

**EMERGING DRUGS: A SYSTEMATIC REVIEW OF THE POTENTIAL
ANTIVIRAL ACTIONS OF AZITHROMYCIN**

**DROGAS EMERGENTES: UMA REVISÃO SISTEMÁTICA DAS AÇÕES ANTIVIRAIS
POTENCIAIS DA AZITROMICINA**

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ABSTRACT

INTRODUCTION: Viruses that cause respiratory infections, commonly called "flu," kill thousands of people annually. In 2020, the World Health Organization declared a pandemic state due to COVID-19 infection. The virus that causes COVID-19, SARS-CoV-2, causes acute respiratory syndrome, which currently has no established treatment and is capable of widespread dissemination. **OBJECTIVE:** Systematically provide evidence of azithromycin's pleiotropic antiviral effects. **METHODOLOGY:** Pubmed database search for articles related by the terms: "antiviral" and "azithromycin". **RESULTS:** Although there are no clinical protocols that can clearly evaluate the antiviral effectiveness of azithromycin, 73,3% of the articles found concluded that azithromycin has potential pleiotropic antiviral activity that should be further investigated. **CONCLUSION:** Azithromycin has the potential to be repurposed as an antiviral drug, however, further studies are needed for targeting the drug's action against specific viral pathogens as well as double-blind, randomized clinical trials.

Keywords: Emerging drugs. Azithromycin. Antiviral. Immunomodulatory effects.

RESUMO

INTRODUÇÃO: Os vírus que causam infecções respiratórias, comumente chamados de "gripe", matam milhares de pessoas anualmente. Em 2020, a Organização Mundial de Saúde declarou estado de pandemia devido à infecção por COVID-19. O vírus que causa o COVID-19, o SARS-CoV-2, causa a síndrome respiratória aguda, que atualmente não tem tratamento estabelecido e é capaz de ampla disseminação. **OBJETIVO:** Fornecer evidências sistemáticas dos efeitos antivirais pleiotrópicos da azitromicina. **METODOLOGIA:** Pesquisa na base de dados Pubmed de artigos relacionados pelos termos: "antiviral" and "azithromycin". **RESULTADOS:**

Embora não existam protocolos clínicos que possam avaliar claramente a eficácia antiviral da azitromicina, 73,3% dos artigos encontrados concluíram que a azitromicina tem potencial atividade antiviral pleiotrópica que deve ser investigada posteriormente. **CONCLUSÃO:** A azitromicina tem potencial para ser reaproveitada como um medicamento antiviral, no entanto, são necessários mais estudos para direcionar a ação do medicamento contra patógenos virais específicos, bem como ensaios clínicos randomizados duplo-cegos.

Palavras-chave: Medicamentos emergentes. Azitromicina. Antiviral. Efeitos imunomoduladores.

1 INTRODUCTION

Macrolides are antibiotics comprised of a group of drugs that are characterized by the presence of the macrocyclic ring lactone, to which erythromycin was considered to be the first representative drug and prototype of this class.^{1,2}

The antibacterial mechanism of action occurs through bacteriostatic properties of the drug, which binds the 50S ribosomal subunits, inhibiting protein synthesis. However, the drug may also exert bactericidal action, depending on the concentration and susceptibility of the target microorganism.³

Kanon and Rubin (2010)³ have demonstrated evidence of macrolides' immunomodulatory effects, including modulation of cytokine synthesis, expression of inflammatory cells and effects on airway secretions, in addition to the established antibacterial molecular mechanisms.

In recent years, due to pleiotropic effects of this class of drugs, macrolides has been repurposed for protocol uses in conditions that are not directly related to bacterial infections, such as asthma, cystic fibrosis, bronchiolitis and bronchiectasis not related to cystic fibrosis.⁴

The main application of macrolides is in respiratory system infections, due to superior drug



penetration and action against common intracellular pathogens, such as mycoplasma. Furthermore, macrolides' immunomodulatory properties are advantageous for prevention of exacerbated immune reactions that could trigger detrimental cytokine storms.^{5,6}

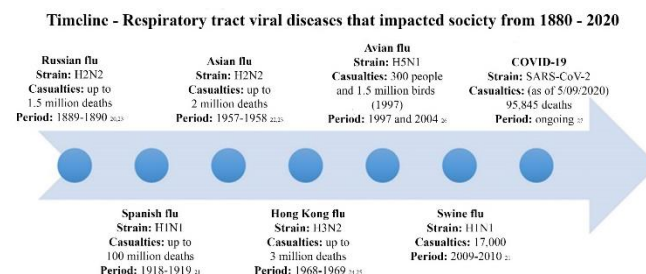
Azithromycin is one of the main representatives of this class of drugs, however it is not widely used due to its adverse side effects, which decrease patient compliance, including nausea and gastritis. However, it is considered as a crucial component in established cystic fibrosis protocols.⁷

This drug has recently aroused interest due to observations related to potential antiviral activity in addition to its antibacterial and immunomodulatory effects. Currently, clinical trials are being performed in addition to both in vitro and in vivo studies, which show remarkable antiviral activity against viruses such as Influenza A (H1N1), Zika virus and Rhinovirus. Additionally, the drug potentiates the action of mainstream antiviral therapy, such as oseltamivir, which is used against Influenza A. 8-19

Respiratory system infections tend to have high prevalence, especially among children, the elderly and the immunocompromised, who are the most vulnerable population for development of respiratory syndromes. Throughout history, there have been numerous epidemics that caused health crises in several countries. Figure 1 represents a timeline that summarizes the history of respiratory system diseases. 20-27

In 2020, the World Health Organization declared a pandemic state due to COVID-19, which currently has no established treatment and is capable of rapid widespread dissemination among humans.²⁸

Figure 1: Timeline of respiratory tract viral diseases from 1889 to 2020.



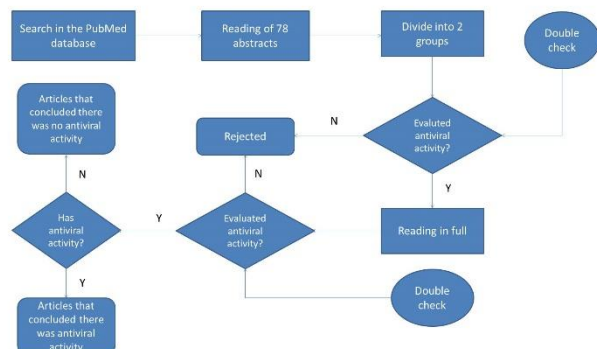
Source: Prepared by the authors, 2020.

2 METHODS

Criteria for selection of relevant literature was based on an extensive search of PubMed database. Strategy for inclusion in the search comprised of the terms "azithromycin" and "antiviral," interconnected with the Boolean term AND. The articles included in this review were published between 2007 and March 2020 and were restricted to publications in the English language. The search yielded a total of 78 articles. There was no utilization of pre-established systematic review protocols that could be implemented to carry out the present work. Lack of standardized clinical protocols for the specific evaluation of azithromycin's antiviral properties was a limitation of the present study. However, this limitation was addressed as one of the study's objectives, which aims to provide evidence for the development of novel clinical protocols that will enable further investigations of azithromycin's potential use against respiratory viral infections. Figure 2 illustrates the search strategy developed for the present work.



Figure 2: Flowchart of the scientific methodology established in the present work



Source: Prepared by the authors, 2020.

The flowchart illustrates the steps taken for selection of publications. At first, abstracts were evaluated in order to exclude those that were not related to antiviral treatments or that were addressing opportunistic bacterial diseases in patients with established viral disease. In other words, publications were excluded if they focused on antibacterial properties, anti-inflammatory or immunomodulatory evaluation and at the same time had not focused on antiviral evaluation of azithromycin. In addition, articles that aimed at prevention of viral diseases were also excluded. Review articles and case reports were not included. Two authors divided the total number of selected articles among themselves and carried out a significance assessment for the purpose of this study. Subsequently, the two authors exchanged the articles in order to independently evaluate which publications to include. Articles that fully met inclusion criteria were fully scrutinized for the assembly of the present work, totaling 16 scientific works analyzed.

thoroughly scrutinized. In the second stage, 6 of the original 22 articles were subsequently excluded for either: (a) failing to demonstrate effectiveness (or lack thereof) of azithromycin's antiviral activity, or (b) focusing solely on evaluation of inflammatory mediators with the purpose of demonstrating immunomodulatory characteristics of the drug. Overall, the assembly of the present work consisted of 15 publications. Table 1 summarizes each of the references used including objectives, results and respective conclusions that could be obtained from reported results.

Table 1: Characterization of scientific articles based on a PubMed search with the objective to evaluate azithromycin's antiviral activity.

3 RESULTS

Initially, 78 publications were selected utilizing the PubMed search, to which 22 articles were found to possibly fit the criteria and were

Reference	Objective	Results	Conclusions
Zeng et al. (2018) ²⁹	To verify antiviral activity of spiramycin and azithromycin against enterovirus A71 <i>in vitro</i> and <i>in vivo</i> .	Azithromycin was shown to inhibit viral replication in cell culture and <i>in vivo</i> .	Demonstrated safety and was shown to be a promising candidate for antiviral therapy against enterovirus A71.
Schögler et al. (2014) ⁸	Evaluate antiviral properties in respiratory airways of cystic fibrosis.	Reduction of RV1B (human rhinovirus) load and replication.	Has shown antiviral activity towards rhinovirus infection in primary bronchial epithelial cells obtained from patients with cystic fibrosis.
Li et al. (2019) ⁹	To show expression up-regulation of pathogen-recognition receptors against Zika virus.	Azithromycin inhibits Zika virus infection <i>in vitro</i> . Pretreatment with azithromycin improves the response of interferon types I and III after Zika virus infection.	Azithromycin is effective in suppressing Zika virus infection. Additionally, it is anti-inflammatory and considered safe for use during pregnancy.
Tran et al. (2019) ¹⁰	To determine whether it has antiviral activity against Influenza A (H1N1) pdm09.	Azithromycin inhibited viral activity via direct interaction. The mechanism was deduced after administration of clarithromycin, which canceled azithromycin's inhibition of viral replication.	Azithromycin has antiviral action against influenza A (H1N1)pdm09.
Wu et al. (2018) ¹¹	To propose an appropriate animal model for analyzes of neurological disorders caused by Zika virus.	Azithromycin was used as control to evaluate the ICR infant mouse model for antiviral tests. As expected, azithromycin bestowed protection against neurological diseases caused by Zika virus.	Azithromycin showed characterized anti-Zika virus activity, clearly demonstrating antiviral properties.
Sioofy-Khojine et al. (2019) ³⁰	Pre-clinical assessment for repurposing of drugs in order to target coxsackieviruses type B associated with type 1 diabetes.	Azithromycin was not shown to be effective against coxsackieviruses type B.	Azithromycin did not have antiviral activity against Coxsackieviruses type B.



Menzel et al. (2016) ¹²	To evaluate the antiviral effects induced by azithromycin in culture of bronchial epithelial cells of patients with chronic obstructive pulmonary disease.	Azithromycin increases expression of type I and III interferon induced by rhinovirus, does not exhibit cytotoxic effects, positively regulates helicases type RIG-I after viral infection, induces expression of interferons independently of viral infection, modestly reduces TNF- α gene expression and reduces viral load.	Azithromycin has antiviral activity against Rinovirus-16.
Grassly et al. (2016) ³¹	To evaluate the effects of azithromycin on immunogenicity of oral poliovirus vaccine.	Azithromycin reduced biomarkers of enteropathies, as well as enterobacteria, but not viral and eukaryotic pathogens.	Azithromycin did not show effect on the immunogenicity of oral poliovirus vaccine.
Menzel et al. (2017) ¹³	To evaluate the increased expression of rhinovirus-induced interferons in experimental models of asthma exacerbations.	Relevant concentrations of azithromycin produced antiviral effects associated with MDA5 and induced by interferons distinctly in bronchial epithelium obtained from asthmatic donors.	Azithromycin has antiviral activity via stimulation of IFN β against rhinovirus in bronchial cells of asthmatics, without affecting healthy cells.
Madrid et al. (2015) ³²	Evaluation of chloroquine and azithromycin combination therapy against Ebola virus.	Azithromycin has shown desirable antiviral characteristics, as well as high tolerability and potency in vitro. In this study, however, it showed low reproducibility in mouse models.	Azithromycin showed less antiviral efficacy when compared to chloroquine. Combination therapy was not efficient to promote recovery from disease in animal models, concluding that further studies to address dosage optimization are needed.
Fage et al. (2017) ¹⁵	To investigate whether the combination of azithromycin and oseltamivir results in additional benefits when compared to oseltamivir monotherapy against	Combination therapy did not show advantages over monotherapy, however, antiviral evaluation showed a significant reduction when compared to untreated group ($p < 0,05$).	Azithromycin demonstrated antiviral effect against Influenza A virus California/07/09 (H1N1).



	Influenza A virus (H1N1)pdm2009.		
Gielen et al. (2010) ¹⁴	To evaluate beneficial effects of macrolides in asthma exacerbations, most likely due to antiviral activity.	Azithromycin treatment resulted in a significant increase in interferon-16, induced by rhinovirus-1B and 16 and expression of interferon mRNA, which stimulated gene, as well as protein expression.	Azithromycin was shown to have antiviral activity in bronchial epithelial cells during rhinovirus infection and up-regulated gene expression of interferon.
Kneyber et al. (2007) ³³	To test whether azithromycin reduces the duration of hospitalization in mild to moderate cases of respiratory syncytial virus in disorders of the lower respiratory tract.	The difference in hospitalization time between the group that used azithromycin and the placebo was not significant. There was no resolution of clinical symptoms.	Azithromycin was not shown to be beneficial against the respiratory syncytial virus.
Bossebouef et al. (2018) ¹⁷	To evaluate whether azithromycin has antiviral activity against Zika virus <i>in vitro</i> .	Azithromycin (50 mg / L) prevents Zika virus replication for 48 hours after infection. Replication is also inhibited when repeated dosage was used in the same concentration.	Azithromycin has antiviral activity against Zika virus.
Retallack et al. (2016) ¹⁶	Evaluate Zika virus cell tropism in the developing human brain and inhibition of the virus by azithromycin.	Reduction of Zika virus infection.	Azithromycin is a promising and safe candidate drug that has antiviral activity against Zika virus.

Source: Prepared by the authors, 2020.

4 DISCUSSION

Taking into consideration the data in Table 1, 73,3% (11 out of 15) of the selected publications have demonstrated that azithromycin has antiviral activity. Two limitations of the studies are the absence of a double blind and placebo control randomized clinical protocol, as well as the absence of an outcome analysis related to in vivo and in vitro studies. Among the positive studies, it is noteworthy that four references concluded that azithromycin has promising antiviral activity and is considered as safe for use during pregnant in the treatment of Zika virus infection. 9,11,16,17 This is an important aspect of the drug, since Zika virus can cross the placenta, reach the fetus and may cause teratogenic effects, such as microcephaly. 16 There are four studies that have demonstrated antiviral activity against rhinoviruses. 8,12,13,14 Two studies have demonstrated antiviral activity against Influenza A (H1N1). 10,15 On a smaller scale, a study using azithromycin demonstrated antiviral effect against enterovirus A17. 22

Azithromycin was also shown to have an antiviral effect against Ebola virus, however, a mouse animal model failed to show treatment effectiveness. It is important to note that in this study, the authors stated that no animal model had been available that could provide susceptible reproducibility for the method. Furthermore, analysis of available drugs has shown that azithromycin was proven to be safe, having with a lower toxicity rate when compared to chloroquine, which in turn, had better antiviral activity against Ebola virus, but greater toxicity. 32

In the study by Kneyber et al. (2007), 33 it was concluded that azithromycin did not show to be advantageous for treatment of respiratory infection that is caused by syncytial viruses. However, the study had not evaluated antiviral activity. The study only mentioned about possible benefits in relation to azithromycin treatment and reduced hospitalization time.

The article by Grassly et al. (2016) 31 there was also no direct evaluation of the drug's antiviral actions against poliovirus. The study mentioned whether there would be effects on the immunogenicity of the vaccine. However, the authors declared potential antibacterial effects, mainly against enterobacteria and they have

mentioned that the drug did not have antiviral activity nor activity against eukaryotic cells.

The publication by Sioofy-Khojine et al. (2019) 30 had as objective the evaluation of azithromycin's potential antiviral activity against Cocksackievirus type B. The authors concluded that azithromycin does not have antiviral action against the tested virus.

Two publications were excluded from the present study because they did not assess antiviral activity, only if the combination of oseltamivir and azithromycin could be more beneficial than oseltamivir monotherapy for the treatment of Influenza A (H1N1). It is not clear whether azithromycin had antiviral activity in either or both studies, however it is suggested in the interpretation of the results that antiviral effects could be present. Further investigations are needed in order to elucidate azithromycin's antiviral activity against Influenza A (H1N1). 18, 19

In several other studies that were excluded from the present analysis, the evaluation of azithromycin's immunomodulatory effects were widely characterized. The drug was shown to not only possess widespread antimicrobial activity, but also to be effective in the attenuation of inflammatory responses, modulating cytokines and increasing the expression of antiviral interferons. Furthermore, these desirable characteristics denominate the drug as a promising candidate for the treatment of respiratory diseases. 4, 12, 14, 15, 34-36

A classical approach towards the development of antiviral drugs is the discovery of agents that directly bind/inhibit viral particles. Classical antiviral drugs tend to have narrow ranges of drug action. The efficacy of such drugs is further limited by the fact that many viruses mutate frequently and quickly fall out of the drug's interacting range. Repurposing macrolides as possible antiviral agents uses a newer approach to antiviral drug development, which is to strategically target host cell factors, and not only direct interaction with viral particles. When drugs are directed towards cellular components, they have the potential to be effective against unrelated viruses, since those viruses need common host cellular components for proper replication and budding. Azithromycin has been shown to possess antiviral actions against unrelated viruses supposedly via shared cellular



antiviral pathways. Examining mechanisms of antiviral action, azithromycin is believed to act in the middle or late stage of viral replication cycles. Some studies have shown that azithromycin blocks the Raf / MEK / ERK intracellular signaling pathway, especially in signaling involving ERK1/2 phosphorylation, which is a process involved in the export of viral ribonucleotide complexes from the nucleus to the cell surface, enabling the formation of new virions. Other studies have suggested that azithromycin stimulates antiviral cytokines and interferon expression genes, but simultaneously suppresses pro-inflammatory cytokines such as IL-6, CXCL8 / IL-8 and TNF without interfering with viral clearance. Possessing both immunomodulatory and antiviral effects, azithromycin becomes a promising drug for the integration of new therapeutic protocols, since it has the potential to influence both the attenuation of symptoms and direct treatment against pathogens. 8, 14, 28, 37-41

5 CONCLUSION

Based on the present study, it can be considered that azithromycin has antiviral activity. The present work makes is based on the hypothesis that azithromycin has potential antiviral action and that it is feasible to integrate protocols against viral pathogens, however, further tests need to be performed for both the characterization of antiviral as well as and immunomodulatory effects of the drug. Therefore, based on the cited bibliographic survey, improvements in clinical investigations that employ randomized and double-blind trials are of high interest for elucidations as to whether azithromycin's antiviral effects can be instrumental as therapy against several virus.

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