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Azithromycin: A Pharmaceutical Studies & Mechanisms of Action

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ABSTRACT

Azithromycin is a broad-spectrum macrolide antibiotic widely used to treat various bacterial infections, including respiratory, enteric, and genitourinary infections. Pharmaceutical studies on azithromycin focus on its formulation, pharmacokinetics, bioequivalence, and therapeutic efficacy. Research has been conducted to develop stable and globally acceptable tablet formulations, considering factors like lubricants, wetting agents, and binders. Additionally, bioequivalence studies compare different formulations of azithromycin tablets under fasting and fed conditions. Azithromycin has also been studied for its potential antiviral activity and its use in treating COVID-19, where it showed promising results in combination with hydroxychloroquine in early studies. The development of analytical techniques, such as reverse-phase high-performance liquid chromatography (RP-HPLC), has been crucial for the simultaneous estimation of azithromycin and other antibiotics like cefixime in bulk and pharmaceutical formulations.

INTRODUCTION

The first macrolide antibiotic was azithromycin. It functions by preventing the growth of germs. It disrupts protein synthesis by attaching itself to the 50S ribosomal subunit of vulnerable species [1, 2]. Nowadays, injections, pills, granules, capsules, dispersible tablets, sustained-release tablets, and so forth are among the frequently utilized clinical forms of azithromycin. It is extensively utilized in clinical practice because of its excellent tissue penetration, acid stability, and noticeably extended half-life (t½) [3]. Many sensitive bacteria, including Haemophilus influenzae, Streptococcus pneumoniae, Chlamydia pneumoniae, Streptococcus pyogenes, Staphylococcus aureus, and Streptococcus agalactis, are susceptible to the antibacterial action of azithromycin. It is mainly used in respiratory infections caused by sensitive bacteria, skin and soft tissue infections, as well as simple genital infections caused by *Chlamydia trachomatis* and *non resistant gonococci* [4, 5].

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The maximal plasma concentration of azithromycin is obtained in about two to three hours due to its fast absorption [6]. After oral dosing, azithromycin's absolute oral bioavailability is estimated to be around 37% [7, 8]. At low pH, azithromycin's antibacterial action is diminished. Its widespread distribution throughout the body may be connected to its therapeutic activity. The complete elimination half-life of azithromycin following a single oral dose is around 68 hours. Azithromycin is primarily cleared via biliary excretion, where it is essentially eliminated in prototype form [9].

Azithromycin (AZT) inhibits RNA-dependent protein synthesis by attaching itself to the 50S component of the 70S bacterial ribosome. Depending on the organism, its sensitivity to AZT, and the amount of AZT present in the infected tissue, ribosomal binding either kills or stops the proliferation of bacteria.[10,11] Aqueous AZT solutions have demonstrated bactericidal activity against respiratory pathogens, Pseudomonas aeruginosa, and Staphylococcus aureus in laboratory tests.[12, 13] Oral AZT administration has been shown to be successful in treating trachoma in ophthalmology.

Topical AZT is preferred in medicine for treating eye surface infections due to the drug's minimal systemic exposure.[14] Given that AZT is hydrophobic and only weakly soluble in water at neutral pH, there are significant issues with topical application.[10] Consequently, a new drug delivery system that can provide the medication topically has to be created. In order to deliver medications for topical or systemic effects, ocular inserts are polymeric systems into which the drug is incorporated as a solution (for hydrophilic drugs) or dispersion (for hydrophobic drugs). The sterile preparations are molded as solid or semi-solid, of suitable size and shape, and are intended to be placed behind the eyelid or held on the eye.

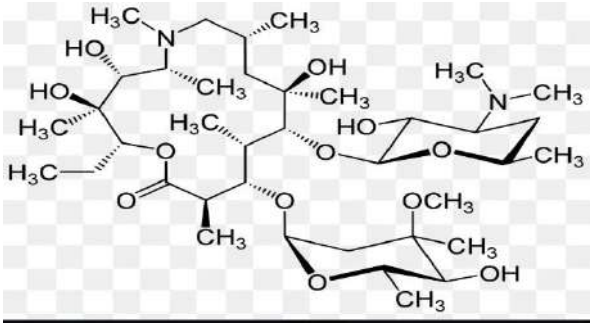
In addition to its antibacterial properties, azi, like the majority of other macrolides, also functions as an anti-inflammatory or an antivirus.

Adults' peak plasma concentrations of azithromycin are seen 12 to 24 hours after oral ingestion, and the drug has a comparatively low oral bioavailability (17–37%) [15].About 30% of proteins bind to plasma [16].

It is well known that azithromycin has a large volume of distribution (23 L/kg) and a quick plasma clearance, which affects metabolism, excretion, and high tissue concentrations. Furthermore, unlike erythromycin, it is not metabolized much, does not produce active metabolites, and does not activate cytochrome (CYP) enzymes. As a result, no clinically significant interactions with p450 enzymes have been documented [17]. For acute bacterial infections, single-dose treatment is made possible by its prolonged intracellular and plasma half-lives (68 hours in plasma and over 60 hours in tissues) [15].

Structure of azithromycin

With the molecular formula C38H72N2O12, AZM (9-deoxo-9a-methyl-9a-aza-9a-homo erythromycin A) is created by substituting methyl nitrogen for carbonyl (9a) in the aglycone ring (figure A). AZM, in contrast to erythromycin (ERY), increases strength and durability, prevents the internal reaction that leads to hemiketal production, and leaves the acid hydrolysis of the ether bond to the neutral sugar of L-cladinosis as the primary breakdown pathway. [18]



(A)

Mechanism of action

Targeting the 50S subunit of the sensitive bacterial ribosome, AZM's primary goal is to suppress bacterial protein synthesis, just like other macrolide antibiotics (Figure 2). There is a correlation between the rise in macrolide concentration and the decrease in protein synthesis.[19] The greater membrane transit rate of the unionized form of AZM may be the cause of its enhanced antibacterial activity at alkaline pH.[20]. The nascent peptide escape tunnel, which is roughly 100 Å long and 10–20 Å wide, is a location close to the peptidyl transferase center on 23S rRNA where AZM binds and partially occludes it.[21,22] AZM's binding mechanism is nearly identical to that of erythromycin. According to research on H. marismortui, the key to this process is the resting of erythromycin on a surface made up of three bases (U2611, A2058, and A2059), using three axial methyl groups that belong to the drug's lactone ring. Additionally, erythromycin is stabilized in place by a hydrogen connection that forms between the N1 atom of A2058 and the 2′ OH group of the desosamine sugar of erythromycin. Because bases are positioned within the van der Waals contact of the amino group of P-site tRNA, these interactions cause base movement and nascent peptide exit tunnel occlusion.[23] Although the nascent peptide exit tunnel has several functions other than being a normal passage to the cytoplasm, such as modifying the ribosome functions in response to sequences of the novel peptide and environment, new findings demonstrate that the context of the nascent peptide plays a significant role in altering the possibility of being allowed to pass from peptide exit tunnel, specifically does not completely obstruct the passage.[21] These occurrences cause the outer membranes to penetrate more quickly, which affects bacterial entry and boosts action against Gram-negative bacteria.[22]

Additionally, AZM exhibited anti-inflammatory effects in a number of studies. For example, Cigana et al. showed that AZM decreases TNF-α mRNA expression, TNF-α protein levels, and NF-κB DNA-binding activity in human cystic fibrosis (CF) cell lines after it was confirmed that CF cell lines had higher rates of TNF-α mRNA expression, TNF-α protein levels, and NF-κB DNA-binding activity when compared to isogenic non-CF cell lines.[24]. The reduction in NF-κB DNA-binding activity is linked to the prevention of IκBα degradation, which prevents NF-κB active subunits from translocating into the nucleus.[25]

The effects of AZM on inflammatory cell signaling include the previously mentioned decrease in NF-κB (and consequent production of IL-6 and IL-8), the inhibition of LPS-induced expression of PLA2, which is involved in the production of cytokines and chemokines in macrophages, neutrophils, and endothelial cells as well as cell signaling pathways that lead to the production of arachidonic acid and eicosanoids, and the inhibition of AP-1 signaling in neutrophils isolated from mice's lungs administered LPS, which lowers IL-1b concentrations.[26] Neutrophils are both directly and indirectly impacted by AZM.[26]The indirect effects of AZM on neutrophils are caused by its anti-inflammatory characteristics. The production of leukotriene B4 (LTB4, a strong neutrophil chemo-attractant that promotes neutrophil IL-8 release), degranulation and degradation of extracellular myeloperoxidase, a decrease in neutrophil oxidative burst, and a decrease in IL-8 release and neutrophil airway infiltration are all examples of direct effects.[27]. Through the inhibition of pro-inflammatory cytokine production, such as IL-12 and IL-6, and the shifting of surface receptor expression, AZM also aids macrophages in their transition from the M1 type to the M2 alternative-like phenotype in vitro.[28].

Pharmacokinetic parameters

The primary metabolic pathway is demethylation, and the metabolites are thought to have negligible antibacterial action[29] Following oral treatment, AZM's bioavailability increased to 37%. AZM absorption can be reduced by as much as 50% when taken with a substantial meal.[30] When AZM is taken with antacids that contain magnesium and aluminum, peak plasma concentrations may drop by 24%; nevertheless, the overall level of absorption remains unchanged.[31] After a single 500 mg oral and intravenous dosage, the average plasma clearance of AZM is 630 ml/min. Biliary excretion is the main method of AZM clearance, especially when the medication is unaltered, and feces are a common route of elimination[29] Urinary excretion of AZM appears to be a modest elimination pathway because, over the course of one week, around 6% of the administered dose is released as an unaltered substance in urine.[29] In humans, AZM has a half-life of roughly 35–40 hours following a 500 mg dosage.[32]. The time needed for plasma/blood concentration to drop by 50% following the achievement of pseudoequilibrium of distribution is known as the terminal half-life. AZM has an elimination half-life of approximately 68 hours, which is the amount of time that the drug's plasma concentration decreases solely as a result of drug removal.[33] Long-term research has shown that AZM does not have the ability to cause cancer or mutation in common laboratory animals or tests.[31] The primary side effects associated with AZM are headache, dizziness, hearing loss, cardiovascular arrhythmias, and upset stomach. Hepatotoxicity has been documented in a small number of cases. When administering AZM to patients with a prolonged QT interval, impaired hepatic function, and renal GFR <10 ml/min, care should be used.[31,34]

New formulation of AZM

After entering the lower portion of the gastrointestinal system, a new formulation of AZM that is formulated as a microsphere with long-term release (ER) to postpone the release of AZM is released gradually by avoiding the top part of the tract. This approach reduces the amount of medication released from the microspheres in the mouth and stomach as well as the microsphere matrix by alkalizing the formulation and raising the pH of the suspension. The solubility of AZM aids in regulating the drug's release. It disperses via the pores created at the microspheres' location. Despite avoiding a tiny section of the upper gastrointestinal system's absorption location, this ER formulation does not materially impair AZM's oral bioavailability. Compared to the IR formulation, the released microsphere formulation of AZM, it achieved about 83% bioavailability, enabling patients to endure a full course of AZM at a dose of 2.0 g. Antacids and this formulation should be taken on an empty stomach.31 The first antibacterial medication authorized in the United States for adult patients suffering from mild-to-moderate acute bacterial sinusitis or community-acquired pneumonia is AZM, a novel oral-free release microsphere formulation.[35] The AZM formulation in question is an oral powder that needs to be reconstituted with water and administered in a single 2.0 g dosage.Diffusion from the microspheres allows for continuous medication release; it takes five hours to reach a peak serum concentration. Free release absorbs AZM effectively. The AUC24 is approximately 8.62 μg/ml, and the mean maximum serum concentration is 0.82 μg/ml. To achieve slower absorption, free-release should be taken without food. The majority of AZM is eliminated unaltered in feces. AZM secretion has a final half-life of 59 hours.[36] Tissue-directed AZM, which offers once-daily meals for five days for the majority of illnesses that respond to oral therapy and seven to ten days for more serious intravenous infections, is

a feature of drug delivery to the infection site by phagocytes and fibroblasts. By using hepatic pathways other than cytochrome P450, metabolism reduces the possibility of medication interactions.[37].

Activity in biofilms

Studies have examined AZM's possible function as an antibiofilm and demonstrated that, when employed in aerobic settings, it takes on a planktonic state. It has been noted that AZM can considerably reduce Pseudomonas aeruginosa's (P. aeruginosa) ability to build and move biofilm.[38] There have also been reports of Porphyromonas gingivalis biofilm mass inhibition in the isolates treated with AZM.[39] When AZM and Dapsone are combined, the glycosaminoglycan and persistence of biofilms formed by isolates of Borrelia burgdorferi can be reduced.[40] Additionally, AZM can eradicate the Bartonella henselae biofilm in six days when used in conjunction with ciprofloxacin (CIP) or rifampin.[41] The AZM pattern's antibiofilm action has also been investigated in isolates of Stenotrophomonas maltophilia, and it has been shown that the combination of tigecycline and AZM can prevent the production of biofilms.[42]

Pharmacodynamic of AZM

Because of its special properties, azithromycin is categorized as a macrolide antibiotic.[43]. Numerous cells, including fibroblasts and white blood cells, actively absorb AZM due to its dual-base composition.[44].

This antibiotic agent is effective in vitro against a variety of beta-lactam-resistant bacteria (such as Legionella and Chlamydia spp.) and pyogenic bacteria (such as Neisseria gonorrhoeae [N. gonorrhoeae] and Moraxella catarrhalis [M. catarrhalis]).[45]. Because of its immunomodulatory, anti-inflammatory, and antibacterial modulatory properties, AZM helps patients with a variety of inflammatory respiratory disorders.[46]. AZM has been used in clinical trials to prevent bacterial infections in patients with COVID-19 and is also successful in these patients. According to reports, hydroxychloroquine (HCQ) and AZM together can reduce the viral load of SARSCoV-2.[47]. Additionally, AZM can alter immune system characteristics, such as lowering cytokine production, preserving the integrity of epithelial cells, and averting lung fibrosis.[48]. AZM treatment lasts for a brief amount of time. In adults, 1500 mg immediate-release (IR) AZM is administered as follows: 500 mg once day for three days, or 500 mg on day one and 250 mg on days two through five.[49] For the treatment of gonococcal urethritis, 2.0 g of IR AZM is the maximum oral dosage that is authorized.[49]

Mechanisms of anti-viral effects against rhinovirus

Macrolides decreased exacerbations of airway illnesses, especially asthma, in a number of clinical trials.[50,51] Since viral infections—most frequently rhinoviruses (RV)—cause most of these exacerbations, the effects of macrolides against RV have been the subject of the most research. When primary human bronchial epithelial cells (PBEC) are infected in vitro, AZM decreases RV replication and release.[52]. This result was confirmed in PBEC from cystic fibrosis patients and healthy controls, where AZM therapy once more resulted in a reduction in viral shedding of seven to nine times, respectively.[53]. Viral-induced interferons (IFNs) and interferonstimulated gene (ISG) mRNA expression, and consequently the generation of these gene products, were elevated by the use of AZM alone[52,53] In the later research, AZM did not inhibit pro-inflammatory reactions, but it did inhibit viral multiplication. The largest clinical trial of a long-term macrolide in airways illness, the AMAZES research, revealed in vivo findings that AZM significantly reduced asthma exacerbations by 40%.[54] Although

metagenomic investigations indicate an antibacterial effect lowering Haemophilus influenzae[55,56] may be the major mechanism, the mechanism is unclear and would be consistent with an antiviral effect. H. influenzae's overexpression of ICAM-1, a key receptor for both Haemophilus and rhinovirus (RV), may be connected to the effect on viruses.[57] Other macrolides also show anti-viral properties in RV infection including Mac5, an oleandomycin macrolide. RV replication was inhibited by both AZM and Mac5, which also increased RV-induced type I and type III IFNs and the ISGs viperin/MxA.[58]. Interleukin (IL)-6 and -8 were unaffected by macrolides in this investigation; however, in a different study of RV,[59] clarithromycin, another macrolide, decreased the secretion of IL-1β, IL-6, and IL-8 in addition to inhibiting viral multiplication and ICAM-1. Macrolides like AZM enhance IFN responses brought on by infection.[58]. This is significant for coronaviruses since type I IFN prevents SARS-CoV[60] and SARS-CoV-2[61] from replicating in vitro. The macrolides bafilomycin[63] and erythromycin[62] also prevented RV replication in PBEC. Macrolides decreased the acidity of endosomes in epithelial cells and the activation of NFκB produced by RV in both investigations. ICAM-1 expression and cytokine production were suppressed by bafilomycin.

ANTI-INFLAMMATORY EFFECTS

Although viruses can directly harm tissue through cytopathic effects on infected cells, the host's inflammatory response is usually responsible for morbidity and mortality in extreme cases, such as COVID-19.[64] Numerous immunomodulatory characteristics of AZM and other macrolides have demonstrated clinical effectiveness in treating a wide variety of respiratory conditions, such as diffuse pan bronchiolitis (DPB), post-lung transplant obliterative bronchiolitis (PLT), COPD, and asthma.[65,66] In DPB, AZM's capacity to block dysregulated IL-1β, IL-2, TNF, and GM-CSF has been linked to a significant rise in survival[65,66,67,68] Consequently, ADM's anti-inflammatory qualities (explained in Table 2 and Figure 1) could be therapeutically significant in the treatment of viral illnesses.

Anti-viral effects in enteroviruses

Young children are susceptible to hand, foot, and mouth illness due to Enterovirus A71 (EV-A71). Mice were significantly protected against EV-A71 infection in vivo by AZM and another macrolide, spiramycin.[69]. After viral entrance, spiramycin and AZM most likely function via a similar mechanism, affecting viral RNA production either directly or indirectly. Spiramycin also inhibited EV-A71 viral RNA synthesis.

Anti-viral effects in Ebola

The effectiveness of AZM as an Ebola treatment was also assessed in a drug screen.[70] Although AZM showed minimal toxicity and great in vitro efficacy (50% effective concentration [EC50] = 5.1 μM), it did not consistently increase mouse or guinea pig survival when evaluated in an in vivo animal model.

Anti-viral effect in Zika virus

In glial cell lines and human astrocytes, AZM decreased viral growth and virus-induced cytopathic effects in a pharmacological screen of 2177 compounds against the flavivirus Zika.[71,72]. By focusing on a late stage of the viral life cycle, AZM was found to successfully reduce Zika infection in a subsequent in vitro research.Twelve Similar to AZM's actions in RV.[52], AZM also increased the expression of type I and III IFNs as well as a number of their downstream ISGs.[53]. Additionally, AZM increased the amounts of phosphorylated TBK1 and IRF3, as well as the expression of the antiviral pattern recognition receptors (PRRs) MDA5 and RIG-1.

Mechanism of effects in influenza A

Five days of supplementary AZM 500 mg daily was linked to faster decreases in plasma concentrations of IL-6, IL-8, IL-17, CXCL9,soluble tissue necrosis factor (TNF), and C-reactive protein (CRP) in patients with influenza A taking oseltamivir in a randomized study.[73] However, the impact was minimal, with no discernible improvements in viral clearance or time to symptom resolution, and the research was open-label and had a small sample size (n = 50). Two days of clarithromycin 500 mg and naproxen 200 mg twice daily decreased 30-day mortality, high dependency unit admission, and hospital stay in 217 elderly patients with H2N2 influenza in a second, bigger, open-label, randomized controlled study.[74]

The study's limitations include the absence of blinding and the possibility that a significant amount of the effect could be due to clarithromycin's antibacterial qualities, given that bacterial pneumonias account for a significant percentage of influenza-related deaths, especially in the elderly. Nevertheless, the effect size was noteworthy. Clarithromycin, however, inhibited viral multiplication in the human lung cell line A549 in vitro.[75] Similarly, on cultured human tracheal epithelial cells, clarithromycin decreased viral titres and supernatant cytokines. This was linked to decreased surface expression of the influenza A receptor Sα2, 6Gal, inhibition of NFκB, and decreased acidification of the endosome, which is necessary for the intracellular release of viral RNA.[76] Additionally, more recent studies shown that AZM reduced H1N1 viral multiplication in A549 cells with an IC50 of 68 μM. This impact was particularly noticeable during viral particle internalization. [77,78] Macrolides have been studied in vivo in a few experiments on mice. Erythromycin decreased inflammatory cells, nitric oxide-derived free radicals, bronchoalveolar lavage (BAL), and IFN-γ, which all contributed to better survival after a severe H2N2 infection. In H1N1 influenza, additional macrolides such as leucomycin A3, spiramycin, and a non-antibacterial erythromycin derivative (EM900) all decreased viral protein expression, enhanced survival, and decreased weight loss.[79] Two days after infection, AZM decreased the expression of viral proteins in a model of a short-term H1N1 infection.[77] Two days after infection, AZM decreased the expression of viral proteins in a model of a short-term H1N1 infection.[77] Nevertheless, the impact was short-lived and unrelated to a shift in virus-induced weight loss, a sensitive indicator of influenza pathophysiology. Although the effects of AZM were not superior to those of oseltamivir in terms of survival, viral titres, or cytokine levels,[80] another investigation discovered that AZM decreased lung viral titres at day 6 post-infection. As a result, these findings are still inconclusive.[81] AZM reduced total leukocyte accumulation in lung tissue and BAL in a separate influenza investigation, with neutrophils showing the most drop. It was also linked to a decrease in inflammatory mediators.

Effects on other cell types

In vitro AZM reduced the expression of CD40, CD86, MHCII, and IL-12.96,97 while regulating the differentiation and maturation of dendritic cells towards a regulatory phenotype with enhanced phagocytic capacity,[82,83]. Similarly, by downregulating perforin, AZM prevented natural killer cells from having a cytotoxic effect.[84] AZM may directly affect epithelial cells by suppressing the release of GM-CSF, TNF,114 inhibiting the production of IL-8,[85] and modulating the antiviral PRRs RIG-I and MDA5. AZM inhibition of AP-1 activation lowers the production of MUCA5C, which is responsible for inflammation-induced alterations in airway mucus.[86],[87] Macrolides directly inhibit neutrophil elastase and suppress mucus production by airway epithelial cells[88.89,90] Increased

epithelial barrier integrity due to changes in tight junction proteins, such as claudins, is another impact of macrolides on airway epithelial cells seen in vitro.[91,92]

All things considered, macrolides have a variety of inhibitory effects on innate and adaptive immune cells' production of pro-inflammatory cytokines, but they most significantly affect pulmonary neutrophil accumulation, adhesion, and death.

The future studies on azithromycin:

Future studies on azithromycin are focusing on several key areas:

- ✓ **Antimicrobial Resistance**: Research is ongoing to understand and combat the rising trends of azithromycin resistance. This includes studying the genetic mutations and environmental factors contributing to resistance, as well as developing strategies to mitigate its impact.
- ✓ **Immunomodulatory Effect**s: Azithromycin's potential as an immunomodulatory agent is being revisited, particularly in the context of COVID-19. Studies are exploring its effects on the immune response, including its ability to inhibit pro-inflammatory cytokine production and its potential benefits in treating severe viral infections.
- ✓ **Combination Therapies**: Researchers are investigating the use of azithromycin in combination with other drugs to enhance its efficacy. This includes exploring its synergistic effects with other antibiotics and antiviral agents.
- ✓ **New Formulations**: Developing new formulations of azithromycin to improve its delivery and effectiveness is another area of ongoing research. This includes exploring different delivery methods and formulations to enhance patient compliance and therapeutic outcomes.

These studies aim to ensure that azithromycin remains an effective treatment option while addressing the challenges posed by resistance and exploring new therapeutic applications.

CONCLUSIONS

Macrolides, and AZM in particular, are intriguing compounds as a therapeutic class because of their solid evidence basis in bacterial illnesses, lengthy therapeutic half-life, and favorable safety profile. In vitro, macrolides surely possess broad-spectrum antiviral properties. Antiviral drug tests against respiratory viruses regularly show AZM as a potential molecule, and clinical investigations to far have shown intriguing signs of clinical effectiveness. Some macrolides, such as AZM, have additional anti-inflammatory qualities that may be clinically significant in lowering immunopathology in some viral infections,not least against the pandemic betacoronaviruses, whose mortality appears to be significantly impacted by the activation of an excessive inflammatory cascade. Currently, there is not enough evidence to support their clinical use; instead, there is a clear mandate to conduct well-designed and conducted randomized trials in patients with respiratory viruses such as influenza A, SARS-CoV-2, and future pandemics of novel coronaviruses, which seem to be an inevitable prospect.

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