Azithromycin was synthesised in the 1980s as a semi-synthetic derivative of erythromycin. This second-generation macrolide gained popularity due to its increased effects on host-defences and chronic human diseases. Furthermore, its popularity increased as it showed improved spectrum of activity, tissue pharmacokinetic characteristics and stability in an acid environment compared to erythromycin. It is also known for its activity against some Gram-negative organisms such as *Haemophilus influenzae*.1-3 Although azithromycin has the same antibacterial mechanism of action as other macrolides, its ability to inhibit quorum sensing and the formation of biofilm further increased its esteem.1

**Chemistry**

In order to provide AZM with acid stability, it consists of a 15-membered macrocyclic lactone ring, with a sugar and an amino sugar attached, compared to the 14-membered macrocyclic lactone ring of the other macrolides. The alcohol and tertiary amino groups on the amino sugar (desosamine) are crucial for activity.1 One major disadvantage of AZM is the fact that it is very poorly soluble in aqueous environments (± 0.1 mg/ml), which contributes to its relatively low absolute oral bioavailability of only 37%.6-8 Poor water solubility could lead to variable dissolution rates, and ultimately it will detrimentally influence the bioavailability and subsequently the treatment effectiveness of patients.9 The amorphous solid-state form of AZM has shown improved aqueous solubility and intestinal membrane permeability. This improved solubility ranged from 1.4 to 4.2 times the solubility of the crystalline form compared to the amorphous solid-state form.9

**Pharmacology**

An additional methyl-substituted nitrogen atom combined into the lactone ring of erythromycin makes AZM a 15-membered lactone ring.10 Its main role is on protein synthesis whereby it acts by inhibiting bacterial protein synthesis through binding to the 50S ribosomal subunit of susceptible organisms.11 AZM’s convenient once-daily dosing for 3–5 days is due to its long half-life thus sustaining high concentration of the drug in the tissue. A 500 mg single dose of AZM achieves 37% bioavailability while the drugs’ delivery into tissues is up to 100-fold higher than in the plasma.1,12,13 Furthermore, AZM’s concentrations are high in macrophages and polymorphonuclear leucocytes, tonsils, lung, prostate, liver and lymph nodes while fat and muscle displayed lower concentrations.13 These high tissue and intracellular concentration levels are dependent on the dosing schedule of AZM.9,13 AZM has shown high concentrations in infected fluids and tissues even after there are reduced concentrations in the plasma.13

**Keywords:** azithromycin, COVID-19, antibacterial, antiviral, immunomodulatory, chloroquine, hydroxychloroquine
**Antimicrobial spectrum**

Due to the similarity of AZM to erythromycin, the antimicrobial spectrum activity extends to erythromycin susceptible, Gram-positive organisms and is much more effective against Gram-negative bacteria compared to the other macrolides.\(^{11}\)

**Clinical uses**

AZM is effective in the treatment of a multitude of conditions.\(^{11}\)

The benefits of AZM have shown clinical effectiveness against many respiratory viral conditions such as influenza and Middle East respiratory syndrome coronavirus (MERS-CoV) and thus its use against the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) that causes the coronavirus disease-19 (COVID-19) is of no surprise. Furthermore, in vitro activity of AZM against viruses such as Ebola, Zika, rhinovirus and influenza has also been shown.\(^{14}\)

**Drug interactions**

AZM has been considered to be a safe drug with adverse drug reactions that affect the gastrointestinal system and central and peripheral nervous system. Ventricular depolarisation (QTC) interval prolongation, torsade de pointes (TdP), ventricular tachycardia and sudden cardiac death have been associated with macrolides, however, the incidences have been low globally. Cardiotoxicity in patients with SARS-CoV-2 pneumonia, however, has been a concern. Furthermore, the combination use of hydroxychloroquine and AZM in hospitalised patients has shown a higher risk of cardiac adverse events with risk being more likely related to the hydroxychloroquine.\(^{14}\) Unlike other macrolide antibiotics such as erythromycin and clarithromycin, AZM is only a weak cytochrome P450 inhibitor.\(^{14}\)

**Contraindications**\(^{14}\)

- Hepatic dysfunction
- Cholestatic jaundice
- Sensitivity to macrolides

**Caution**\(^{14}\)

- Hepatotoxicity
- Infantile hypertrophic pyloric stenosis
- Clostridiodes difficile-associated diarrhoea
- Myasthenia gravis (this antibiotic may exacerbate muscle weakness)
- Patients with the previous prolongation of QTC interval or TdP

**Azithromycin for COVID-19**

In contrast to chloroquine (CQ) or hydroxychloroquine (HCQ), AZM antiviral activity has been shown in vitro and/or in vivo on a large panel of viruses: Ebola, Zika, respiratory syncytial virus, influenza H\(\text {N}\), virus, enterovirus, and rhinovirus.\(^{15-24}\) Its activity against respiratory syncytial virus has been demonstrated in a randomised study in infants.\(^{21}\) AZM exhibited a synergistic antiviral effect against SARS-CoV-2 when combined with HCQ both in vitro\(^{22}\) and in a clinical setting.\(^{24}\) Andreani et al. also reported a significant antiviral effect of AZM alone on SARS-CoV-2.\(^{22}\) The mechanisms of the antiviral effect of AZM support a large-spectrum of antiviral activity. AZM appears to decrease the virus entry into cells.\(^{19,23}\) In addition, it can enhance the immune response against viruses by several actions. AZM up-regulates the production of type I and III interferons (especially interferon-β and interferon-λ), and genes involved in virus recognition such as melanoma differentiation-associated (MDA)5 gene and retinoic acid-inducible gene (RIG)-I.\(^{18,23,24,26,27}\) These mechanisms are universally involved in the innate response against infectious agents, and potentially against SARS-CoV-2. The immunomodulation properties of AZM are the rationale of its use against inflammatory manifestations leading to interstitial lung disease.\(^{28,29}\)

AZM regulates and/or decreases the production of interleukin (IL)-1β, IL-6, IL-8, IL-10, IL-12, and Interferon alfa (IFN-α).\(^{21,30,31}\) AZM and HCQ both decrease the production of major inflammatory cytokines such as IL-1 and IL-6. However, the different profiles of immunomodulation between the two drugs may be crucial for selecting one of them for the treatment of COVID-19, in relation to the pathogenicity of the virus. Indeed, HCQ may decrease IL-2 levels but not AZM, while AZM may decrease IL-8 levels but not HCQ. AZM could allow a sufficient memory T-cell count to be maintained and therefore better immunisation.\(^{32}\) Another property of AZM is its antibacterial effect, which may be most interesting to prevent or treat co-infection by bacteria and SARS-CoV-2. Recent data suggested that anaerobic bacteria of lung microbiota may be involved in the SARS-CoV-2 pathogenesis. Prevotella cells, which have been found in abnormal quantities in patients with severe disease, could internalise SARS-CoV2 and enhance its pathogenicity.\(^{33-35}\) AZM is a possible treatment for Prevotella infections and decreases Prevotella-induced inflammation.\(^{36,37}\) In addition, AZM is extensively distributed into tissue, especially in the lungs.\(^{38}\)

**Conclusion**

Azithromycin acts as an antibacterial, antiviral and an immunomodulator. It is used successfully in the treatment of respiratory conditions, urethritis and recently in COVID-19. Although most of the side-effects are manageable, there is a cardiovascular risk especially when used in combination with HCQ or CQ and patients need to be monitored carefully.

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