



Azithromycin in COVID-19 Patients: Pharmacological Mechanism, Clinical Evidence and Prescribing Guidelines

Janet Sultana¹ · Paola Maria Cutroneo¹ · Salvatore Crisafulli¹ · Gabriele Puglisi¹ · Gaetano Caramori¹ · Gianluca Trifirò¹

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Abstract

The global COVID-19 pandemic has led to a race to find medications that can improve the prognosis of the disease. Azithromycin, in association with hydroxychloroquine or chloroquine, has been proposed as one such medication. The aim of this review is to describe the pharmacological mechanism, clinical evidence and prescribing guidelines concerning azithromycin in COVID-19 patients. There is weak evidence on the antiviral and immunomodulating effects of azithromycin, which in addition is not based on results from COVID-19 patients specifically. Therefore, this antibacterial should be considered only as empirical treatment of community-acquired pneumonia (CAP), although not all current treatment guidelines are in agreement. After the initial expectations raised by a small trial, more recent evidence has raised serious safety concerns on the use of hydroxychloroquine or chloroquine with azithromycin to treat COVID-19 patients, as all these drugs have arrhythmogenic potential. The World Health Organization has not made recommendations suggesting the use of azithromycin with hydroxychloroquine or chloroquine as treatment for COVID-19, but some national organisations have taken a different position, recommending this as first-line treatment. Several scientific societies, including the American College of Cardiology, have cautioned about the risks of this treatment in view of the lack of evidence concerning its benefits.

Key Points

Azithromycin has been proposed as a drug to treat COVID-19 infection, although this drug has torsadogenic potential which is cause for concern, especially if concomitantly administered with hydroxychloroquine/chloroquine

There is currently no evidence to support the efficacy of azithromycin treatment in COVID-19 infection, as completed trials are methodologically flawed and underpowered

Major public health organisations, drug regulatory agencies and scientific societies do not recommend the use of azithromycin as a drug to treat COVID-19 infection, unless bacterial superinfections occur

1 Introduction

The global COVID-19 pandemic has led to 9,400,295 infected patients and 482,468 deaths worldwide between 31st December 2019 and 25th June 2020, according to the European Centre for Disease Control [1]. This public health emergency has triggered a race to find medications to improve the prognosis of disease. In turn, this has led to a tug of war between proponents of the conservative approach of not using medications in COVID-19 infection unless their risk–benefit profile has been scientifically proven and the proponents of the non-conservative approach proposing to offer new treatment even in absence of strong scientific evidence, on the basis of clinical intuition or in vitro findings only [2]. Making such decisions under the pressure of a pandemic is not easy. On one hand, scientific evidence is needed to confirm that the benefits of treatment outweigh the risks, but on the other hand, the clinical trials needed to do this can be difficult to plan, implement and ultimately generate robust scientific evidence in a short time. There is currently great interest in drug repurposing or repositioning to manage COVID-19 infection, that is, the evaluation of the usefulness of a drug for an indication different to that for

✉ Gianluca Trifirò
trifirog@unime.it

¹ Department of Biomedical and Dental Sciences and Morphofunctional Imaging, University of Messina, Messina, Italy

which it was marketed. One such case is the use of the macrolide azithromycin, often in association with the disease-modifying anti-rheumatic drugs hydroxychloroquine/chloroquine, in COVID-19 patients. It is important to critically analyse the available evidence in favour or against the use of azithromycin, in particular in association with hydroxychloroquine/chloroquine, in COVID-19 patients, both in terms of benefit and risk. At present, the World Health Organization (WHO) as well as the European Medicines Agency (EMA) have indicated the lack of evidence supporting the efficacy of any medication in COVID-19 [3, 4].

Clinical evidence on the antibacterial effect in community-acquired pneumonia (CAP) as well as immunomodulating and antiviral actions as a rationale for the use of azithromycin in COVID-19 are reviewed and prescribing guidelines discussed in detail. The main risks underlying the use of this antibacterial, that is, torsadogenic potential, especially in association with hydroxychloroquine/chloroquine, is also described.

2 The Potential Role of Azithromycin in COVID-19 Infection: A Pharmacological Perspective

The strongest evidence of effectiveness for azithromycin concerns its role as an antibacterial drug. Although there is no direct evidence of the effectiveness of azithromycin in COVID-19, some scientific bodies have suggested that the antibacterial properties of azithromycin remain clinically useful in the empirical treatment of CAP occurring in COVID-19 patients. Not all current treatment guidelines agree on azithromycin use in CAP. There is weak evidence on the antiviral and immunomodulating effects of azithromycin, which in addition was not derived from persons with COVID-19 specifically. The available evidence is discussed below.

2.1 Antibacterial Effect in Bacterial Community-Acquired Pneumonia

In most patients with suspected or confirmed SARS-CoV-2 infection, lung damage correlates with the severity of viral infection; however, bacterial co-infection has been reported in several patients affected by COVID-19 pneumonia [5–7]. Thus, some guidelines have been adapted in the context of the COVID-19 pandemic to promote the appropriate use of antibiotics and to delineate the role of these drugs, including azithromycin, in COVID-19 patients.

The United Kingdom's National Institute for Health and Care Excellence (NICE) has developed a guideline aiming to improve antibiotic prescribing in COVID-19 patients with concomitant bacterial CAP or hospital-acquired pneumonia

(HAP) [8]. In the absence of bacterial co-infection, antibiotic therapy is contraindicated for COVID-19 pneumonia, because it would be ineffective, considering its viral aetiology. Therefore, according to NICE the use of antibiotics should be limited only to the management of those situations in which bacterial pulmonary co-infections are suspected or confirmed. The decision-making process in choosing antibiotic therapy should be based on clinical tests, such as microbiological tests, chest imaging, complete blood count, urine tests for legionella and pneumococcal antigens. Moreover, for the treatment of severe bacterial CAP in COVID-19 patients, the NICE guideline suggests the use of clarithromycin among macrolide antibiotics, in association with co-amoxiclav, orally or intravenously, or in co-administration with cefuroxime as an alternative to co-amoxiclav. Although, in a systematic review, it was found that the clinical efficacy and number of adverse events of azithromycin was not significantly different from clarithromycin in adults with low- to moderate-severity CAP [9], azithromycin is not recommended for the treatment of CAP or HAP in the NICE guideline because its long half-life could increase the risk of antibacterial resistance [10]. However, in another guideline on the treatment of bacterial CAP in COVID-19 patients proposed by the American Thoracic Society (ATS) and Infectious Diseases Society (IDS), antibiotic macrolides are recommended as first-line therapy in combination with β -lactams in low-risk patients, and both azithromycin and clarithromycin are indicated [5].

The use of azithromycin alone to prevent bacterial co-infections in COVID-19 patients is not supported by the above-mentioned guidelines adapted for the SARS-CoV-2 pandemic. According to the NICE guidelines, antibiotic therapy should be limited only to COVID-19 patients where bacterial co-infection is suspected or confirmed [8].

2.2 Immunomodulating Effect

Since cytokine release syndrome (CRS), also known as cytokine storm, seems to be a major driver of mortality in COVID-19, several drugs with immunomodulating activity have been proposed as potential agents to be repurposed for the treatment of COVID-19 patients [11]. Indeed, several immunomodulatory effects of azithromycin have been found in many experimental studies [12–14]. It has been demonstrated that in mammalian cells, azithromycin influences intracellular mitogen-activated protein kinase (MAPK), in particular extracellular signal-regulated kinases 1/2 (ERK1/2) and the NF- κ B pathway downstream of ERK [12]. Because these pathways are involved in many cellular functions, including inflammatory cytokine production, cell proliferation and mucin secretion, effects on ERK1/2 and NF- κ B can explain most of the reported

immunomodulatory effects of the macrolides [12]. Due to these immunomodulatory effects, azithromycin has proven effective in the management of several chronic lung diseases, such as cystic fibrosis (CF), non-CF bronchiectasis, chronic obstructive pulmonary disease, chronic rhinosinusitis, sepsis and diffuse panbronchiolitis [12, 13].

In murine experimental models of *Pseudomonas aeruginosa* lung infection and lipopolysaccharide-induced inflammation, studies described a reduction of lung leukocytes, inflammatory cytokines, levels of myeloperoxidase, tumour necrosis factor (TNF)- α and interleukin (IL)-1 β and a change of macrophage activation [12, 14]. The cytokine storm and the excessive immunological response are considered to be the main cause of morbidity and mortality in viral pneumonia caused by the severe acute respiratory syndrome (SARS) and MERS coronaviruses, as well as for SARS-CoV-2. Therefore, modulation of the inflammatory response may theoretically reduce the complications of viral pneumonia [11]. However, the use of immunomodulatory agents, such as corticosteroids, in patients with SARS has not shown significant beneficial effects [15]. However, very recently announced results from the Oxford University Recovery Trial seem to suggest that dexamethasone reduced mortality among patients receiving invasive mechanical ventilation or oxygen, but not among those not receiving respiratory support [16]. There is also no evidence that the use of azithromycin in COVID-19 mitigates the cytokine storm.

2.3 Antiviral Effect

Azithromycin is also thought to have antiviral properties that may work in synergy with antiviral drugs. Preclinical studies have found that this macrolide antibiotic can exert antiviral effects against Zika virus, rhinovirus and Ebola virus [17–20]. However, antiviral effects specifically in COVID-19 patients have not yet been demonstrated. Clinical studies on the use of azithromycin in patients with pneumonia caused by respiratory viruses had conflicting findings. In a multi-centre, open-label, randomised clinical trial conducted among patients with influenza A, a combination therapy of oseltamivir plus azithromycin (2 g/day, extended-release formulation) was associated with improvement of some influenza-related symptoms, but with no difference in inflammatory cytokine levels [21]; furthermore, the azithromycin dosage used in this study was higher than that recommended by the ATS guideline. There is also limited evidence concerning the usefulness of azithromycin in viral infections that are similar to COVID-19 infection. A retrospective cohort study conducted in 14 tertiary-care hospitals in five cities in Saudi Arabia from 2012 to 2018 [22] demonstrated that in 349 patients with laboratory-confirmed Middle-East Respiratory Syndrome (MERS), caused by a

coronavirus similar to SARS-CoV-2, treatment with macrolides (97 patients treated with azithromycin, 28 treated with clarithromycin and 22 treated with erythromycin) was not associated with a reduction in 90-day mortality (adjusted odds ratio 0.84; 95% confidence interval (CI) 0.47–1.51; $p=0.56$) or improvement in MERS-CoV RNA clearance (adjusted hazard ratio 0.88; 95% CI 0.47–1.64; $p=0.68$). To date, there is no robust evidence on the effectiveness of azithromycin (plus hydroxychloroquine/chloroquine) for COVID-19, alone or in combination, even for the treatment of viral infections similar to SARS-CoV-2.

3 Clinical Evidence on the Role of Azithromycin in COVID-19 Patients

The main clinical ‘evidence’ concerning the benefit of azithromycin with or without hydroxychloroquine or chloroquine in COVID-19 infection comes from an open-label non-randomised trial in France recruiting 42 hospitalised persons with COVID-19 over 14 days. Patients were treated with hydroxychloroquine 600 mg daily with add-on azithromycin (500 mg on day 1 followed by 250 mg per day for the next 4 days) in six patients to prevent bacterial superinfection. The investigators found that on day 6 after enrolment, 100% of patients treated with hydroxychloroquine and azithromycin ($n=6$) had no detectable viral load, compared with 57.1% in patients treated with hydroxychloroquine monotherapy ($n=14$) and 12.5% in the control group ($n=16$) ($p<0.001$). There are several methodological issues with this paper that have been described in detail elsewhere, including poor reporting, missing PCR data and unjustified exclusion of patients with clinically important outcomes [23]. These limitations critically affect the quality of this study, making the reliability of the results obtained questionable. A conflicting finding was reported in a recent small French study on eleven COVID-19 patients who were treated with hydroxychloroquine plus azithromycin, at the same dosage used by Gautret et al. Of these 11 patients, one died, two were transferred to intensive care and one developed a prolongation of QT interval and interrupted the treatment. By the end of the study, eight patients (73%) were still positive for SARS-CoV-2, 5–6 days after the start of treatment [24]. Like the trial by Gautret et al., this trial was also limited by the very small population and the lack of randomisation. A recent observational study has also raised concerns about the benefits of hydroxychloroquine/chloroquine, used alone or with a macrolide, in COVID-19 patients. One study enrolled 1438 hospitalised patients with a diagnosis of COVID-19. Of these, 735 (51.1%) received hydroxychloroquine plus azithromycin, 271 (18.8%) received hydroxychloroquine alone, 211 (14.7%) were treated with azithromycin alone and 221 (15.4%) were treated with other drugs. Adjusted

statistical analyses showed no significant differences in in-hospital mortality for patients receiving hydroxychloroquine plus azithromycin, hydroxychloroquine alone or azithromycin alone, compared with patients receiving neither drug [25].

Major scientific societies, drug regulatory agencies and public health organisations have not recommended the use of azithromycin in COVID-19, to our knowledge. For example, the WHO and EMA have not issued any statement about the safety and efficacy of this combination in COVID-19 infection. The Italian Drug Agency (AIFA) stated that the use of azithromycin, alone or in combination with hydroxychloroquine/chloroquine, for the treatment of COVID-19 patients is not recommended, unless bacterial superinfections occur [26]. However, the benefit–risk profile of these drugs in COVID-19 patients is still coming to light. To date there are 20 ongoing clinical trials concerning the use of azithromycin, alone or in combination with other drugs, in COVID-19 registered in clinicaltrials.gov.

4 Torsadogenic Effects of Azithromycin

Given the limited evidence on the benefits of azithromycin (with or without hydroxychloroquine/chloroquine) in COVID-19 patients or even as a first-line agent for CAP, it is imperative to weigh its risks. Some macrolides are well known to be arrhythmogenic, notably erythromycin [27–32]. Azithromycin is believed to be one of the safest macrolides [33] but there is conflicting information on the risk of arrhythmia. At the pre-clinical level, the proarrhythmogenic effects of azithromycin were investigated in different animal models (guinea pigs, rabbits and dogs), showing that azithromycin is not associated with torsades de pointes (TdP) or early afterdepolarisations, although this drug increases QT interval and monophasic action potential duration [34–36].

Clinical studies suggest that azithromycin does not alter the risk of cardiac events as was shown in two randomised controlled trials evaluating the efficacy of antibiotic therapy with azithromycin for the secondary prevention of coronary events [37]. These results were further confirmed by two meta-analyses of randomised clinical trials showing that azithromycin was not significantly associated with either a reduction of the frequency of recurrent cardiac events [38] or with an increased risk for mortality or cardiovascular events in patients with coronary artery disease [39]. However, there are several case reports describing QT-interval prolongation [40–42], TdP [43–45] and polymorphic ventricular tachycardia [46] during treatment with azithromycin. These proarrhythmogenic effects are pharmacologically plausible [47].

Moreover, there is evidence from post-marketing surveillance data supporting concerns about the potential torsadogenic effects azithromycin. A pharmacovigilance

study analysed the FDA Adverse Event Reporting System (FAERS) from 2004 to 2011 and identified a total of 203 reports of arrhythmia-related events (e.g. QT prolongation, TdP, ventricular arrhythmia, sudden cardiac death) associated with azithromycin [48]. The public version of Eudravigilance, the European Medicines Agency's Adverse Drug Reactions (ADR) database (<http://www.adrreports.eu/en/search.html>), has 188, 87 and 55 cases of QT prolongation in patients treated with azithromycin, hydroxychloroquine and chloroquine, respectively, out of a total of 12,764, 15,129 and 1644 reports for each suspected drug (Table 1). In addition, several observational studies investigated the association of cardiovascular death (as a potential consequence of QT prolongation) with azithromycin use. These studies report conflicting evidence [49–56]. There is very limited and contrasting real-world evidence concerning the risk of azithromycin use and ventricular arrhythmia [57–59].

In light of the above-mentioned data, caution is warranted if azithromycin is used concomitantly with chloroquine or hydroxychloroquine to treat COVID-19, as both drugs have known risk of TdP [60]. There is increasing and contrasting data evaluating the safety of combination therapy. A recent observational study evaluated the effects of the association of azithromycin with chloroquine or hydroxychloroquine on QT interval in 201 COVID-19 patients. Of these, ten patients (5.0%) received chloroquine, 191 (95.0%) were treated with hydroxychloroquine and 119 (59.2%) also received azithromycin. The authors found that, although the maximum QT during treatment was significantly longer in the combination group compared with the monotherapy group (470.4 ± 45.0 ms vs 453.3 ± 37.0 ms; $p = 0.004$), no instances of TdP or arrhythmogenic death were reported [61]. However, these findings have been refuted by several recent studies evaluating the effects of this association on QT interval in COVID-19 patients. These studies indicate that the use of azithromycin with chloroquine/hydroxychloroquine could significantly prolong QT interval, especially in patients affected by severe COVID-19 and in the presence of comorbidities, suggesting using this association with caution [62–66]. According to the Liverpool Drug Interactions group, electrocardiogram monitoring is recommended in patients treated with chloroquine/hydroxychloroquine and other QT-prolonging drugs including azithromycin [67]. No interactions are reported for other classes of antimicrobials such as penicillins or cephalosporins, which may therefore be a safer therapeutic alternative to azithromycin, even when combined with chloroquine/hydroxychloroquine.

The risks of combining torsadogenic drugs such as azithromycin and hydroxychloroquine/chloroquine were highlighted by several scientific societies or drug agencies. On 30 March 2020, the French drug safety agency (ANSM) warned of potentially serious side effects, in particular cardiac risk, of treatments being tested against the new

Table 1 Number of individual safety case reports in Eudravigilance for serious cardiac arrhythmias during azithromycin, hydroxychloroquine and chloroquine treatments at 30 May, 2020

	Azithromycin	Hydroxychloroquine	Chloroquine
Overall reports in Eudravigilance	12,764	15,129	1644
Arrhythmia ^a	109	63	14
Cardiac arrest	93	46	33
Torsades de pointes	50	22	11
Atrioventricular block ^b	20	51	62
ECG QT prolonged	271	245	71
Long-QT syndrome	24	17	
Ventricular fibrillation	45	21	17

ECG electrocardiogram

^aIncludes ventricular and supraventricular arrhythmia

^bIncludes complete atrioventricular block, first and second degree block

coronavirus (hydroxychloroquine and lopinavir/ritonavir) after the deaths of three people possibly linked to self-medication. ANSM also pointed out how this cardiac risk could be increased by using hydroxychloroquine in association with other potentially torsadogenic drugs such as azithromycin, or in patients with specific metabolic disorders (e.g. hypokalaemia) [68]. The American College of Cardiology (ACC) noted that COVID-19-infected patients are likely to have longer baseline QTc and higher potential arrhythmic risks as a result of the metabolic and physiologic sequelae of their illness, and a typically greater burden of comorbid disease [69]. Recently, the ACC suggested that safety concerns regarding the use of hydroxychloroquine–azithromycin combination for COVID-19 should be considered in the context of several important mitigating factors, such as the short duration of treatment and the potential benefit among specific subgroups with COVID-19 infection (in particular, ICU-hospitalised patients with serious illness). Furthermore, the ACC highlighted that close monitoring and optimisation of known risk factors for TdP (e.g. structural heart disease, congenital long-QT syndromes, electrolyte disturbances, hepatic/renal failure, etc.) could maximise the safety of potential QT-prolonging medications [69]. Both AIFA and ACC stated that a clinical trial evaluating the effectiveness and safety of these drugs is urgently needed. Mayo Clinic has recently published its own recommendations for the treatment of COVID-19 patients with potentially arrhythmogenic drugs. This guidance suggests that it is essential to identify the small subset of patients who, either due to a genetic predisposition and/or due to QT risk factors, have a high baseline risk of QT prolongation and/or have an inherent tendency to develop an exaggerated QT response after being treated with QT-prolonging medications [70]. Elderly patients in particular may be at higher risk, especially because of the likelihood of being prescribed QT-prolonging drugs and of polypharmacy in this population [71].

5 Conclusion

There is no clear evidence that azithromycin may exert beneficial effects in COVID-19 beyond antibacterial activity in bacterial superinfection. In COVID-19 infection, empirical broad-spectrum antibiotic therapy should be chosen only to treat superinfection, preferably based on CAP treatment guidelines from scientific societies, which never recommend macrolide use alone as first-line treatment. Although the arrhythmogenic potential of azithromycin is lower as compared with other macrolides or other antibacterial drug classes, such as fluoroquinolones, the use of drugs with even a low risk of arrhythmia with other potential QT-prolonging drugs such as hydroxychloroquine/chloroquine warrants close electrocardiogram monitoring. If not possible, as may be the case in an outpatient setting, a thorough evaluation of potential risk factors for arrhythmia has to be considered with the ultimate goal to carefully weigh the risks against the benefits of different antibiotics for the treatment of bacterial superinfection in COVID-19 patients.

Compliance with Ethical Standards

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Conflict of interest Gianluca Trifirò, has served on advisory boards for Sandoz, Hospira, Sanofi, Biogen, Ipsen and Shire; is the principal investigator of observational studies funded by several pharmaceutical companies (e.g. Amgen, AstraZeneca, Daiichi Sankyo and IBSA) to the University of Messina; and is scientific coordinator of the Master's program 'Pharmacovigilance, pharmacoepidemiology and pharmaco-economics: real-world data evaluations' at the University of Messina, which is partly funded by several pharmaceutical companies. Janet Sultana, Paola Maria Cutroneo, Salvatore Crisafulli, Gabriele Puglisi and Gaetano Caramori have no conflicts of interest that are directly relevant to the content of this article.

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