International Journal of Pharma Research and Health Sciences, 2022; 10(4): 3445-3448.
DOI:10.21276/ijprhs.2022.04.02
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CODEN (USA)-IJPRUR, e-ISSN: 2348-6465

Review article

Azithromycin: Updated Review

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ARTICLE INFO:
Received: 01 July 2022
Accepted: 12 Aug 2022
Published: 31 Aug 2022

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ABSTRACT:
As a macrolide antibiotic of the second generation, azithromycin (AZM) is effective against a wide range of bacteria. A full stomach slows down the absorption process of the drug Azithromycin. Azithromycin has a 68-hour apparent terminal elimination half-life. COVID-19, the virus that causes corona virus illness, is one of the viruses being examined that Azithromycin is potential as a cure for Treatment. To treat *S. agalactiae, S. aureus* and *or S. pyogenes* infections of skin, azithromycin may be prescribed. The combination of hydroxychloroquine and azithromycin has cardiac toxicity. It is effective against MRSA and *P. aeruginosa*, as well as in combination treatment for individuals with underlying conditions. Azithromycin shows 37% bioavailability. Any patient with a history of hepatic dysfunction or cholestatic jaundice as a consequence of azithromycin use or those who are allergic to any ketolide or macrolide, erythromycin, azithromycin treatment should avoid using this medicine. Azithromycin does not need any particular stomach protection precautions since it is acid-stable. Most of azithromycin's biliary excretion takes place. The most serious toxicities of azithromycin were cardiac adverse reactions. Increasing the dose increased the risk of ADRs.

Keywords: Azithromycin, Macrolide, SARS-CoV-2, Comorbidities, Translation, *gonococcus*.

1. INTRODUCTION

Azithromycin, second-generation synthetic macrolide antibiotic, has been used to treat mycobacterial and bacterial infections of respiratory system and skin since the early 1980s. As a result, it is listed as an essential medicine by the World Health Organization and is widely produced across the world. Because of its capacity to hold on to 50S ribosomal sub-unit and prevent synthesis of protein, it possesses antibacterial properties. It also has antiviral and anti-inflammatory qualities, and it's being researched as a probable treatment for viruses like SARS-CoV-2, which is reason for COVID-19 (coronavrius-19 disease). Previous coronavirus illnesses, such as SARS in 2003 and MERS 5 in 2012, were treated with it [1]. Antibiotic resistance in Gonococcus against Sulphonamide was discovered in the early 1940s. Since then, resistance to penicillin, cephalosporins, macrolides, fluoroquinolones and tetracyclines has spread fast. Because of its long $t_{1/2}$ and high tissue levels, azithromycin revolutionised gonococcal therapy, reducing treatment time from seven to fourteen days and boosting patient compliance.

Antimicrobial activity:

Although activity varies by species, azithromycin has an in vitro action range similar to erythromycin. While less effective than roxithromycin and clarithromycin, azithromycin has been shown to be effective against *S. aureus* isolates, including generating strains of beta-lactamase. Several isolates of *S. epidermidis* and other negative *staphylococci* were also susceptible to azithromycin. Nonetheless, macrolide-resistant *staphylococci* were frequent, and azithromycin was ineffective in these cases. It also shows effectiveness against viruses, i.e., antiviral activity. On August 1, 2010, this entry was published [2].

Chemical structure of Azithromycin:

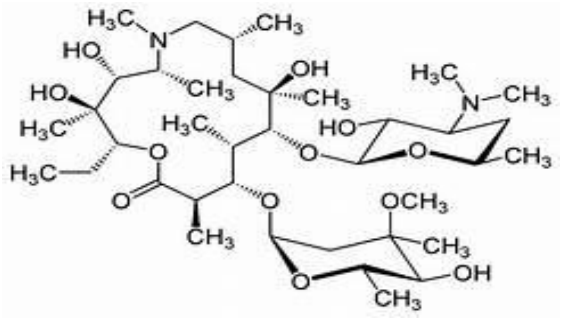

Fig 1: Structure of Azithromycin

Molecular mass: 748.996 $gmol^{-1}$

Molecular Formula: $C_{38}H_{72}N_2O_{12}$

IUPAC Name: 2-Ethyl-3,4,10-trihydroxy-3,5,6,8,10,12,14-heptamethyl-15-oxo-11-{[3,4,6-trideoxy-3-(dimethylamino)hexopyranosyl]oxy}-1-oxa-6-azacyclopentadecan-13-yl-2,6-dideoxy-3-C-methyl-3-*O*-methylhexopyranoside [3].

Dose: In patients with acute outbreaks of sinusitis, tonsillitis, pneumonia, pharyngitis, otitis media and chronic bronchitis,

3day oral routine of once a day of azithromycin was effective as 5-10day courses of other antibacterial drugs like phenoxymethylpenicillin (penicillin V), amoxicillin-clavulanic acid and erythromycin.

Adults: 500 mg orally on Day first, then 250 mg orally once a day for at least 5 days as part of a combination treatment for patients with simultaneous presence of two or more diseases. The length of therapy should be based on how stable the patient is in the clinic. The FDA approved labelling suggests a 5-day course of treatment.

Adults (Hospitalized):

As part of a combination treatment, 500 mg orally once a day for at least 5 days. The length of therapy should be based on how stable the patient is clinically.

Adolescent, Infants and Childrens:

- 500 mg orally for day 1, then 250 mg orally once a day for 4 days. Azithromycin is recommended as the first oral medicine for people with atypical infections. Azithromycin used as combination therapy in HIV infected peoples.
- 500 mg orally for day 1, then 250 mg orally once a day for 4 days. Azithromycin is recommended as the first oral medicine for people with atypical infections. Azithromycin used as combination therapy in HIV infected patients with atypical pathogens.

Adults:

As a single dosage, 2g PO [per oral]. Patients who are sick to the point of being moderately or severely ill or who have other underlying risk factors that make oral medication unsuitable for them should not take this type of dose [4].

Mechanism of action:

Azithromycin works in a similar way to erythromycin in terms of how it works. It binds to the 50s ribosomal subunit's 50s component, preventing cell-free polypeptide synthesis guided by natural messenger RNA. Extracellular concentration, pH, cell viability, temperature, infection status, and cytokine administration all have an impact on absorption. As shown by decreased intracellular concentrations in Mycobacterium avium complex-infected cells, infected cells may have reduced absorption. Azithromycin inhibits bacteria from growing by interfering with protein synthesis. It binds to the 50S component of the bacterial ribosome and prevents mRNA translation but the Nucleic acid synthesis is unaffected [5]. The mechanism of action mentioned in figure 2 [6].

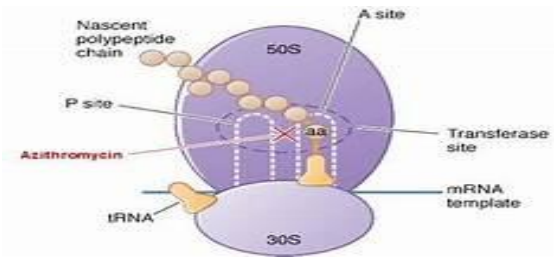

Fig 2: Mechanism of Action of Azithromycin [6]

2. PHARMACOKINETIC PROFILE

Absorption:

Because azithromycin is acid-stable, it may be taken orally without stomach acid protection. It is readily absorbed, however it absorbs more quickly when consumed on an empty stomach. Tmax ranges from 2.1 to 3.2 hours for oral dose formulations in humans. Because it is found in high amounts in phagocytes, azithromycin is rushed to the site of the infection. When phagocytosis is going on, a lot of stuff is discharged. Due to ion trapping and high lipid solubility, Azithromycin concentrations in tissues may be more than 50 times higher than in plasma [7].

Bioavailability: Bioavailability of the azithromycin 37%.

Plasma protein Binding: Azithromycin binds to human plasma proteins only 7% of the time at 1mg per L, but 50% of the time at doses of 0.02 to 0.05 mg per L. Azithromycin binds less than Erythromycin or Roxithromycin (72% at 0.4 mg per L or 96% at 2.5 mg per L respectively), more free azithromycin may available for distribution at the sites of infection. The antibiotic azithromycin seems to be broadly dispersed throughout the body, with amounts found in tissues, tissue fluids, organs, and a number of cell types, especially phagocytes, greater than the level in the blood. Dispersion volumes have been found to range between 23 and 31 L/kg [8].

Half-life: Azithromycin have long half-life, a large single dose is given and bacteriostatic level in infected tissues maintained for many days. Terminal elimination half-life of azithromycin after administration of single dose 500 mg is 68 hours.

Metabolism: Metabolism of the drug azithromycin is through Liver.

Excretion: A main route of elimination for azithromycin is biliary excretion, which is mostly unchanged. Approximately 6% of the supplied dosage shows as an unaltered medication in the urine and kidneys (4.5%) after a week [9].

Drug Interaction: Azithromycin is a modest inhibitor of CYP3A4 when it comes to drug–drug interactions. However, no clinically significant interaction has yet been identified. Azithromycin is a potent inhibitor of the drug transporter Pgp. Other Pgp substrates, such as tacrolimus, an immunosuppressant, and anticoagulants like apixaban, should be taken with care, especially if their therapeutic index is narrow.

The combination of hydroxychloroquine with azithromycin causes cardiac toxicity [10].

Adverse effects:

- Gastrointestinal upset
- Headache
- Dizziness
- QT Prolongation
- Hearing loss or impairment has been reported with azithromycin, especially in COPD patients who had

normal hearing at the outset, and it seems to be permanent in some instances [11]

- Abdominal pain
- Drowsiness
- Irregular or slow heart rate
- Nausea or vomiting
- Elevated liver enzymes
- Change in WBCs count
- Diarrhoea or loose stool

Side Effects:

Generally azithromycin is well taken, Stomach upset, Dizziness and Headache are some common adverse effects (1–5% patients). Level of Transient transaminase increases have been seen in around a quarter of peoples. Impairment or Hearing loss has reported with azithromycin, specifically in COPD patients who had normal hearing at the outset, and it seems to be permanent in some instances [11].

Contraindication: Any ketolide or macrolide, erythromycin, azithromycin

Azithromycin, erythromycin, any macrolide or ketolide prescription, or a history of hepatic dysfunction or cholestatic jaundice linked to previous azithromycin therapy should be avoided. According to the data sheet, individuals with hepatotoxicity, infantile hypertrophic pyloric stenosis, Hepatotoxicity, Myasthenia Gravis (Muscular weakness), and history of QT interval prolongation should take this antibiotic with caution [12].

Clinical Uses: Azithromycin is a drug that is used to treat a various of illnesses, including:

1.Prevention and treatment of acute bacterial exacerbations of chronic obstructive pulmonary disease due to *H. influenzae, M. catarrhalis, or S. pneumoniae*. The benefits of long-term prophylaxis must be weighed on a patient-by-patient basis against the risk of cardiovascular and other adverse effects.

2. Community-acquired pneumonia due to *C. pneumoniae, H. influenzae, M. pneumoniae*, or *S. pneumoniae.*

3. Uncomplicated skin infections due to *S. aureus, S. pyogenes,* or *S. agalactiae*

4. *C. trachomatis* or *N. gonorrhoeae* induce urethritis and cervicitis in women. When coupled with ceftriaxone, azithromycin is part of a Gonorrhea treatment regimen suggested by the USCDC. Although azithromycin is effective on its own in most cases, it is recommended that it be used in combination with ceftriaxone because to developed low barrier to resistance in *gonococci* and the predominant co-infection with *N. gonorrhoeae* and *C. trachomatis. Chlamydia trachomatis* produce Trachoma.

5. *H. ducrey* causes genital ulcer disease (chancroid) in males.

6. An infection of middle ear is caused by *M. catarrhalis, S. pneumoniae* or *H. influenzae*. Azithromycin, on the other hand, is not recommended as a front-line therapy for this condition. Another beta-lactam antibiotics or Amoxicillin is preferred in most circumstances.

7. *S. pyogenes*-caused pharyngitis or tonsillitis as alternative to front-line therapy in patients those are unable to tolerate first-line therapy.

3. DISCUSSION

- Maintenance therapy with azithromycin improves respiratory function in cystic fibrosis patients (CF) [13].
- Azithromycin is a widely used antibiotic in general. In periodontal therapy, medicine has recently discovered a niche. This study's goal was to compare azithromycin versus amoxicillin plus metronidazole in vitro antibacterial efficacy [14].
- During pregnancy and lactation, avoid azithromycin and lopinavir/ritonavir. The use of hydroxychloroquine and/or azithromycin is unlikely to cause harm. raising the chance of birth abnormalities and other negative effects in breastfeeding children and infants [15].
- In some individuals, azithromycin might have side effects. They looked studied how well azithromycin worked as a supplementary treatment for those who had uncontrollable asthma symptoms [16].
- The FDA has amended the labelling on azithromycin packaging to warn of the risk of prolonged cardiac repolarization and QT prolongation, both of which may lead to cardiac dysrhythmias in the elderly [17].
- Azithromycin is the antibiotic with the fewest drug interactions, but clarithromycin and erythromycin both increase drug interactions [18].
- When delivered to infection sites by direct absorption and focused phagocyte distribution, azithromycin may achieve high tissue concentrations. High tissue concentrations may be maintained for a long period because to azithromycin's lengthy half-life [19].
- In the list of safest antibiotics, Azithromycin is one in the market, with good tolerability and distinct pharmacokinetic properties. It also has an antibacterial spectrum that is rather broad. Azithromycin is an antibiotic that used to treat different eye conditions [20].
- Antibiotic, Azithromycin. From its discovery, Azithromycin has been FDA-approved for respiratory disorders like genitourinary infections like chlamydia, and enteric infections like typhoid, malaria, as well as pneumonia [19].
- A sulfonamide-resistant *Gonococcus* strain was found in the early 1940s. Penicillin, tetracycline, macrolide, fluoroquinolone, and cephalosporin resistance has expanded quickly since then. Because of its high tissue levels and long half-life, azithromycin revolutionised gonococcal therapy, reducing treatment time from seven to fourteen days and boosting patient compliance [20].

4. CONCLUSION

Macrolides, particularly azithromycin, are appealing medical agents due to their lengthy therapeutic half-life, favourable safety profile, and extensive evidence base in bacterial diseases. In vitro, macrolides show antiviral activity throughout a wide range. Azithromycin is often identified in antiviral medication for respiratory infections causing viruses, and clinical efficacy has been shown in studies. The most common negative effects of azithromycin were cardiac adverse events. When the dose was increased, the risk of ADRs grew. This macrolide has been associated to improved clinical outcomes in the treatment of a variety of viral infections, activity against COVID-19 has been proven in vitro, and azithromycin may act at different phases of the viral cycle.

The fact that azithromycin is a promising in Corona virus disease-19 therapy, safety concerns have been raised due to its potential cardiotoxicity, especially when used with hydroxychloroquine.

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ACKNOWLEDGEMENT: None

CONFLICT OF INTEREST: The authors declare no conflict of interest, financial or otherwise.

SOURCE OF FUNDING: None.

AVAILABILITY OF DATA AND MATERIALS: Not applicable.

CONSENT FOR PUBLICATION: Not applicable.

ETHICS APPROVAL AND CONSENT TO PARTICIPATE: Not applicable.