

Azithromycin: characteristics and clinical indications for bacterial and virus infections, including SARS-CoV-2 infections

Azitromicina: características e suas indicações clínicas contra infecções bacterianas e virais, incluindo infecções pelo SARS-CoV-2

Azitromicina: características e indicaciones clínicas de las infecciones bacterianas y virales, incluidas las infecciones por SARS-CoV-2

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Abstract

Objective: to accomplish a literature review to research the clinical characteristics of azythromycin, and its indications and associations for SARS-CoV-2 infections. Methodology: Electronic searches were carried out on PUBMED Central, BVS/BIREME, Web of Science and The Cochrane Library with the aid of key-words. Results: Azithromycin is a secure antibiotic belonging to the macrolide class, effective for a vast number of infections, especially respiratory diseases. It seems to have viral indirect activity due to its being capable of altering the cell machinery, including

mitochondrias, for changing the normal functioning of mitochondrial ribosomes. Conclusion: It is uncertain whether azithromycin is eligible for the treatment of virus infections in general and especially for COVID-19. Its combination with hydroxychloroquine, however, should be better researched in order to answer if it can be applied as a clinical approach for this matter.

Keywords: COVID-19; SARS-CoV-2; Clinical trial; Hydroxychloroquine; Azithromycin.

Resumo

Objetivo: realizar uma revisão da literatura para pesquisar as características clínicas da azitromicina, e suas indicações e associações para infecções por SARS-CoV-2. Metodologia: As buscas eletrônicas foram realizadas no PUBMED Central, BVS/ BIREME, Web of Science e The Cochrane Library com o auxílio de palavras-chave. Resultados: A azitromicina é um antibiótico seguro pertencente à classe dos macrolídeos, eficaz para um grande número de infecções, especialmente doenças respiratórias. Parece ter atividade viral indireta por ser capaz de alterar o maquinário celular, inclusive as mitocondrias, por alterar o funcionamento normal dos seus ribossomos. Conclusão: É incerto se azitromicina é elegível para o tratamento de infecções virais em geral e especialmente para COVID-19. Sua combinação com a hidroxiquina, entretanto, deve ser mais bem pesquisada a fim de responder se pode ser aplicada como uma abordagem clínica para essa questão.

Palavras-chave: COVID-19; SARS-CoV-2; Ensaio clínico; Hidroxiquina; Azitromicina.

Resumen

Objetivo: Realizar una revisión de la literatura para investigar las características clínicas de la azitromicina y sus indicaciones y asociaciones para las infecciones por SARS-CoV-2. Metodología: Se realizaron búsquedas electrónicas en PUBMED Central, BVS/ BIREME, Web of Science y The Cochrane Library con la ayuda de palabras clave. Resultados: La azitromicina es un antibiótico seguro perteneciente a la clase de los macrólidos, eficaz para un gran número de infecciones, especialmente enfermedades respiratorias. Parece tener actividad viral indirecta porque es capaz de alterar el maquinario celular, incluidas las mitocondrias, al alterar el funcionamiento normal de sus ribosomas. Conclusión: No está claro si la azitromicina es elegible para el tratamiento de infecciones virales en general y especialmente para COVID-19. Sin embargo, su combinación con hidroxiquina debe investigarse más a fondo para responder si se puede aplicar como un enfoque clínico a esta pregunta.

Palabras clave: COVID-19; SARS-CoV-2; Ensayo clínico; Hidroxiquina; Azitromicina.

1. Introduction

The 2020 pandemic named Coronavirus disease (COVID-19), a contagious respiratory disease still on going, brought back old drugs into light in an attempt to find efficient treatments to halt its devastation in the world.

In this context, azithromycin's capacity of altering ribosomal activity made it become a probable candidate to be used against a wide range of bacteria, as well as, indirectly, against virus replication, including SARS-CoV-2. Part of azithromycin success is due to its capacity of changing the cell machinery metabolism by altering the normal functioning of mitochondrias, a cell organelle present in the majority of eukaryotic and prokaryotic cells, involved in the processes of respiration and energy production. This specific feature has made it an interesting drug against COVID-19 infection.

Azithromycin is also well tolerated by the human organism showing few side effects when compared to other antibiotics. When it happens, it generally includes nausea, abdominal pain and gastrointestinal symptoms, such as diarrhea, stomach pain, hearing loss and vomiting (Hopkin, 1991). The characteristic of being toxic for mitochondrias made azithromycin be dangerous for cardiopathic patients, simply because it may cause damages, such as swelling of the cardiomyocyte mitochondrias, making it the starting point for QT prolongation and arrhythmias in some patients (Salimi et al., 2016), which may lead to sudden deaths.

The aim of this work was to accomplish a literature review concerning the main characteristics of azithromycin and its usage in virotic infections, including COVID-19.

2. Literature Review

Azithromycin is an antibiotic that belongs to the macrolide group, particularly the azalide. It was discovered in 1980, but only approved to be used in humans in 1988. Due to its potential in plasmatic concentrations and within the cytoplasm of

different cell types, it has a broad action in different sorts of pathologies that make it useful for infectious diseases, but also for the treatment of inflammatory and auto-immune diseases(Labro ,1998; Labro ,2004; Čulić et al.,2001; Amsden,2005 ; Sassa et al.,1999). Azithromycin dihydrate is an antibiotic that works by preventing bacteria sensitive to azithromycin from producing proteins, which are the basis of its growth and reproduction. Its peak of action is 2 to 3 hours after oral administration.

Due to its capacity of causing mitochondrial dysfunction, it is also indicated as antimalarial, antiparasitic in general, and antitumor agent; this latter due to its capacity of modulating TNF- α production (Peric et al.,2021; Wolter et al.,2002; Marjanović et al.,2011; Piacentini et al.,2007; Hernando-Sastre,2010). Azithromycin also shows antifungal and antiviral indications, as well as for tuberculosis treatment (Vandeputte et al.,2012; Omura S., Shiomi K.,2007; Tacar et al.,2013; Hecht, 2003; Omura,2002).

Such versatility comes from its bacteriostatic features against a vast number of Gram-positive and Gram-negative bacteria; as well as some protozoa; making it a broad-spectrum antibiotic, like the macrolide class. Azithromycin is also able to concentrate in intracellular compartments, remaining there for a considerable time; targeting especially in fibroblasts, and in some white blood cells, including and phagocytic cells from the innate immunity, such as PMN neutrophils and macrophages. Another study concludes that patients who take oral 500 mg of azithromycin show tissue concentrations 1000 times higher than plasma concentrations on Day 1(Hand W.L, Hand D.L, 2001; Kagkellaris et al.,2018; McDonald P.J, Pruul H.,1991; Matzneller et al.,2013). The dynamic of inflammation requires interactions between innate and adaptive immunities for recruitment, proliferation and arrival in the site of microbiological injury. In this sense, with the incorporation of azithromycin into the cytoplasm of inflammatory cells, it accumulates and is transported by these mobile cells to the infected tissues, which will unleash chemoattractant molecules, such as interleukins. The chemotaxis induced attracts PMN neutrophils loaded with this macrolide, accumulating it right into the surrounding tissues, combating infection properly(Amsden,2001).

Ribosomes and azithromycin

Ribosomes are tiny organelles responsible for protein synthesis. They are formed of one only type of ribonucleic acid; the ribosomal RNA, or rRNA, although each one totalizes an average of 50 proteins. When their structure is analyzed, it can be observed that it is composed of two subunits, one being virtually the double size of the other, and are made in the nucleolus, although separately. Their function consists of synthesizing proteins from amino acids that come within the cytoplasm of the cell in question by using RNA as a template, making proteins within the cytoplasm for a vast number of reasons, according to the cell needs; and can be found in free units away from each other, or aggregated in small clusters(Ramakrishnan,2014).

Ribosomes are present scattered in the cytoplasm, depending on the cell situation. Some of them are even found attached to the outer surface of the nuclear membrane, but mainly to a more complex extensively folded membrane named endoplasmic reticulum; synthesizing specific proteins for the other organelles; this is made for insertion, in the plasma membrane, or for exporting away from the same cell. While other free ribosomes synthesize proteins used in the cytosol, others are located within the mitochondria, producing mitochondrial proteins necessary for the metabolism of the cell. Depending on type of cell as well as their amount of energy production, there can be more or less ribosomes in the mitochondrias, producing mitochondrial proteins(Gerard 12th edition Principles of Anatomy and Physiology) .

Structurally, ribosomes are composed of two functional subunits. They work together in order to carry out messenger ribonucleic acid (mRNA)-directed polypeptide synthesis, in a process that require a dynamic interplay of both units with a number of other factors. In this sense, protein biosynthesis is more advanced for bacteria containing overall 70 Svedberg units meaning rate of sedimentation, or simply 70S ribosomes, which are usually composed of 30S, belonging to the small unit, and 50S to the larger one. Together both units confer the organelle stages which range from initiation and elongation, up to the

termination, and finally the recycling step. The functional stages during each step mentioned above varies dramatically depending on the cell situation. Infectious diseases, for instance, may in fact alter the differentiation depending on which injuring agent is acting (Agrawal et al.,1998).

Azithromycin intake is incorporated in the cell cytoplasm, altering ribosomal activity; more specifically, within the mitochondria. Such incorporation is due to ribosome-targeting features of macrolides in general. They express their biochemical and structural activity by blocking nascent protein progression through the exit tunnel basically. Another way is by halting the bond formation of the peptide at the peptidyl transferase center, which is the site of the peptide formation located on the surface of the ribosome; as well as the target for a chemically diverse of many antibiotics, located in the larger 50S subunit, leading into a peptide exit tunnel which goes through the body of it (Gabashvili et al.,1999).

The peptidyl transferase center is the site of peptide bond formation on the ribosome and the target for a chemically different sets of antibiotics. It is located in a cavity on the 50S subunit that leads into a peptide exit tunnel that passes through the body of this subunit. This specific site is active in a deep cleft which is involved by nucleotides from the internal loop domain V from 23S ribosomal rRNA, known as peptidyl transferase loop. The single stranded nucleotides located within the loop constitute the closest active site from the catalytic center. This bonding alters the normal metabolism of ribosomes, diminishing their effectiveness in transcribing genetic materials. Therefore, if ribosomal activity is diminished, the cell machinery is lowered in speed as protein syntheses is diminished, altering the normal metabolic functions of the cell, retarding even their division(Ogle et al.,2001). Only very small macrolides bind to this center, such as erythromycin and azithromycin, the latter being reported to show different step process of inhibiting ribosome function of some species, including human cells.

Adverse symptoms associated with azithromycin

Azithromycin dihydrate is well tolerated, usually with a low incidence of side effects. Nevertheless, side effects have been reported; although with less frequency than in other antibiotic classes.

Transient episodes of slight reduction in neutrophil count (blood defense cells), thrombocytopenia (decrease of blood clotting cells: platelets), moniliasis, vaginitis, anaphylaxis, anorexia, aggressive reactions, nervousness, agitation, anxiety, dizziness, seizures, headaches, hyperactivity, hypoesthesia, paresthesia (abnormal sensation such as burning, tingling and itching, perceived on the skin and for no apparent reason, drowsiness, fainting, rare cases of taste/smell disorders and/or loss, dizziness, hearing disorders, including hearing loss, deafness and/or tinnitus, palpitations and arrhythmias including ventricular tachycardia (acceleration of heartbeat), rare reports of QT prolongation, and Torsades de Pointes (heart rhythm disturbances), hypotension (low blood pressure), vomiting/diarrhea rarely resulting in dehydration, and dyspepsia have also been reported.

Intestinal alterations have also been reported by some patients. Constipation, colitis pseudomembranous (infection of the intestine with bacteria of the species *C. difficile*), pancreatitis, abdominal discomfort (pain/colic), flatulence, rare reports of tongue discoloration, liver dysfunction, hepatitis, cholestatic jaundice (yellowing of the skin and mucous membranes due to accumulation of bile pigments e due to obstruction), rare cases of liver necrosis (death of liver cells) and liver failure which rarely resulted in death, allergic reactions including pruritus (itching), rash (skin redness), photosensitivity,

edema (swelling), urticaria (skin allergy), angioedema, severe dermatological conditions, including erythema multiforme (red spots, blisters and ulcerations all over the body) have scarcely been reported over the

years of follow up patient outcomes throughout azithromycin clinical history. In spite of all these reports, azithromycin has shown consistent signs of being able to improve lung conditions. It been described as able to cause improvement of the pulmonary function, due to antimicrobial and anti-inflammatory activity of the macrolides in general. Nevertheless, a study carried out in canines showed that azithromycin seems to have a direct relaxant effect on precontracted rabbit airway smooth muscle (Tagaya et al.,1994).

Azithromycin and COVID-19 treatment

When the SARS-CoV-2 pandemic was officially announced on December 31st, some medications began to be used even without clinical evidence, since there was no specific treatment for the infection. In the course of the devastation caused by the illness, azithromycin began to be tested in numerous studies assessing its effect on the virus, alone or in combination with other drugs, particularly hydroxychloroquine. Although controversial, researchers have not yet found the answer for this question, but the studies continue.

Azithromycin, has thereafter been proposed as a treatment for COVID-19 pandemic, with in-vitro studies suggesting activity against some RNA viruses. Therefore, speculations of its indication for coadjuvant medicine of SARS-CoV-2 have been accomplished since the beginning of the pandemic, along with the exponential consumption and production of this macrolide (Touret et al.,2020; Oliver ME, Hinks TSC,2020)^{9,30}. Part of this speculation comes from its ability of altering the functioning of the cell machinery, lowering cell metabolism, and therefore interfering in virus replication, as mentioned above in this paper. Azithromycin is thought to increase the pH of Golgi network and recycling endosome, a fact that might interfere with the activity of SARS-CoV-2, jeopardizing its cycle within the cell. Theoretically, this capacity would be able to jeopardize SARS-CoV-2 ability to enter the cells, as it is believed to possess a furin-like cleavage site in its spike protein(Poschet et al.,2020).

Azithromycin also seems to reduce the levels of proinflammatory interleukins, such as IL-6. This interleukin promotes, among other things, vascular alterations that potentialize inflammatory signs. This very capacity would be able to interfere with the cytokine storm which is the main cause of mortalities and morbidities in COVID-19 physiopathology. Due to its excellent clinical outcome in pulmonary disorders and long term clinical use, and also for the fact that azithromycin can efficiently combat this sort of infection, it has been indicated for part of the treatment of COVID-19.

It's a common fact that interned patients develop respiratory illnesses as secondary bacterial infections due to the contaminated hospital environment. Should this situation happen, azithromycin could effectively combat the resulting infections in the majority of the patients(Min JY,Jang YJ,2012; De Lusignan et al.,2021). In fact, for primarily infections, it is indicated for the treatment of lower respiratory infections, such as bronchitis, and also for the upper respiratory tract infections, including tonsillitis/pharyngitis and sinusitis as well. The association with other drugs has also been tried. Azithromycin has been associated with hydroxychloroquine as a combination for the treatment of COVID-19. The reason for so was that both drugs have allegedly the ability to decrease cell metabolism during viral infections, decreasing SARS-CoV-2 viral load(Liu et al.,2020; Gautret et al.,2020). On the course of the disease, azithromycin and hydroxychloroquine have been prescribed by some practitioners in Brazil and Spain as a clinical approach for COVID-19; more specifically in Brazil, this fact was reinforced due to the authorization of the Brazilian national regulatory agency to use hydroxychloroquine in hospitalized patients with COVID-19 (Ministério da Saúde,2020).

The expectancy for such unusual association was due to some promising results obtained from chloroquine experiments with and without azithromycin. The former, used as hydroxychloroquine (an analogue of chloroquine), has been mentioned as being useful for the treatment of SAR-CoV-2, as clinical trials went on(WHO,2020). Controversial results have

been reached pro and against such combination, with some bias present in both opinions. For instance, some studies have used the combination in hospitalized patients, while others assessed it in the beginning of the symptoms. Most specifically in Brazil, politization has impeded experiments that might bring light to the matter, since the country is one of the most affected in absolute numbers by the pandemic; which is lamentable because randomized studies, had they been carried out, might have saved numbers of lives if confirmed positive. One way or another, at least there is a possibility that the treatment with this combination may be associated with viral load reduction, or even disappearance, in SARS-CoV-2 bearers.

In this sense, this paper concludes that more studies should be accomplished to respond the question whether azithromycin and hydroxychloroquine could be established officially as an adequate clinical approach for COVID-19.

Despite its small sample size, our survey shows that hydroxychloroquine treatment is significantly associated with viral load reduction/disappearance in COVID-19 patients and its effect is reinforced by azithromycin.

Posology

In adults, for the treatment of sexually transmitted diseases caused by *Chlamydia trachomatis*, sensitive *Haemophilusducreyi* or *Neisseria gonorrhoeae*, the dose is 1000 mg in a single oral dose. For all other indications where the oral formulation is used, a total dose of 1500 mg should be administered in 500 mg daily doses for 3 days.

3. Conclusion

Azithromycin, an antibiotic belonging to the macrolide group and used since 1980 in routine clinical practice, seems to be a worthy drug to be used not only for bacterial infections, but also for fungi and virus diseases. Due to its antivirotic activity, researchers should then investigate, through randomized double blind studies, if its characteristics are relevant enough to be used effectively against SARS-CoV-2 infections.

4. Final Considerations

Azithromycin main role in bacterial and virus infections lay on the fact that it alters ribosomal activity; especially the mitochondrial ribosomes. Such ability is attributed mainly to the macrolide molecular size that allows it to act within the mitochondrias, interfering in the cellular ability to generate energy. In this sense, the cell ATP production is temporarily damaged, which leaves the immunological system able to halt the various sorts of infections. The fact that they halt bond formation of the peptidyl transferase center on the surface of the ribosome interferes in virus replication within the cells of the human body, as well as jeopardizes cell replication of bacteria and fungi responsible for the infection. Therefore, azithromycin indication for COVID-19 treatment may not imply in cure, but may indeed help control virus replication within the cells while promotes adequate antibacterial support against secondary pulmonary infections. In this sense, this review has reached the objectives of this paper.

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