



# A short focus, azithromycin in the treatment of respiratory viral infection COVID-19: efficacy or inefficacy?

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## Abstract

Azithromycin is a macrolide antibiotic. Recent evidence has demonstrated *in vitro* activity against a wide variety of respiratory tract viruses, including SARS-CoV-2 responsible for the current global pandemic COVID-19. A mechanism of action acting on different phases of the viral cycle is assumed. In addition to its *in vitro* antiviral properties, some evidence also suggests immunomodulatory and antifibrotic activity. These properties of azithromycin could be useful in the treatment of viral respiratory tract infections such as COVID-19. However, clinical data on the antiviral efficacy of azithromycin in the treatment of respiratory tract infections are inconsistent, both when used as monotherapy and in polypharmacological combination. In addition, cases of azithromycin-induced QT long and malignant arrhythmias are reported. In this short review, we attempt to determine the role of azithromycin in the treatment of viral respiratory tract infections such as COVID-19, therapeutic efficacy, or inefficacy?

**Keywords** Azithromycin · Pneumonia · Pulmonary · Virology

## Introduction

To date, there are no antivirals directed against SARS-CoV-2 [1, 2]. Pharmacological treatments used are directed at avoiding serious complications of infection [3–6]. Antiviral and immunomodulatory agents used are some of the pharmacological options proposed [7–10]. Various pharmacological agents such as remdesivir, dexamethasone, colchicine, baricitinib, and tocilizumab have been studied, with mixed results [11–14]. In view of the viral cycle of SARS-CoV-2, several potential molecular targets for the use of antiviral agents can be considered. One molecular target could be the inhibition of endocellular penetration of the virus by acting on the entry receptor ACE-2 [15–17], the (S) spike protein, and the transmembrane serine protease type II (TMPRSS2). Another target is the inhibition of viral replication by acting

on virus proteinases. In addition, another molecular target is represented by viral structural proteins such as envelope protein E or membrane protein M [18, 19]. In association with drugs with SARS-CoV-2 antiviral activity, pharmacological agents directed at reducing the generalized hyperinflammatory state caused by the cytokinic storm are used. In general, for all of these pharmacologic agents, the clinical evidence is conflicting [20]. Among the clinical trials conducted, only remdesivir and corticosteroids improved clinical outcomes in patients hospitalized with SARS-CoV-2. Azithromycin is an antibacterial of the macrolide class; some evidence has associated potential antiviral and immunomodulatory therapeutic efficacy, in monotherapy and in combination, for the treatment of SARS-CoV-2 infection [21], although further clinical evidence is needed to demonstrate the true therapeutic role of azithromycin in viral infections of the respiratory tract.

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## Azithromycin in the treatment of respiratory viral infections

*In vitro* evidence has shown for azithromycin antiviral activity against many respiratory viruses [22]. Azithromycin use inhibited rhinovirus replication at 10 and 50  $\mu\text{M}$  [23]. In

Zika virus, the use of azithromycin showed an EC<sub>50</sub> of 1.23–6.59  $\mu\text{M}$  [24]. Azithromycin also showed in vitro antiviral activity against SARS-CoV-2 with an EC<sub>50</sub> of 2.12  $\mu\text{M}$ , an EC<sub>90</sub> of 8.65  $\mu\text{M}$ , and a cytotoxic concentration of 50% > 40  $\mu\text{M}$ . In addition, azithromycin has been associated with immunomodulatory properties [25], which could be potentially useful in the treatment of the hyperinflammatory state caused by the cytokine storm in the most severe stages of COVID-19. In vitro, azithromycin showed a decrease in the secretion of proinflammatory cytokines and chemokines, decreasing the concentration of IL-1 $\beta$ , IL-4, IL-5, IL-6, TNF- $\alpha$ , and GM-CSF [26] and increasing the release of an anti-inflammatory cytokine (IL-10) related to the repair of inflamed tissues [27]. In lymphocytes, azithromycin was shown to suppress the activation of CD4 + T cells. Azithromycin also has been shown to reduce the accumulation of inflammatory cells in the bronchoalveolar lavage [28]. In addition in fibroblasts, it has been shown to inhibit proliferation and collagen production by reducing the concentration of transforming growth factor (TGF- $\beta$ ) and demonstrating pulmonary antifibrotic activity [29, 30]. Finally, azithromycin is associated with a mucoregulatory effect, reducing mucus hypersecretion and improving mucociliary clearance [31]. Several mechanisms of antiviral action against SARS-CoV-2 have been proposed. Among them, studies have suggested that azithromycin may alter ACE2 glycosylation and prevent endocellular penetration of the virus. Another proposed mechanism of antiviral action suggests that azithromycin is a GM1 ganglioside-mimetic. The SARS-CoV-2 spike protein shows a binding site to gangliosides; azithromycin binding to this target prevents the virus spike protein from reaching gangliosides on the host plasma membrane [32].

## Clinical efficacy

A clinical study demonstrated that signs and symptoms of SARS-CoV-2 infection were significantly reduced in response to a treatment regimen containing hydroxychloroquine and azithromycin. The most common side effects reported were stomach pain, hypoglycemia, dizziness, pruritus, rash, and QT prolongation [33]. Another study conducted demonstrated the efficacy of the combination of hydroxychloroquine and azithromycin on both viral clearance and shorter hospitalization time for COVID-19 patients [34]. Another study conducted in 16,442 hospitalized SARS-CoV-2 patients demonstrated that azithromycin did not improve survival or other prespecified clinical outcomes concluding that the use of azithromycin in hospitalized COVID-19 patients should be limited to patients in whom there is a clear antimicrobial indication [35]. A large study conducted demonstrated that the findings do not justify the routine use of azithromycin to

reduce recovery time or risk of hospitalization for persons with suspected SARS-CoV-2 infection [36]. These findings have important implications, as inappropriate antibiotic use leads to increased antimicrobial resistance. However, the risk benefit profile of azithromycin in severe COVID-19 patients has yet to be fully identified. To date, there are many ongoing registered clinical trials regarding the use of azithromycin alone or in combination for SARS-CoV-2 infection treatment.

## Safety

The therapeutic treatment of SARS-CoV-2 infection is complex and involves the administration of multiple pharmacologic agents. Polypharmacy may increase the risk of drug-drug interactions. The most common side effects reported during treatment with azithromycin are gastrointestinal, such as diarrhea, abdominal pain, and nausea. However, some macrolides are well-known to be primogenic. The proarrhythmogenic effects of azithromycin have been demonstrated in preclinical trials showing that azithromycin increases the QT interval and the duration of the action potential [37, 38]. Several observational studies have investigated the association of cardiovascular death (as a potential consequence of QT prolongation) with azithromycin use. In light of the data described above, any administration of azithromycin and hydroxychloroquine, and azithromycin in association with remdesivir, should be carefully monitored, as these are drugs that may prolong QT. In the largest reported cohort of patients with coronavirus disease 2019 to date treated with chloroquine/hydroxychloroquine  $\pm$  azithromycin, no cases of torsade de pointes or arrhythmogenic death were reported. Although the use of these drugs has resulted in QT prolongation, physicians have rarely had to discontinue therapy [39]. In addition, dosage modification should also be considered for azithromycin in cases of decreased hepatic and renal function to avoid increased plasma concentrations and risk of QT long. The risk of drug-induced arrhythmias is much higher in critical COVID-19 patients. In addition, silent genetic variants of QT long, present in approximately 4% of people, may make a person more vulnerable to malignant and fatal arrhythmias from azithromycin. Finally, in the severe COVID-19 patient, other risk factors that may cause arrhythmias in the COVID-19 patient should be considered, for example, hypokalemia, profound hypoxemia, and cytokine storm [40, 41] (Table 1).

## Discussion

Azithromycin has, in addition to antibacterial effects, antiviral and immunomodulatory properties that could be useful in the treatment of the various stages of SARS-CoV-2 infection. Although the use of azithromycin has been associated

**Table 1** Pharmacological agents with antiviral activity against COVID-19

Drugs	Mechanism of action against Sars-CoV-2	Inhibition of SARS-CoV-2 in vitro 50% inhibitory concentration (IC50) $\mu$ M	Dose used for the treatment of SARS-CoV-2	Side effects
Azithromycin	Alter ACE2 glycosylation and prevent endocellular penetration of the virus, GMI ganglioside-mimetic	2.12	500 mg/day	Stomach pain, hypoglycemia, dizziness, pruritus, rash, and QT prolongation
Remdesivir	RNA-dependent RNA polymerase inhibitor	26.90	A 10-day course of remdesivir treatment, 200 mg intravenously on day 1, 100 mg for the next 9 days	None noted (similar to placebo in severe COVID patients)
Chloroquine/hydroxychloroquine	Binds sialic acids and gangliosides	4	Chloroquine: 500 mg daily for 10 days. HCQ: weight > 50 kg, 500 mg $\times$ 2/day for 7 days; weight < 50 kg, 500 mg $\times$ 2/day on days 1 ~ 2, 500 mg/day on days 3 ~ 7	Hemolytic anemia, cardiomyopathy, neutropenia, GI disturbances, retinopathy, rash, QT prolongation
Lopinavir/ritonavir	Lopinavir: protease inhibitor Ritonavir: protease inhibitor and inhibitor of CYP3A4	26.10 > 100	Oral, 400 mg/100 mg, twice daily	QT prolongation, CV events, dyslipidemia, liver injury, GI disturbances
Darunavir	3CL protease inhibitor, substrate of CYP3A4	> 100	800 mg/day	Liver injury, dyslipidemia, sulfonamide allergy
Favipiravir	Nucleotide analogue inhibitor of the SARS-CoV-2 RNA polymerase	> 100	1600 mg twice daily on the first day followed by 600 mg twice daily	Increased hepatic enzymes, nausea and vomiting, tachycardia, and diarrhea
Oseltamivir	Neuraminidase inhibitors	> 100	75 mg BID	Diarrhea nausea vomiting abdominal or stomach pain

with clinical improvements in several viral infections of the respiratory tract, for the treatment of SARS-CoV-2 infection to date, the clinical evidence does not coincide with the in vitro evidence. Azithromycin in fact has shown in vitro antiviral activity against SARS-CoV-2, acting at different points of the viral cycle including the binding or activation of the fusion process by lysosomal proteases. Furthermore, given that in the most severe stages of SARS-CoV-2 infection the hyperinflammatory state caused by the cytokine storm is responsible for the severe lesions, the potential of azithromycin to reduce cytokine production, preserve epithelial integrity, and prevent lung fibrosis could play an important role. Probably the paucity of clinical efficacy data for azithromycin is a consequence of this macrolide being mostly administered with hydroxychloroquine, which has been shown to provide no benefit in the treatment of SARS-CoV-2 pneumonia. In addition, the paucity of clinical data also stems from the failure to identify an optimal dose of azithromycin. According to the RECOVERY study, in severe patients, 500 mg/day should be used. However, in view of the pharmacokinetic properties of azithromycin to concentrate in the respiratory tract and lungs, allowing the achievement of optimal and prolonged therapeutic concentrations, and that immunomodulatory and antiviral actions could be achieved with lower doses, one could consider the hypothesis that the benefits obtained with this macrolide could be obtained with lower and safer doses. Future clinical trials will determine the optimal dose of this drug in this context. Finally, azithromycin has not yet been adequately studied in which subgroup of patients it might offer the greatest clinical benefit.

## Conclusions

In the context of pharmacological treatment of SARS-CoV-2 infection, azithromycin has demonstrated inconsistencies between in vitro and clinical evidence. Azithromycin has a well-known safety profile, some safety concerns have been raised because of its potential cardiotoxicity, especially when combined with hydroxychloroquine, in COVID-19 patients.

To date, there is no clear evidence demonstrating the efficacy of azithromycin use in COVID-19 patients; further clinical trials are needed to identify the optimal dose in COVID-19 patients. The use of drugs with potential proarrhythmic effect such as azithromycin in severe COVID-19 patients should be carefully monitored.

**Author contribution** All authors contributed equally to the manuscript and had the opportunity to revise and approve the final text.

## Declarations

**Ethics approval and consent to participate** Not applicable.

**Consent for publication** No available supporting data.

**Conflict of interest** The authors declare no competing interests.

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