final results of the studies involving the efficacy of this use did not come out, some countries, including Brazil, established protocols early and recommended the use of the AZT+HCQ/CQ combination for all types of cases, ignoring the caution recommended by several national and international health organizations. During this period there were also studies dealing with the possible adverse effects that such drugs could cause, highlighted the prolongation of the QTc interval, especially in patients with risk factors. At the end of 2020, with the publication of several double-blind and randomized clinical studies, it can be affirmed that the administration of AZT+HCQ/CQ does not promote improvement in the clinical evolution of patients. All this situation experienced during the COVID-19 pandemic underscored the importance of well-designed and conducted science. As for the use of AZT for treatments of diseases other than bacterial infections, where efficacy is already scientifically proven, further studies are necessary.

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