Clinical Pharmacology Perspectives on the Antiviral Activity of Azithromycin and Use in COVID-19

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Azithromycin (AZ) is a broad-spectrum macrolide antibiotic with a long half-life and a large volume of distribution. It is primarily used for the treatment of respiratory, enteric, and genitourinary bacterial infections. AZ is not approved for the treatment of viral infections, and there is no well-controlled, prospective, randomized clinical evidence to support AZ therapy in coronavirus disease 2019 (COVID-19). Nevertheless, there are anecdotal reports that some hospitals have begun to include AZ in combination with hydroxychloroquine or chloroquine (CQ) for treatment of COVID-19. It is essential that the clinical pharmacology (CP) characteristics of AZ be considered in planning and conducting clinical trials of AZ alone or in combination with other agents, to ensure safe study conduct and to increase the probability of achieving definitive answers regarding efficacy of AZ in the treatment of COVID-19. The safety profile of AZ used as an antibacterial agent is well established.[1] This work assesses published *in vitro* and clinical evidence for AZ as an agent with antiviral properties. It also provides basic CP information relevant for planning and initiating COVID-19 clinical studies with AZ, summarizes safety data from healthy volunteer studies, and safety and efficacy data from phase II and phase II/III studies in patients with uncomplicated malaria, including a phase II/III study in pediatric patients following administration of AZ and CQ in combination. This paper may also serve to facilitate the consideration and use of *a priori*–defined control groups for future research.

A single-arm, nonrandomized study in Marseilles, France suggested that hydroxychloroquine (HCQ) alone or in combination with azithromycin (AZ) reduced viral load in coronavirus disease 2019 (COVID-19) patients.[2] AZ was added to prevent bacterial superinfection in a subset of patients, while untreated patients from another center and those refusing treatment served as unmatched controls. At Day 6, 100% of patients (6/6) treated with HCQ and AZ had negative severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) nasopharyngeal polymerase chain reaction (PCR) test, compared with 57.1% patients (8/14) treated with HCQ alone, and 12.5% controls (2/16) ($P < 0.001$). The authors concluded in this study that HCQ was associated with viral load reduction and its effect was complemented by AZ. In a separate report (preprint), a subsequent single-arm study from the same center, 80 COVID-19 patients (including 6 patients from the prior study) received HCQ and AZ. A rapid fall in nasopharyngeal viral load tested by quantitative PCR (qPCR) was noted, with 83% negative at Day 7, and 93% at Day 8. Virus cultures from patient respiratory samples were negative in 97.5% of patients at Day 5, which the authors noted was much earlier than untreated patients in prior cases.[3] The authors concluded that HCQ with AZ was potentially effective in reducing transmission and in the therapy of COVID-19.

To help determine the validity of these early clinical findings, it is important to understand if AZ demonstrates antiviral properties *in vitro* and *in vivo*, and the activity of AZ and HCQ in combination. AZ is a broad-spectrum macrolide antibiotic primarily used for the treatment of respiratory, enteric, and genitourinary bacterial infections and has a well-established safety profile.[1] AZ is indicated for infections caused by susceptible bacterial pathogens in respiratory tract infections such as bronchitis and pneumonia. The minimum inhibitory concentrations for AZ against most of these bacterial pathogens are ≤2.0 mg/L (2.67 μM).[1] The antibacterial mechanism of action of AZ is the binding to the 23S rRNA of the 50S ribosomal subunit of microorganisms, inhibiting bacterial protein synthesis and impeding the assembly of the 50S ribosomal subunit.[1] AZ is not approved for antiviral therapy but has been studied *in vitro* and in clinical trials for activity against several viruses. This review was undertaken to assess key AZ published data on *in vitro* antiviral activity and clinical studies across a variety of viral infections to support the design of future controlled studies.

Azithromycin antiviral properties *in vitro*

Numerous investigations have reported *in vitro* antiviral activity of AZ against viral pathogens with 50% inhibitory concentrations ranging from ∼ 1–6 μM, with the exception of H1N1 influenza

Table 1 *In vitro* antiviral activity of azithromycin

Targeted virus	Antiviral activity screening system	Time of drug addition to infected cell culture	Incubation period	MOI	IC_{50} OR EC_{50} (μM)	CC_{50} (μM)	SI^a	References
SARS-CoV-2	Vero cells	15 minutes pre-treatment	72 hours	0.002	2.12 EC_{90}: 8.65	>40	>19	4
Zika	Vero cells	12 hours pre-treatment	48 hours	0.1	6.59	810	123	8
	Huh7 cells				1.23–4.97	1,360	>273	
	A549 cells				4.44	—	—	
	Hela cells				—	3,560	—	
	U87 cells	>1 hour pre-treatment	48 hours	0.01	2.1	53	25	9
				0.1	2.9	—	18	
				3	5.1	—	10	
	Astrocytes			1	15	44	2.9	
Ebola	Ebola VLP entry assay (Hela cells)	1 hour pre-treatment	2 hours	N/A	2.79 IC_{90}: 15.8	>500	>179	10
	Ebola pseudovirion entry assay (Hela cells)	8 hours pre-treatment	72 hours	N/A	0.69 IC_{90}: 4.16	—	—	11
	Pseudotype Ebola entry assay (Hela cells)	1 hour pre-treatment	19 hours	N/A	1.3	—	—	12
	Ebola replication assay (Vero 76 cells)	1 hour pre-treatment	48 hours	0.2	5.1	>130	>25	
Influenza (H1N1)	A549 cells	Simultaneous	48 hours	1	68	>600	>8.8	13
Dengue (Serotype 2)	Vero cells	12 hours pre-treatment	48 hours	0.01	3.71	810	218	8
Rhinovirus	Human bronchial epithelial cells	24 hours pre-treatment	48 hours	1	IC_{50} not calculated; RV replication was inhibited at 10 μM and 50 μM ($P < 0.01$)	—	—	14

CC_{50}, 50% cytotoxic concentration; EC_{50}, 50% effective concentration; EC_{90}, 90% effective concentration; H1N1, influenza A virus subtype H1N1; h, hour; IC_{50}, 50% inhibitory concentration; IC_{90}, 90% inhibitory concentration; MOI, multiplicity of infection; N/A, not applicable; RV, rhinovirus; SARS-CoV-2, severe acute respiratory syndrome coronavirus 2; SI, selectivity index (CC_{50}/IC_{50}); VLP, virus-like particle; —, not available.
^{a}Reported or calculated.

(**Table 1**). The *in vitro* EC_{50} (50% effective concentration) for AZ against SARS-CoV-2, the virus responsible for COVID-19, was 2.12 μM (EC_{90}: 8.65 μM) following a 72-hour incubation period post infection, with a ratio of infectious virions to cells in culture (multiplicity of infection; MOI) of 0.002.[4] In the same study, under the same experimental conditions, the *in vitro* EC_{50} for HCQ was 4.17 μM.

In other studies, the calculated *in vitro* EC_{50} for HCQ against SARS-CoV-2 ranged from 0.72 to 17.31 μM at an MOI from 0.01 to 0.8, measured at 48 hours post infection.[5,6] The selectivity index for HCQ is high, with a reported 50% cytotoxic concentration of 250 μM.[6] In a separate study (preprint), following a 60-hour incubation period, a synergistic effect with the combination HCQ 2 μM + AZ 10 μM was observed *in vitro* on SARS-CoV-2 at concentrations expected in human lung, leading to total inhibition of viral replication.[7]

Caution should be exercised in comparing the EC_{50} values across these studies due to the differences in experimental conditions (e.g., different cell lines, MOI, time of drug addition to culture, incubation times, and analytical methods).

Potential mechanisms of antiviral activity

The precise mechanism is unknown; however, multiple mechanisms have been proposed for the putative antiviral properties observed with AZ. Endosome maturation and function require an acidic environment. AZ is a weak base and preferentially accumulates intracellularly in endosomal vesicles and lysosomes, which could increase pH levels, and potentially block endocytosis and/or viral genetic shedding from lysosomes, thereby limiting viral replication.[15,16] An acidic environment is also required for the uncoating of enveloped viruses such as influenza and HIV,[17] and a similar mechanism is plausible for coronaviruses, also enveloped viruses. These mechanisms have also been proposed for the antiviral effect noted with HCQ and chloroquine (CQ);[5,6] in fact, evidence suggests that AZ causes a more severe impairment of acidification than CQ.[15]

The putative antiviral effects of AZ may also be mediated by a global amplification of the host's interferon (IFN) pathway-mediated antiviral responses. Data suggest that AZ has the ability to induce pattern recognition receptors, IFNs, and IFN-stimulated genes, leading to a reduction of viral replication.[8,14,18] In addition, AZ directly acts on bronchial epithelial cells to maintain their function and reduce mucus secretion to facilitate lung function.[19]

Specific to SARS-CoV-2, recent quantum mechanical modeling suggests a potential role of AZ in interfering with viral entry via binding interaction between the SARS-CoV-2 spike protein and host receptor ACE2 (angiotensin converting enzyme-2) protein;[20] further experimental work on this is necessary to confirm the model.

Pharmacology

The pharmacokinetics of AZ are well understood. AZ is rapidly absorbed following oral administration, has a long serum half-life (68 hours),[1] and large volume of distribution (31 L/kg).[21] AZ is taken up by leucocytes at concentrations that are about 300-fold higher than plasma.[22] In infected tissues, AZ concentrations are higher than in plasma, due to recruitment of leucocytes at the site of infection. Numerous studies have shown excellent penetration of AZ in a variety of infected tissues, and selected data pertinent to lung penetration are provided in **Table 2**.

Excellent tissue penetration in the lung allows for the treatment of respiratory infections for indicated bacterial pathogens for which the pharmacokinetic–pharmacodynamic target is linked to area under the curve / minimum inhibitory concentration. The pharmacokinetic–pharmacodynamic target(s) for the potential antiviral activity of AZ is unknown. Hence, for informational purposes only, calculated ratios for maximum concentration (C_{max}) vs. reported EC_{50} for SARS-CoV-2 are presented in **Table 2**.

As indicated (**Table 2**), lung tissue homogenates and alveolar macrophages have AZ concentrations well in excess of the EC_{50} for SAR-CoV-2, as well as for other respiratory viruses listed in **Table 1**, following approved doses of AZ. One limitation of these data is that concentrations in lung homogenates may not represent concentrations in infected cells.

Once in the lung, concentrations of AZ persist for several days after plasma concentrations become undetectable.[24,26] The estimated terminal half-life in lung tissue and bronchial washings were 133 and 74 hours, respectively.[23] It is plausible that due to this unique pharmacokinetic property of AZ, coupled with target tissue concentrations in excess of *in vitro* EC_{50} against several viruses, AZ could play a potential therapeutic role in respiratory viral infections, including SARS-CoV-2.

Additional considerations for elderly patients may be applicable for COVID-19 infections. As per the product label, AZ exposures in geriatric patients were shown to be similar to those in young adults. In subjects with mild-to-moderate renal impairment, there was little increase in mean C_{max} (5.1%) and AUC (4.2%) following a single 1 g dose of AZ.[1] Dose adjustment is not considered to be required for geriatric patients with normal renal and hepatic function; however, it should be noted that elderly patients may be more susceptible to the development of torsades de pointes.[1] In subjects with severe renal impairment, the mean AUC and C_{max} increased 35% and 61%, respectively, compared with subjects with normal renal function; thus caution should be exercised when dosing AZ in this population.[1]

Clinical studies

Table 3 summarizes available clinical data on the efficacy of AZ alone, or in combination with other drugs, against various viral infections. With some exceptions, the studies in **Table 2** have been observational, single-arm, nonrandomized studies or retrospective evaluations. Many of these studies have reported clinical observations or conducted *post hoc* analyses. Studies in COVID-19 patients have mainly focused on viral load as an end point, and detailed evaluation of clinical outcomes has not been reported. Notwithstanding the limitations of these studies, collectively they present preliminary evidence that inclusion of AZ in various treatment regimens can influence the course of viral infection and has the potential to influence clinical outcomes. Confirmatory evidence with randomized controlled trials is essential to understand the role of AZ in the treatment of COVID-19.

Table 2 Pharmacokinetics of azithromycin in plasma, serum, and lung

AZ dose	Matrix	AUC (mg·h/L)	C_{max} (mg/L)	Ratio[a] C_{max}/EC_{50}	References
500 mg daily × 3 days	Plasma	20.48	0.26	0.16	23
	Bronchial washings	60.6	0.72	0.45	
	Lung tissue homogenate	1,318	9.13	5.75	
1,000 mg daily × 3 days	Plasma	25.6	0.32	0.2	23
	Bronchial washings	135.1	1.41	0.89	
	Lung tissue homogenate	2,502	17.85	11.24	
500 mg daily × 3 days	Plasma	11.62	0.18	0.11	24
	Bronchial washings	70.29	0.83	0.52	
	Lung tissue homogenate	1,245.4	8.93	5.62	
1,000 mg daily × 3 days	Plasma	19.83	0.32	0.2	24
	Bronchial washings	139.9	1.49	0.94	
	Lung tissue homogenate	2,514.2	18.6	11.71	
500 mg single dose	Serum	3.1	0.39	0.25	25
	Epithelial lining fluid	18.8	1.2	0.76	
	Lung tissue homogenate	432	8.3	5.23	
	Alveolar macrophages	5,804	194	122.18	

AUC, area under the curve; AZ, azithromycin; C_{max}, maximum concentration; EC_{50}, 50% effective concentration.
[a]Ratio calculated using molecular weight of AZ of 749 g and *in vitro* EC_{50} against SARS-CoV-2 (severe acute respiratory syndrome coronavirus 2) of 2.12 μM[4]:
(X mg/L × (1 mol/749.0 g) × 1,000)/ 2.12 mg/L.

SAFETY

The safety profile of AZ used as an antibacterial agent is well established, and the risks associated with its use are minimized through provision of relevant information in product labeling[1] to support safe use of the product.

There have been numerous studies using dosing regimens of AZ and CQ either coadministered as separate tablets (AZ + CQ) or administered as fixed-dose combination tablets (AZCQ). These studies include three phase I studies in healthy adult subjects; nine safety and efficacy phase II or phase II/III studies in adult patients with uncomplicated malaria; a single phase II/III study in pediatric patients with uncomplicated *Plasmodium falciparum*; and two phase III studies in asymptomatic pregnant women for intermittent preventative treatment of *P. falciparum* in pregnancy. Details of some of these studies are presented in **Table 4**.

From these studies, AZ + CQ at doses up to 2,000 mg AZ and 600 mg CQ (base), administered for up to 3 days, was shown to be generally well tolerated, safe in patients with uncomplicated malaria, and safe to be used in different age groups (age range from 18 to > 75 years), including pediatric patients (age range from 6 months to 12 years) and pregnant women. However, at the higher doses (≥1,500 mg) AZ was less well tolerated due to adverse events (AEs) such as vomiting. In the studies in pregnant women, AZCQ combination therapy was less well tolerated than sulfadoxine-pyrimethamine; AEs such as vomiting, dizziness, headache, and asthenia were reported more frequently in the AZCQ treatment group than the sulfadoxine-pyrimethamine group, and serious AEs and discontinuations due to AEs were more frequent in the AZCQ treatment group. In general, the most frequently reported AEs associated with the treatment of AZCQ or AZ + CQ were generally gastrointestinal in nature and included diarrhea, nausea, vomiting, and abdominal pain. Pruritus was also reported, which was considered to be secondary to CQ. Prolonged cardiac repolarization and QT interval, which may impart a risk of torsade de pointes, has been seen in treatment with macrolides, including AZ; CQ is also known to prolong the QT interval. In the studies presented in this document (**Table 4**), in a total of > 2,000 subjects exposed to 3-day regimens of AZ and CQ combinations, no relevant cardiovascular serious AEs of concern were reported. Available data on the concomitant use of AZ and CQ in these studies indicated no increased risk of QT prolongation above that observed with CQ alone.

DISCUSSION

During drug development, it is essential to demonstrate robust *in vitro* evidence of activity prior to further study in humans. Subsequently, for a development candidate to have potential to elicit the desired effect over the necessary period of time *in vivo*, three fundamental "pillars" need to be demonstrated:[33]

1. Exposure at the target site of action over a desired period of time
2. Binding to the pharmacological target as expected for its mechanism of action
3. Expression of pharmacological activity commensurate with the demonstrated target exposure and target binding

The *in vitro* evidence presented here suggests that AZ has antiviral properties, including activity against SARS-CoV-2, at concentrations that are physiologically achievable with doses used to treat bacterial infections in the lung. One plausible mechanism for the antiviral properties is the intracellular sequestration of AZ resulting in an increase in endosomal and/or lysosomal pH. Lack of an

Table 3 Selected clinical studies in respiratory viral infections

Study Population	Study design	Treatments	Key results	Conclusion	References
COVID-19, >12 years (N = 36)	Observational, nonrandomized, external control, open-label	Nonrandomized Control HCQ (200 mg q.8h. × 10 days) HCQ + AZ (500 mg D1 and 250 mg D2-5)	At D6 post-inclusion, negative nasopharyngeal PCR in: 100% (6/6) pts. HCQ + AZ 57.1% (8/14) HCQ 12.5% controls (P < 0.001).	The authors concluded that HCQ is significantly associated with viral load reduction and its effect is reinforced by AZ. Additional studies are needed in more severe patient population (NEWS score) with a robust control group.	2
COVID-19, >18 years (N = 80)	Observational, single arm	HCQ (200 mg q.8h. × 10 days) + AZ (500 mg D1 and 250 mg D2-5)	Decrease in nasopharyngeal viral load (qPCR): 83% negative at D7, and 93% at D8. Patients presumably contagious (PCR Ct < 34) decreased and reached zero on D12.	The authors concluded that these results corroborated the efficacy of HCQ with AZ and its potential effectiveness in the early impairment of contagiousness. This finding provides further evidence in uncontrolled case series, deserving replication.	3
COVID-19, 20–77 years, (N = 11)	Observational, single arm	HCQ + AZ (unspecified doses)	Within 5 days, one patient died, two were transferred to the ICU. One patient discontinued after 4 days due to QT interval of 460 msec to 470 msec (baseline 405 msec). At D6, 8/10 patients were positive for SARS-CoV-2 RNA in nasopharyngeal swabs.	No evidence of strong antiviral activity with the combination of HCQ and AZ.	27
Healthy children < 5 years (N not specified)	*Ad hoc* analysis of an interventional, randomized, cluster-controlled, blinded study.	Placebo AZ suspension every 6 months for 2 years	At 24 months, an 8x reduction (via RNA-seq) in alpha-coronavirus and a 14x reduction in beta-coronavirus in AZ group vs. placebo. At 36 months, number of children with coronavirus was not different between groups.	AZ may decrease viral load but not prevalence of colonization.	MORDOR II Study[b]
MERS (N = 349)	Retrospective, multicenter cohort database	Macrolide, n = 136 (39%), (71.3% with AZ) No macrolide	90-day mortality (adjusted OR: 0.84; 95% CI 0.47–1.51) or MERS-CoV RNA clearance (adjusted HR: 0.88; 95% CI: 0.47–1.64)	Macrolide therapy was not associated with a reduction in 90-day mortality or improvement in MERS-CoV RNA clearance.	28
Confirmed SARS (2003) 16–84 years (N = 190)	Retrospective review	Ribavirin + C/S (N = 40) FQ + AZ+IFN-α (+steroid) (n = 30) Q + AZ (+IFN-α + steroid) (n = 60) Levo + AZ (+IFN-α + steroid) (n = 60)	Early use of high-dose steroids with a quinolone plus AZ showed improvement of clinical symptoms and signs and a decreased incidence of ARDS, mechanical ventilation, and mortality. Respiratory improvement and mean time to discharge was shorter in Q + AZ and Levo + AZ groups.	The early use of high-dose steroids with a quinolone plus AZ gave the best clinical outcome.	29

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Table 3 (Continued)

Study Population	Study design	Treatments	Key results	Conclusion	References
Influenza A infection, >20 years (N = 107)	Prospective, randomized, controlled, open-label, multicenter	Oseltamivir (75 mg q.12h. × 5 days) (n = 56) Oseltamivir (75 mg q.12h. × 5 days) + AZ (2,000 mg single dose extended release) (n = 51)	No significant treatment differences in inflammatory markers. Trends in favor of combination therapy for reduction in max temp on D3–5 ($P = 0.048$); improvement in sore throat on D2.	Combination therapy showed an early resolution of some symptoms.	30
Diagnosed for Influenza-A (H1N1) pdm09 strain (N = 329)	Retrospective chart review	Oseltamivir Oseltamivir + AZ (500 q.d.)	Monotherapy vs. combination: secondary bacterial infections (23.4% vs. 10.4%), length of hospitalization (6.58 vs. 5.09 days), incidences of respiratory support (38.3% vs. 17.6%), influenza symptom severity score D5 (12.7 vs. 10.7).	Combination therapy was more efficacious compared with oseltamivir alone in rapid recovery of influenza-associated complications in high-risk patients.	31
RSV Otherwise healthy infants (N = 40)	Randomized, double-masked, placebo-controlled, proof-of-concept	AZ Placebo (14 days)	Azithromycin did not reduce serum IL-8 levels at D8 ($P = 0.6$) but reduced nasal lavage IL-8 by D15 ($P = 0.03$). ≥3 wheezing episodes (22% in AZ vs. 50% in placebo) ($P = 0.07$).	Azithromycin treatment during RSV bronchiolitis reduced upper airway IL-8 levels, prolonged the time to the third wheezing episode and reduced overall respiratory morbidity.	32

ARDS, acute respiratory distress syndrome; AZ, azithromycin; CI, confidence interval; CoV, coronavirus; COVID-19, coronavirus infectious disease-2019; C/S, cefoperazone/sulbactam; Ct, cycle threshold; D, day; FQ, fluoroquinolone; HCQ, hydroxychloroquine; HR, hazard ratio; ICU, intensive care unit; IFN, interferon; IL, interleukin; Levo, levofloxacin; MERS, Middle East respiratory syndrome; N, number of patients; n, subgroup or subpopulation; NEWS, National Early Warning Score; OR, odds ratio; PCR, polymerase chain reaction; Q, quinolone; q.8h., every 8 hours; q.12h., every 12 hours; q.d., once daily; qPCR, quantitative PCR; RSV, respiratory syncytial virus; RNA-seq, RNA sequencing; SARS, severe acute respiratory syndrome.
[a]In press: Doan T, Hinterworth A, Arzika A, et al. "Reduction of coronavirus burden with mass azithromycin distribution."

Table 4 Summary of azithromycin and chloroquine combination studies

Study code and study title	Age range of treated subjects	Dose regimen (Number tested)	Safety summary
A0661139: A multiple-dose study to assess the effects of AZ + CQ on electrocardiograms in healthy subjects	Adults, age 18–55 years	Five treatment groups; each treatment administered for 3 days: 1. 600 mg[a] CQ (N = 24) 2. 600 mg CQ + 500 mg AZ (N = 24) 3. 600 mg CQ + 1,000 mg AZ (N = 24) 4. 600 mg CQ + 1,500 mg AZ (N = 23) 5. placebo (N = 24)	Most AEs were mild or moderate; no SAEs were reported which were considered related to study drug. Three subjects in the 1,500 mg AZ + CQ group discontinued due to AEs (diarrhea; loss of appetite; nausea, diarrhea, and vomiting). AE rates were similar across the combination treatment groups, although events of diarrhea, nausea, and vomiting were greater in the higher dose groups. The primary end point was change from baseline in triplicate ECG measurements at each of 10 timepoints post dose on Day 3 vs. time-matched triplicate ECGs on study Day −1 (baseline). Maximum mean increases in QTcF vs. placebo of approximately 35–37 msec were similar among all AZ + CQ and CQ alone treatments. In comparison with CQ alone, the maximum mean (90% CI) increases in QTcF were approximately 5.3 (0.2, 10.4) msec, 6.5 (1.4, 11.6) msec and 8.9 (3.6, 14.2) msec for the 500 mg, 1,000 mg and 1,500 mg AZ + CQ groups, respectively. Mean changes from time-matched baseline QTcF (compared with placebo alone) ranged from 18.4 msec to 35.0 msec in the CQ alone group; 21.5 msec to 36.2 msec in the 500 mg AZ + CQ group; 19.9 msec to 36.9 msec in the 1,000 mg AZ + CQ group; and from 20.2 msec to 35.3 msec in the 1,500 mg AZ + CQ treatment group.
066-191: a randomized, double blind, comparative study of AZ vs. CQ as treatment of Plasmodium falciparum and Plasmodium vivax malaria	Adults, age 18–60 years (AZ) and 18–45 years (CQ)	Two treatment groups: 1. 1,000 mg AZ; once daily for 3 days (N = 16) 2. 600 mg CQ once daily on Days 1 and 2, then 300 mg CQ on Day 3 (N = 16) (due to poor activity of either agent alone against P. falciparum, study was modified to 066-191B)	Two subjects treated for P. vivax were discontinued from the study due to AEs related to CQ (maculopapular rash (moderate), pruritus (severe)) There was one treatment-related SAE of urticaria in the AZ treatment group.
066-191B: A randomized, double blind, comparative study of AZ vs. CQ as treatment of P. falciparum and P. vivax malaria	Adults, age 18–55 years	1,000 mg AZ + CQ (600 mg CQ days 1 and 2, and 300 mg on day 3), for 3 days (N = 64)	There were no SAEs following treatment with AZ + CQ, and no discontinuations due to AEs. Treatment with AZ + CQ was better tolerated than monotherapy with AZ or CQ alone in subjects with P. falciparum malaria
A0661120: A phase II/III, randomized, comparative trial of AZ plus CQ vs. SP plus CQ for the treatment of uncomplicated P. falciparum malaria in India	Adults, age 18–75 years (AZ + CQ) and 18–60 years (SP + CQ)	Three treatment groups: 1. 1,000 mg AZ + 600 mg CQ; once daily, for 3 days (N = 83) 2. 500 mg AZ + 600 mg CQ; once daily, for 3 days (N = 67) 3. 1,500 mg/75 mg SP on Day 0, 600 mg CQ on Days 0 and 1, and 300 mg on Day 2 (N = 80)	Fewer than 10% subjects in all three groups reported treatment-related AEs, and no subjects discontinued the study due to AEs related to study drug. One subject reported a treatment-related SAE ("abnormal behaviour") in the SP + CQ group which was attributed to CQ. All treatment-related AEs occurred at an incidence of < 5% (≤ 4) subjects (vomiting, diarrhea, abdominal pain, pruritis, and gastritis) and all were mild or moderate. In the 500 mg AZ + CQ group, one (1.5%) subject reported vomiting and one (1.5%) subject reported pruritus. In the 1,000 mg AZ + CQ group, vomiting was reported by four (4.8%) subjects and pruritus was reported by two (2.4%) subjects. In addition, two (2.4%) subjects reported abdominal pain, and diarrhea and gastritis were reported by one (1.2%) subject each.

(Continued)

Table 4 (Continued)

Study code and study title	Age range of treated subjects	Dose regimen (Number tested)	Safety summary
A0661126: A phase II/III, randomized, double blind, comparative trial of AZ plus CQ vs. A-P for the treatment of uncomplicated *P. falciparum* malaria in South America	Adults, aged 18–86 years (AZ + CQ) and 18–74 years (A-P)	Three treatment groups; each treatment administered for 3 days: 1. 1,000 mg AZ + 600 mg CQ (N = 114) 2. 500 mg AZ + 600 mg CQ (N = 14)[b] 3. 1,000 mg A + 400 mg P (A-P) (N = 116)	One subject in the 1000 mg AZ + CQ treatment group discontinued due to a treatment-related AE of vomiting. The treatment-related AEs most frequently reported by subjects treated with 500 mg AZ + CQ were pruritus (4 subjects; 28.6%), gastritis (1 subject (7.1%)) and mouth ulceration (1 subject (7.1%)); and with 1,000 mg AZ + CQ were pruritus (28 subjects; 24.6%), diarrhea/loose stools (8 subjects (7.1%)), and paresthesia (6 subjects (5.3%)). Most events were mild to moderate; three treatment-related AEs were assessed as severe: pruritus (1,000 mg AZ + CQ), gastritis (500 mg AZ + CQ), and abdominal pain (A-P). There were no treatment-related SAEs. The incidence of AEs was higher in the AZ combination treatment groups than in the A-P group and was attributed primarily to the incidence of pruritus which is secondary to CQ treatment.
A0661134: A phase II/III, randomized, double-blind, comparative trial of AZ plus CQ vs. mefloquine for the treatment of uncomplicated *P. falciparum* malaria in Africa	Adults, aged 18–63 years (AZ + CQ) and 18–68 years (mefloquine)	Three treatment groups: 1. 1,000 mg AZ + 600 mg CQ, once daily for 3 days (N = 114) 2. 500 mg AZ + 600 mg CQ, once daily for 3 days (N = 9)[b] 3. 750 + 500 mg mefloquine on Day 0 (N = 115)	Most frequently reported treatment-related AEs with 500 mg AZ + CQ were pruritus (2 subjects (22.2%)), abdominal pain (1 subject (11.1%)), dyspepsia (1 subject (11.1%)), loose stools (1 subject (11.1%)), and vomiting (1 subject (11.1%)); and with 1,000 mg AZ + CQ were pruritus (58 subjects (50.9%)), vomiting (18 subjects (15.8%)), and headache (15 subjects (13.2%)); the majority of AEs were mild. There was one severe treatment-related AE of vomiting in the 1,000 mg AZ + CQ treatment group, and two subjects from this treatment group discontinued the study due to vomiting and vomiting/dizziness/tinnitus. There were no SAEs which were considered related to AZ + CQ.
A0661154: A phase II, open label, noncomparative trial of AZ 2,000 mg plus CQ 600 mg base daily for three days for the treatment of uncomplicated *P. falciparum* malaria	Adults, aged 18–77 years	2,000 mg AZ + 600 mg CQ (N = 110), each administered for 3 days	Most frequently reported treatment-related AEs were nausea (30.0%), vomiting (18.2%), and diarrhea (11.8%) which were all mild or moderate with the exception of one severe event of vomiting. There were no SAEs or discontinuations due to AEs. Triplicate ECGs were measured on Days 0 (predose), Days 1 and 2 (predose and postdose) and on Days 3 and 7. Mean increases in QTcF from baseline ranged from 12 msec to 49.9 msec and overall, 30 (29%), 6 (6%), and 2 (2%) subjects met the criteria of absolute QTcF values of 450 to < 480 msec, 480 to < 500 msec, and ≥ 500 msec, respectively. The QTcF prolongation observed was consistent with that reported for CQ alone and for AZ + CQ in previous studies. Coadministration of AZ did not worsen the QT prolongation associated with CQ.
A0661155: A phase III, randomized, open-label, comparative trial of AZ plus CQ vs. mefloquine for the treatment of uncomplicated *P. falciparum* malaria in Africa	Adults, aged 17–58 years (AZ + CQ) and 18 to 71 years (mefloquine)	Two treatment groups: 1. 1,000 mg AZ + 600 mg CQ (N = 113), once daily for 3 days 2. 750 + 500 mg mefloquine (N = 116)	There were no SAEs in the AZ + CQ treatment group and all AEs in the AZ + CQ group were mild or moderate. One subject in this group discontinued due to an AE of pruritus. The most frequently reported treatment-related AEs in the AZ + CQ group were pruritus (28.3%), headache (17.7%), dizziness (15.9%), abdominal pain (11.5%), nausea (8.8%), and vomiting (3.5%).

(Continued)

Table 4 (Continued)

Study code and study title	Age range of treated subjects	Dose regimen (Number tested)	Safety summary
A0661157: phase II/III, open-label, comparative trial of AZ plus CQ vs. AL for the treatment of uncomplicated *P. falciparum* malaria in children in Africa	Children, aged 6 months to 12 years (both treatment groups)	Two treatment groups, each treatment administered for 3 days: 1. AZCQ fixed-dose combination tablet[c] (N = 179) 2. AL 20 mg/120 mg (N = 182)	There were no SAEs considered to be related to study treatment and no permanent discontinuations from the study due to AEs; subjects discontinued from dosing more frequently in the AZCQ group, mostly due to vomiting. Most AEs were mild or moderate. Vomiting and pruritus were more frequently reported in the AZCQ cohorts than the AL cohorts. The most frequently reported treatment-related AEs (≥5%) in the AZCQ cohorts were vomiting, abdominal pain, parasitemia, malaria, pyrexia, and pruritus. The QTc changes observed in this study were similar to those reported in African children with uncomplicated malaria treated with AL, SP, or CQ. The only AE reported was one of mild QT prolongation in a subject treated with AL, who had concurrent pyrexia.
A0661158: phase III, open-label, randomized, comparative study to evaluate AZ plus CQ, and sulfadoxine plus pyrimethamine combinations for intermittent preventive treatment of *falciparum* malaria infection in pregnant women in Africa	Pregnant subjects, aged 16–35 years (both treatment groups)	Two treatment groups: 1. 1,000 mg/620 mg AZCQ (4× fixed-dose combination tablet[d], for 3 treatment days (N = 1446) 2. 1500 mg/75 mg SP (3× 500 mg/25 mg tablets on Day 0) (N = 1445)	**Maternal group** There were three (0.2%) deaths in the AZCQ group and one (0.1%) in the SP group, but none were considered related to study drug. Most treatment-related AEs were mild or moderate; 0.9% in the AZCQ group were considered severe. Five (0.3%) subjects had SAEs which were considered related to AZCQ (vomiting (three), dizziness (two), diarrhea and asthenia (one each)). The most common treatment-related AEs in the AZCQ group were vomiting (44.6%), dizziness (31.4%), headache (15.3%), asthenia (15.2%), diarrhea (14.2%), nausea (14.2%), and blurred vision (10.0%). **Neonatal group** There were 25 (2.2%) neonatal deaths in the AZCQ group and 22 (1.8%) in the SP group, but no deaths were considered related to study drug. There were no SAEs considered related to study drug. Treatment-related AEs in neonates exposed *in utero* to AZCQ were low birth weight baby (0.2%), anemia (0.1%), and jaundice neonatal (0.1%).
A0661201: An open label, noncomparative study to evaluate parasitological clearance rates and pharmacokinetics of AZ and CQ following administration of a fixed dose combination of AZCQ in asymptomatic pregnant women with *P. falciparum* parasitemia in sub-Saharan Africa	Pregnant subjects, aged 16–34 years	1,000 mg/620 mg AZCQ fixed-dose combination tablet[d], for 3 treatment days (N = 168)	**Maternal group** No deaths occurred in the maternal group. The most common treatment-related AEs occurring in ≥ 5 subjects were vomiting (20.2% subjects), dizziness (19.6% subjects), pruritus (7.1% subjects), headache and generalized pruritus (5.4% subjects each), fatigue (4.2% subjects), and nausea (3.6% subjects). All maternal TEAEs were mild or moderate. No SAEs were reported which were related to study drug and no AEs leading to discontinuations from the study. **Neonatal group** No treatment-related AEs were reported for the neonatal group. There were four deaths, none of which were considered related to study drug. No SAEs were reported which were related to study drug.

AE, adverse event; AL, artemether-lumefantrine; A-P, atovaquone + proguanil; AZ, azithromycin; AZCQ, fixed-dose combination of azithromycin and chloroquine; CQ, chloroquine; ECG, electrocardiogram; QTcF, corrected QT interval by Fridericia; SP, sulfadoxine-pyrimethamine; SAE, serious adverse event; TEAE, treatment-emergent adverse event.

[a]For all CQ treatment administered in the studies in this table, CQ is noted as base amounts; e.g., 600 mg CQ base derived is from 1,000 mg CQ. [b]Treatment arm discontinued due to high failure rate of that arm. [c]AZCQ fixed dose combination: 300 mg AZ and 100 mg CQ, or 150 mg AZ and 50 mg CQ; tablets scored to allow for dosing by body weight. [d]AZCQ fixed dose combination tablet: 250 mg AZ and 155 mg CQ.

optimal acidic environment in the intracellular milieu potentially attenuates viral replication. This mechanism is similar to that proposed for CQ and HCQ, and could explain how two drugs, both weak bases, can act in a complementary manner to inhibit viral replication. In a companion *in vitro* study by investigators in Marseilles, France, when AZ was dosed in combination with HCQ,[2,3] a synergistic effect was observed *in vitro* against SARS-CoV-2; however, no EC_{50} was determined.[7] The determination of *in vitro* EC_{50} for agents administered alone and in combination against SARS-CoV-2 under similar experimental conditions is needed to further understand the putative antiviral effect of this combination. Other possible mechanisms including the amplification of the host's IFN pathway-mediated antiviral responses as well as AZ's potential to interfere with viral entry requires further experimental work.

Drugs known to interact with AZ, HCQ, or CQ are noted in their respective product labels.[1,34,35] In a study designed specifically to evaluate interaction between AZ and CQ, drug–drug interactions were not observed[36] and similar results would be expected with HCQ. CQ and HCQ are both substrates and potential inhibitors of P-glycoprotein (P-gp);[37-39] however, given that AZ is not a sensitive substrate of P-gp,[40] potential inhibition of P-gp by HCQ would not be expected to significantly impact the systemic exposure of AZ as observed in the aforementioned study with CQ. Furthermore, CQ and HCQ are metabolized by multiple cytochrome P450 pathways, including cytochrome P450 3A, which AZ has not been shown to substantially modulate.[1,41,42] Although AZ has been shown to be an inhibitor of P-gp,[43] AZ is unlikely to affect the lung penetration of HCQ, given that HCQ is highly permeable; thus P-gp efflux would not be expected to be rate limiting. The lung penetration of HCQ in humans has not been reported; however, data in toxicology studies in albino rats, at human-equivalent plasma exposure, suggests HCQ distributes to the lung at concentrations of approximately 92 μM,[44] which is far in excess of its EC_{50} values against SARS-CoV-2.[4]

A favorable clinical outcome is unlikely without clearance of the pathogen. However, translating the effect on viral (or bacterial) clearance into a clinical outcome in patients is confounded by the disease, variability in patients, design of the studies, and end points measured. This is apparent in the literature on clinical studies and observations with AZ in a variety of viral infections, which present a mixed picture of the utility of AZ dosed alone or with other drugs in the treatment of viral infection. Nonetheless, RNA-sequencing data from the MORDOR II (Macrolides Oraux pour Réduire les Décès avec un Oeil sur la Résistance) study on the reduction in both alpha-coronavirus and beta-coronavirus burden and from the recent studies in COVID-19 patients[3] provides exploratory evidence on AZ, alone or in combination, against SARS-CoV-2, a novel beta-coronavirus.

AZ has been reported to exhibit antiinflammatory activity.[45,46] These effects are described as an acute phase inhibition of inflammation and a late phase of resolution of chronic inflammation. HCQ also has antiinflammatory properties and is approved for the treatment of lupus erythematosus and rheumatoid arthritis.[34] These effects, while unlikely to contribute to antiviral activity, could ameliorate the inflammatory processes caused by SARS-CoV-2 infection. Furthermore, as bacterial coinfection has been noted in COVID-19 patients, AZ may have a role in treatment of indicated pathogens.

Although not an approved indication, the combination of AZ and CQ was well tolerated in healthy subjects and patients infected with malaria. Available data on the concomitant use of AZ and CQ in these studies indicated no increased risk of QT prolongation above that of CQ alone. In a recent preprint,[47] it was reported that in COVID-19 patients ($N = 84$), 11% of patients treated with an unspecified dosage regimen of HCQ and AZ had recorded QT intervals > 500 msec and 12% of patients had a change from baseline of > 60 msec; there were no events of torsade de pointes recorded.

In conclusion, the literature presented here provides a foundation for the study of AZ combined with HCQ in prospective randomized clinical trials or other control methods defined *a priori* for the treatment of COVID-19 that evaluate clinical outcomes, in addition to reductions in viral burden. As of April 8, 2020, there are 19 studies listed on clinicaltrials.gov (https://clinicaltrials.gov/) using the search terms "azithromycin" and "COVID-19" that will further examine the use of AZ.

CONFLICT OF INTEREST
The authors are employees of Pfizer Inc.

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