AZITHROMYCIN

Indications

Azithromycin is indicated for:

1) Treatment of bacterial infections caused by pathogens susceptible to azithromycin:
    a. Lower respiratory tract infections (bronchitis and pneumonia)
    b. Upper respiratory tract infections (otitis media, sinusitis, tonsillitis, and pharyngitis)
    c. Genital infections, gonorrhea
    d. Prostatitis and urethritis (not caused by Neisseria gonorrhoeae)
    e. Chancroid (caused by Haemophilus ducreyi)
    f. Infections by Mycoplasma hominis
    g. Odontostomatological infections
    h. Skin and soft tissue infections;
2) Treatment of community-acquired pneumonia (outside the hospital setting);
3) Treatment of Legionnaire's disease (severe acute pneumonia with an average mortality rate of 10%, which can rise to 80% in immunocompromised patients);
4) Prophylaxis of Mycobacterium Avium Complex infections, either as monotherapy or in combination with rifabutin; treatment of these infection in patients with advanced HIV in combination with ethambutol;
5) Treatment of Crohn's disease (if Mycobacterium paratuberculosis is involved as a causal factor), in combination with rifabutin;
6) Treatment of protozoal infections caused by Toxoplasma (Martindale, 1999);
7) Treatment of pelvic inflammatory disease;
8) Treatment of Mediterranean spotted fever in children;
9) Eradication of Helicobacter pylori in combination with other drugs;
10) Treatment of mild acute bacterial sinusitis in patients allergic to penicillins or cephalosporins;
11) Treatment of inflammatory acne as an alternative to tetracyclines and erythromycin, in combination with topical retinoids and benzoyl peroxide;
12) Treatment of bacterial conjunctivitis;
13) Treatment of severe traveler's diarrhea in patients allergic to sulfonamides or unable to take fluoroquinolones.

Dosage

Below is the dosage regimen for azithromycin in various therapeutic indications.

Monotherapy

Generic use

Oral administration.

Adults: 500 mg/day of azithromycin for 3 days. Alternatively, 500 mg as a single dose on the first day followed by 250 mg once daily.

Children (weight <15 kg): 10 mg/kg/day of azithromycin for 3 days.

Children (weight: 15-25 kg): 200 mg/day of azithromycin for 3 days.

Children (weight: 26-35 kg): 300 mg/day of azithromycin for 3 days.

Children (weight: 36-45 kg): 400 mg/day of azithromycin for 3 days.

Children (weight >45 kg): 500 mg/day of azithromycin for 3 days.

Pharyngitis and tonsillitis

Oral administration.

Adults: 500 mg/day of azithromycin for 3 days or 500 mg on the first day followed by 250 mg/day for the next 4 days.

Children: 10 mg/kg/day of azithromycin for 5 days. In cases of streptococcal pharyngitis, a dose of 20 mg/kg/day may be administered as a single daily dose for 3 days of therapy. Do not exceed a maximum azithromycin dose of 500 mg/day.

Otitis, respiratory tract infections, skin infections

Oral administration.

Adults: 500 mg/day of azithromycin for 3 days or more days. Alternatively, an initial dose of 500 mg followed by 250 mg/day for 4 days.

Children: 10 mg/kg on the first day of treatment (do not exceed 500 mg/day) and 5 mg/kg/day for days 2-5.

Acute otitis media

Oral administration.

Children: 10 mg/kg of azithromycin as a single dose on the first day, followed by 5 mg/kg as a single dose for 4 days, with a maximum daily dose of 250 mg.

Inflammatory acne

Oral administration.

Adults: 250 mg/day of azithromycin three times a week (for a duration of 3-6 months).

Prophylaxis for endocarditis in dental procedures

Oral administration.

Adults: 500 mg of azithromycin 30-60 minutes before dental procedures (cleanings, extractions, suture removal, biopsies, orthodontic band placement) or surgical interventions involving oral mucosal perforation. Endocarditis prophylaxis is indicated for patients with a history of infective endocarditis, those with prosthetic heart valves, patients with uncorrected cyanogenic congenital heart disease, and patients with corrected congenital heart disease with implanted medical devices.

Non-gonococcal urethritis and cervicitis

Oral administration.

Adults: 1 g/day of azithromycin as a single dose.

Mycobacterium avium complex

Oral administration.

Adults: 1.2 g of azithromycin as a single daily dose, once a week for prophylaxis. Adults: 600 mg/day of azithromycin for 16-24 weeks in combination with ethambutol for the treatment of confirmed infection.

Children: in clinical studies, a dose of 20 mg/kg of azithromycin yielded systemic exposure similar to that in adult patients with a dose of 1200 mg.

Uncomplicated gonorrhea

Oral administration.

Adults: 1 g/day of azithromycin as a single dose.

Legionnaire’s disease

Oral administration.

Adults: 500 mg/day of azithromycin as a single dose for 3-5 days for mild cases. Intravenous Administration.

Adults: 500 mg/day of azithromycin as a single dose for 7-10 days for severe cases, in hospitalized or immunocompromised patients. Administer azithromycin via intravenous infusion lasting at least 1 hour; do not administer as a bolus injection.

Interstitial pneumonia

Oral administration.

Adults: 500 mg/day of azithromycin.

Community-acquired pneumonia (CAP)

Intravenous administration.

Adults: 500 mg/day of azithromycin for at least 2 days, than continue with 500 mg orally for 7-10 days.

Children: 10 mg/kg/day of azithromycin for 2-5 days. Administer azithromycin via intravenous infusion lasting at least 1 hour; do not administer as a bolus injection.

Pelvic inflammatory disease

Intravenous administration.

Adults: 500 mg/day of azithromycin for 1-2 days, followed by 250 mg/day orally for 7 days. Administer azithromycin via intravenous infusion lasting at least 1 hour; do not administer as a bolus injection.

Mediterranean spotted fever

Oral administration.

Children: 600 mg/day of azithromycin for 3 days.

Chlamydia trachomatis prostatitis

Oral administration.

Adults: 500 mg/day of azithromycin for 3 days per week for 3 weeks.

Helicobacter pylori eradication in combination with other drugs

Oral administration.

Adults: 500 mg of azithromycin on the first day, followed by 250 mg/day for the next 4 days of therapy.

Traveler’s Diarrhea

Oral administration.

Adults: 1000 mg of azithromycin as a single dose or 500 mg/day for 3 days.

Children: 10 mg/kg of azithromycin on the first day and 5 mg/kg on the second and third days of treatment.

Contraindications

Contraindications to the use of azithromycin:

1) Hypersensitivity to macrolides;
2) Allergic diathesis;
3) Severe hepatic insufficiency;
4) Breastfeeding;
5) Pediatric patients (age <1 year) (insufficient literature data regarding safety and efficacy).

Warnings

Risk of superinfections: Prolonged and repeated administrations of azithromycin may lead to the development of superinfections. In such cases, discontinuation of antibiotic treatment and initiate of appropriate therapy are recommended.

Patients on digoxin therapy (cardiac glycosides): in patients concurrently taking digoxin therapy and azithromycin, it is advisable to monitor serum digoxin levels (digoxinemia). If elevated plasma levels are detected, a reduction in the digoxin dose should be considered.

Patients with cardiac disorders: administering azithromycin to patients with a high baseline cardiovascular risk or risk factors for prolongation of the QT interval on electrocardiogram should be approached with caution. Based on findings from a large retrospective clinical study evaluating cardiovascular mortality risk associated with various antibiotics, azithromycin was found to increase the risk of cardiovascular mortality, especially in patients with a pre-existing high cardiovascular disease risk (azithromycin was associated with prolonged QT interval on the electrocardiogram) (Ray et al., 2012). Consequently, the U.S. Food and Drug Administration (FDA) issued a warning in 2013 regarding the potential for fatal arrhythmia associated with azithromycin use (FDA, 2013). However, more recent clinical study, utilizing data from the Danish national registries from 1997 to 2010, have not confirmed an increased risk of cardiovascular mortality in patients treated with azithromycin or those who have used the antibiotic (adjusted cardiovascular mortality rate: 1.1 vs. 1.5 per 1000 patients/year for azithromycin and penicillin V, respectively) (Svanstrom et al., 2013). This lack of correlation between azithromycin and cardiovascular mortality was also observed in another more recent clinical study conducted on over 260,000 patients, utilizing data from the Oregon Public Health Division for the period 1996-2012 and Public Health-Seattle and King County data for the period 1993-2010) (Khosropour et al., 2014). Similarly, The ARITMO (Arrhythmogenic Potential of Drugs) study, conducted across five European countries (Denmark, Germany, Italy, the Netherlands, and the United Kingdom) involving over 14 milion outpatients, found that the risk of ventricular arrhythmia observed with azithromycin appeared to be more dependent on the patient's health status than the antibiotic itself. By comparing the risk of arrhythmia between azithromycin and no antibiotic use and between azithromycin and amoxicillin, and adjusting for confounding factors (primarily related to comorbidities in patients, such as cardiovascular and metabolic diseases or treatments with drugs that could induce hypocalcemia or QT interval prolongation), an increased risk with azithromycin was observed compared to no antibiotic use (Hazard ratio, HR: 1.97; 95% CI: 1.35-2.86), but not compared to amoxicillin (HR: 0.94; 95% CI: 0.50-1.77) (Trifirò et al., 2017).

Patients on HMG-CoA enzyme inhibitors: caution is advised when administering azithromycin due to the potential risk of rhabdomyolysis. If a macrolide is necessary, azithromycin is preferred due to its lack of effects on hepatic cytochrome.

Patients exhibiting allergic reactions: administering azithromycin to patients with severe allergic reactions (such as angioedema, anaphylaxis, Stevens-Johnson

syndrome) requires caution. In hypersensitivity reactions occur, symptomatic therapy should be initiated; if symptoms do not improve, azithromycin administration should be discontinued.

Antacids containing magnesium salts: simultaneous administration of azithromycin and antacids containing magnesium should be avoided.

Warfarin: in patients on warfarin therapy who are also taking azithromycin, monitor prothrombin time.

Diarrhea: as azithromycin can induce pseudomembranous colitis, in cases of diarrhea, the underlying cause should be investigated, and if necessary, the medication should be discontinued.

Renal insufficiency: no dosage adjustment is required in patients with mild to moderate renal insufficiency (CLcr 30-80 ml/min). Azithromycin should be used with caution in patients with severe renal insufficiency (GFR < 30 ml/min) due to the potential for increased systemic exposure.

Hepatic Insufficiency: azithromycin undergoes hepatic metabolism and is excreted through bile; therefore, it should not be administered to patients with severe liver impairment (risk of significantly elevated plasma levels with potentially severe side effects).

Pregnancy: although azithromycin is not considered embryotoxic or fetotoxic, it is recommended to administer the drug during pregnancy only when absolutely necessary, after a careful assessment of the clinical benefits and potential risks (in vivo studies are not always predictive of human responses).

Breastfeeding: azithromycin is excreted in breast milk, so its administration should be avoided during this period, or breastfeeding should be discontinued.

Sucrose: azithromycin suspension may contain high levels of sucrose, up to 3.9 g/5 ml. Evaluate the possibility of administering this formulation to patients with genetic or acquired carbohydrate metabolism disorders.

Interactions

Astemizole, midazolam, alfentanil: there are no available literature data regarding interactions with astemizole, midazolam, and alfentanil. Caution is recommended during concurrent use of these substances with azithromycin due to documented potentiation of their effects when used simultaneously with the macrolide antibiotic erythromycin.

Atorvastatin: co-administration of atorvastatin (10 mg/day) and azithromycin (500 mg/day) did not reveal any pharmacological interactions.

Antacids containing magnesium and aluminum: they decrease the oral absorption of azithromycin, resulting in a lower peak plasma concentration (reduction of 24%), but do not alter the 48-hour AUC (Foulds et al., 1991). Since the therapeutic efficacy of azithromycin is independent of plasma concentration, this pharmacological interaction is not of high clinical relevance. However, it is recommended to separate the administration of azithromycin and magnesium and/or aluminum-containing antacids by at least two hours (Pai et al., 2000).

Calcium channel blockers: unlike erythromycin and clarithromycin, azithromycin has not been shown to increase the risk of hypotension and shock in patients treated with calcium channel blockers (Wright et al., 2011).

Carbamazepine, cimetidine, didanosine, methylprednisolone, efavirenz, indinavir, fluconazole, trimethoprim/sulfamethoxazole, zafirlukast: no significant interactions with azithromycin have been reported (Pai et al., 2000).

Cetirizine: co-administration of cetirizine and azithromycin did not reveal any pharmacokinetic interactions, and no significant changes in the QT interval were reported.

Cyclosporine: azithromycin can alter its plasma concentration (Ljutic, Rumboldt, 1995).

Cisapride: cisapride is metabolized in the liver by the enzyme CYP3A4. Since azithromycin, unlike other macrolides, has a minimal effect on cytochrome enzymes, the clinical relevance of a potential azithromycin-cisapride pharmacological interaction is likely to be minimal.

Digoxin, digitoxin: azithromycin can increase the blood concentration of digoxin and digitoxin, leading to toxicity (Ten Eick et al., 2000; Thalhammer et al., 1998). Proposed mechanisms for this pharmacological interaction involve the inhibition of tubular secretion of digitalis glycosides mediated by P-glycoprotein and/or an increase in glycoside serum concentration due to azithromycin's effect on Eubacterium lentum, a microorganism in the intestinal flora capable of metabolizing them. Co-administration of azithromycin with these glycosides requires careful monitoring for signs and symptoms of cardiac toxicity.

Ergotamine, dihydroergotamine: the combination with azithromycin can lead to acute ergot toxicity characterized by peripheral vasospasm and paresthesia. This combination is contraindicated.

Lovastatin: an episode of rhabdomyolysis has been reported in a patient receiving lovastatin and azithromycin. The role of azithromycin in triggering this adverse effect has not been definid; it is believed that rhabdomyolysis induced by lovastatin in combination with macrolides may be due to drug inhibition of HMG-CoA metabolism mediated by cytochrome. In reality, azithromycin does not affect hepatic cytochrome activity. In the absence of more precise and detailed information, caution is advised when administering azithromycin to patients receiving HMG-CoA enzyme inhibitors (Grunden et al., 1997).

Nelfinavir: administration of azithromycin (single dose of 1200 mg) to patients receiving nelfinavir (750 mg every 8 hours for 11 days) resulted in a statistically significant but clinically irrelevant reduction in systemic exposure to nelfinavir and its active metabolite. Nelfinavir, in turn, caused a more than 100% increase in the peak plasma concentration and AUC of azithromycin (likely P-glycoprotein inhibition). Since patients receiving both drugs reported only a slight increase in the most common gastrointestinal side effects, the pharmacological interaction may increase the antibacterial activity of azithromycin without substantially affecting gastrointestinal tolerability (Amsden et al., 2000).

Rifabutin: increased toxicity (neutropenia) has been reported in patients receiving rifabutin in combination with azithromycin (Apseloff et al., 1998).

Theophylline: there are conflicting data regarding the potential theophylline-azithromycin pharmacological interaction. In the absence of further information, monitoring the serum levels of both drugs is recommended (Pollak et al., 1997; Gardner et al., 1992).

Terfenadine: administration of azithromycin (500 mg/day on the first day, than 250 mg/day for 4 days) to patients on terfenadine therapy (120 mg/day) did not alter its pharmacokinetic profile. The increase in the QTc interval observed with azithromycin and terfenadine was comparable to that of the placebo and terfenadine group (Harris et al., 1995).

Triazolam: azithromycin did not alter the pharmacokinetic profile of triazolam (Greenblatt et al., 1998).

Warfarin: azithromycin can increase the anticoagulant effect of warfarin, leading to a further increase in coagulation time (Lane et al., 1996).

Zidovudine: Aaministration of azithromycin (single dose of 1 g or repeated doses of 1200 mg/day and 600 mg/day) in patients treated with zidovudine 500 mg/day (100 mg 5 times/day) did not alter the peak plasma concentration and AUC of the antiviral, but it increased the peak plasma concentration by 44% and intracellular exposure to phosphorylated zidovudine (the active form of the antiviral by 110%. The clinical relevance of these changes is unknown; the two drugs can be administered together (Amsden et al., 2001).

Side effects

Cardiovascular: angina and palpitations (1%), hypotension; (rare) prolongation of the QT interval on electrocardiogram, including arrhythmias such as ventricular tachycardia, torsades de pointes, and myocardial infarction in patients with previous history of arrhythmia; vasculitis.

In a clinical study that included patients on therapy with azithromycin (347,795 prescriptions), amoxicillin (1,348,672 prescriptions), ciprofloxacin (264,626 prescriptions), levofloxacin (193,906 prescriptions), and patients not receiving antibiotics (1,391,180 control periods), a 5-day course of azithromycin was associated with an increased risk of cardiovascular mortality (HR 2.88, $p<0.001$) and all-cause mortality (HR 1.85, $p=0.002$) compared to the controls (subjects not on antibiotic therapy). Azithromycin showed an increased risk of cardiovascular mortality and all-cause mortality compared to amoxicillin (no increased mortality risk was observed in patients on amoxicillin). Among the hypothesized mechanisms, the potential effect of azithromycin on the QT interval on the electrocardiogram was considered. This interval corresponds to the depolarization-repolarization phase of the heart's ventricles. Prolongation of the QT interval, indicative of a slowed ventricular repolarization phase, predisposes to potentially fatal cardiac arrhythmias. the study found that patients at higher cardiovascular risk prior to treatment were more susceptibile. In comparison to other antibiotics, the risk of cardiovascular death was higher with azithromycin compared to ciprofloxacin but not compared to levofloxacin (Ray et al., 2012). However, the association between cardiovascular mortality risk and azithromycin was not confirmed in a subsequent clinical study that considered health data from the Danish national registry. Based on data collected between 1997 and 2010, the adjusted cardiovascular mortality rate was 1.1 per 1000 patients/year treated with azithromycin and 1.5 per 1000 patients/year treated with penicillin V (Svanstrom et al., 2013). Similar results were also found in a more recent clinical study involving over 260,000 patients with chlamydia and/or gonorrhea treated with azithromycin. Approximately 84% of the treated patients had chlamydia. In this clinical study, no patients treated with the antibiotic died from cardiovascular causes (Khosropour et al., 2014). Azithromycin is recommended as a first-line treatment for chlamydia by the U.S. Centers for Disease Control and Prevention (CDC). A clinical study considering seven population databases from five European countries found no significant difference in potentially fatal ventricular risk between azithromycin and amoxicillin. Data analysis revealed an increased risk of ventricular arrhythmia between azithromycin and no antibiotic use (HR: 1.97; 95% CI: 1.35-2.86), but not between the two antibiotics (HR: 0.94; 95% CI: 0.50-1.77) (Trifirò et al., 2017).

Azithromycin can cause vasculitis (inflammation of blood vessel walls) as a secondary reaction to drug therapy (Dietz et al., 1998; Adverse Drug Reaction Bulletin, 2013). Drug-induced vasculitis typically affects small-caliber vessels but can rarely involve medium-caliber vessels. The mechanism is not yet fully understood, but cell-mediated immunity and humoral immunity are believed to play significant roles.

Endocrine system: (rare) syndrome of inappropriate antidiuretic hormone secretion (SIADH) (Cadle et al., 1997; Kintzel et al., 1998).

Gastrointestinal: the most common side effects, including nausea, vomiting (6.6%), abdominal cramps (1.9%), diarrhea (8.5%); pseudomembranous colitis; (less than 1% of patients) dyspepsia, flatulence, stomatitis, gastritis, anorexia, pancreatitis, discoloration of the tongue.

General: hypersensitivity reactions (angioedema); after intravenous administration, inflammation and pain at the injection site have been reported.

Genitourinary: vaginitis (2.8%), candidiasis.

Hematological: transient alterations in neutrophil count; eosinophilia accompanied by fever and skin rash (Hubern et al., 1997); leukopenia, neutropenia, decreased platelet count.

Liver/biliary: jaundice; (rare) abnormal liver function including hepatitis and cholestatic jaundice.

Metabolic disorders: increased ALT (SGPT), AST (SGOT), creatinine (4-6% of patients); LDH and bilirubin (1-3% of patients); alkaline phosphatase (1% of patients).

Musculoskeletal: arthralgia.

Nervous system: headache, dizziness, fatigue, drowsiness, and weakness; (rare) seizures, aggressive behavior, agitation, anxiety, nervousness, depersonalization, delirium (in elderly patients), paresthesia, hyperactivity, syncope.

Ototoxicity: reversible hearing loss (in association with clofazimine and ethambutol, during treatment of disseminated Mycobacterium avium complex infection) (Wallace et al., 1994); tinnitus, deafness (reported in clinical studies where azithromycin was administered at higher dosages and/or longer durations than recommended).

Renal: (rare) acute interstitial nephritis, acute kidney injury progressing to renal failure (Mansor et al., 1993).

Skin: mucopapular rash, urticaria, photosensitivity, itching (1.9%), reversible alopecia; (rare) erythema multiforme, Stevens-Johnson syndrome, toxic epidermal necrolysis.

Special sense: alteration of taste.

Toxicity

Reproductive toxicity: azithromycin does not influence animal fertility and is not associated with embryofetal toxicity.

Mutagenesis: azithromycin has not demonstrated mutagenic or clastogenic effects.

LD50: after oral administration: 3000 mg/kg (male mice); 4000 mg/kg (female mice); >2000 mg/kg (male and female rats). After intraperitoneal administration: >400, <600 mg/kg (male and female mice); >500, <900 mg/kg (male rats).

Pharmacology

Azithromycin (N-methyl-11-aza-10-deoxy-10-dihydroerythromycin) is a semi-synthetic antibiotic belonging to the macrolide class and is the sole representative of the azalide subclass. Chemically related to erythromycin, it exhibits a different pharmacokinetic profile and fewer side effects, particularly in the gastrointestinal tract.

It possesses both bacteriostatic and bactericidal activity depending on the concentration and type of pathogen. Microorganisms are considered sensitive to azithromycin when the minimum inhibitory concentration (MIC) is equal to or less than 2 mcg/ml, with the exception of H. influenzae, which has an MIC of equal to or less than 4 mcg/ml (Goodman, Gilman, 1997).

Azithromycin is primarily used in the treatment of genital infections caused by Chlamydia trachomatis (Martin et al., 1992) and in the treatment of gonorrhea (Handsfield et al., 1995).

The American Centers for Disease Control (CDC) recommend the use of oral azithromycin (1 g/day for 7 days) in combination with cephalosporins (ceftriaxone intramuscularly or cefixime orally) or as an alternative (2 g single dose) to cephalosporins in patients with hypersensitivity for gonorrhea treatment, regardless of the affected body area (urethra, cervix, rectum, throat) (MMWR Morb. Mortal Wkly Rep., 2013).

The pharmacological characteristics of azithromycin make it a suitable drug for the prophylaxis of recurrent bacterial infections of the upper respiratory tract, including those affecting the middle ear, in patients, especially children, prone to recurrent exacerbations during the winter. It is also used in the treatment of recurrent febrile tonsillitis with plaques.

In vivo, repeated administration of azithromycin has led to the accumulation of phospholipids in some body tissues; the effect is reversible after discontinuation of antibiotic treatment. The clinical significance in humans remains unknown.

Azithromycin’s spectrum of action includes both Gram-positive and Gram-negative bacteria.

Gram-positive pathogens: it is effective against Staphylococcus aureus, Streptococcus agalactiae, Staphylococcus epidermidis, S. pyogenes, and S. pneumoniae. It also demonstrates therapeutic efficacy against streptococci of groups C, F, G, Streptococcus viridans strains, Clostridium perfringens, Peptostreptococcus (Hamilton-Miller, 1992).

Gram-negative pathogens: it is effective against strains of Haemophilus influenzae, Moraxella catarrhalis, Bordetella pertussis, Haemophilus ducreyi, Legionella pneumophilia, Campylobacter jejuni, Neisseria gonorrhoeae, Bacteroides bivius (Gordilo et al., 1993). It is also used against Enterobacteriaceae strains such as Escherichia coli, Salmonella, and Shigella spp.

Azithromycin also exhibits therapeutic efficacy against mycoplasma strains (Mycoplasma pneumoniae, genitalium, and hominis), spirochetes (Treponema pallidum), and chlamydiae (Chlamydia pneumoniae and C. trachomatis). It has also shown therapeutic activity against Toxoplasma gondii and Plasmodium falciparum.

If case of suspected anaerobic microorganism co-infection with azithromycin-sensitive pathogens, therapy should include a drug active against anaerobic microorganisms in addition to azithromycin.

Azithromycin inhibits the 50S subunit of the bacterial ribosome, resulting in the inhibition of bacterial protein synthesis. The inhibition of protein synthesis is due to:

1) Inhibition of the initial complex formation for peptide chain synthesis;
2) Inhibition of the translocation of amino acid units.

A single dose of azithromycin is effective in the treatment of uncomplicated urethral or cervical infections caused by Chlamydia trachomatis.

The antibiotic has been found effective in the treatment of non-chlamydial non-gonococcal urethritis (NGU), caused by Ureaplasma urealyticum, Mycoplasma genitalium, or other unknown pathogens. Patients unresponsive to azithromycin typically respond to erythromycin or ofloxacin.

The efficacy of azithromycin in the treatment of idiopathic cervicitis in women is doubtful (The Medical Letter, 1999).

All patients with gonorrhea should be treated with azithromycin, even in cases of suspected chlamydia infection.

A single dose of azithromycin can be effective in the treatment of chancroid, caused by Haemophilus ducreyi, a disease that occasionally occurs in sporadic localized epidemics and remains a common cause of genital ulceration.

The macrolide is also effective in patients with HIV infection.

Azithromycin has shown therapeutic activity in chlamydial conjunctivitis in pediatric patients (Hammerschlag et al., 1998).

In cases of Mycobacterium avium infections (secondary to AIDS), azithromycin reduces bacteremia in 75% of treated patients (Young et al., 1991). The drug should not be used in monotherapy due to the risk of resistance.

Azithromycin is not considered a first-line treatment for erythema migrans in Lyme disease due to a high rate of clinical failures (Loewen et al., 1999).

The antibiotic has not been found effective in the treatment of babesiosis (Babesia canis tick-borne infection), for which first-line drugs are clindamycin and quinine (The Medical Letter, 2000).

In patients with coronary artery disease and positive for Chlamydia pneumoniae, azithromycin administration reduced inflammatory markers and decreased the need for antibiotic treatment at 3 months (Drugs Fut., 2000).

Since Chlamydia pneumoniae appears to be associated with the onset of ischemic heart disease, it has been hypothesized that adequate antibiotic therapy in at-risk patients could play a role in "prophylaxis" against ischemic heart events. However, the administration of azithromycin to patients with a history of myocardial infarction, bypass surgery, stenosis of at least 50% in at least one coronary artery, and positivity for Chlamydia was not more effective than a placebo in reducing the number of ischemic events (22 vs. 25 ischemic events observed with azithromycin and placebo, respectively) (Muhlestein et al., 2000). These outcomes were confirmed by subsequent clinical studies (Cercek et al., 2003; O'Connor et al., 2003; Grayston et al., 2005).

Azithromycin has been found to improve respiratory function in pediatric patients with cystic fibrosis. In a study involving patients aged 8 to 18 years, azithromycin was compared to a placebo. After 6 months of treatment and 2 months of washout, the treatments were crossed over. The primary clinical outcome was the mean relative difference in FEV1 (forced expiratory volume in 1 second) between azithromycin and placebo. At the end of the study, this value was 5.4%; 31.7% of patients showed improvement greater than 13%, and 12.2% showed deterioration greater than 13% (Equi et al., 2003).

In cases of bronchiectasis (abnormal dilation of a bronchus or bronchiole) not caused by cystic fibrosis, azithromycin has been found effective in reducing the number of pulmonary exacerbations (average number of exacerbations: 0 vs. 2 with azithromycin or placebo, respectively) and improving lung function (forced expiratory volume in 1 second, FEV1: +1.03% with azithromycin after 3 months vs. -0.10% with placebo after 3 months). However, the therapeutic benefit has been associated with an increased risk of resistance to the antibiotic (88% vs. 26%) and gastrointestinal side effects (40% vs. 5%) (Altenburg et al., 2013, BAT study).

In children with bronchiolitis, a viral infection of the lower respiratory tract, the administration of azithromycin did not reduce the duration of oxygen therapy (Pinto et al., 2012).

Azithromycin has been evaluated as a potential prophylactic therapy for bronchiolitis obliterans syndrome in patients with hematologic tumors undergoing HSCT in a randomized, placebo-controlled clinical trial (Bergeron et al., 2017). Bronchiolitis obliterans syndrome is one of the complications associated with allogeneic hematopoietic stem cell transplantation (HSCT). In the reference clinical study, early administration (prophylaxis) of azithromycin was intended to improve survival by preserving respiratory function 2 years after HSCT. The study was terminated earlier than planned because the antibiotic-treated group exhibited a higher rate of tumor recurrence compared to the placebo group (77 vs. 48 patients; hazard ratio, HR: 1.6 (1.12-2.4)). The mechanism behind the increased recurrence in patients treated with azithromycin is unknown. Nevertheless, the study revealed a negative benefit-risk ratio for long-term azithromycin administration in HSCT patients.

Azithromycin has been found effective in reducing exacerbations in patients with chronic obstructive pulmonary disease (COPD). In treated patients (azithromycin dose of 205 mg/day), the time to the first exacerbation was shorter compared to the

control group (266 days vs. 174 days with azithromycin vs. placebo, p <0.001). The exacerbation rate per patient/year was 1.48 vs. 1.83, respectively, with azithromycin and placebo, and the NNT (number needed to treat, indicating the number of patients needed to be treated to prevent one COPD exacerbation) was 2.86. In the clinical study, azithromycin was associated with a higher incidence of ototoxicity (25% vs. 20% with azithromycin and placebo, p=0.04) and macrolide resistance (81% vs. 41% with azithromycin and placebo) (Albert et al., 2011).

Azithromycin (500 mg/day for 3 days), combined with omeprazole (20 mg/day for 7 days) plus amoxicillin (2 g/day) or omeprazole (20 mg/day for 7 days) plus tinidazole (1 g/day for 3 days), has been effective in eradicating Helicobacter pylori infection in 62.5% and 71.2% of patients, respectively (Anagnostopoulos et al., 2003).

Azithromycin has been effective in reducing the incidence of ocular infections caused by Chlamydia trachomatis in regions where this type of infection is endemic. The administration of a single oral dose of the antibiotic to over 97% of a community in Tanzania reduced the prevalence of infection from 9.5% (baseline) to 2.1% and 0.1% at 2 and 24 months, respectively, indicating that incidence and intensity remained low in the two years following treatment (Salomon et al., 2004).

In developing countries where the use of penicillin injections can be problematic, azithromycin represents a valid alternative for the treatment of syphilis. Indeed, a single oral dose (2 g) administered to 163 patients in Tanzania resulted in a cure rate of 97.7% compared to 95% in 165 patients treated with intramuscular benzathine penicillin (2.4 million units). However, azithromycin does not cross the placental barrier and is therefore not useful for preventing congenital syphilis.

Azithromycin exhibits superior activity to erythromycin against Haemophilus influenzae, Haemophilus parainfluenzae, Legionella pneumophilia, Brahamelia catarrhalis, Mycoplasma pneumoniae, Pasteurella multocida, Neisseria gonorrhoeae, Ureaplasma urealyticum (Scaglione, Fraschini, 1990). It is less active against streptococci and staphylococci. It demonstrates similar activity in the treatment of sinusitis, acute bronchitis, and atypical pneumonia.

Azithromycin exhibits greater activity than amoxicillin in the treatment of lung infections (Corriere Medico, 1991); it has higher therapeutic efficacy and fewer side effects compared to amoxicillin plus clavulanic acid (Corriere Medico, 1991).

Azithromycin has greater activity than penicillin in the treatment of streptococcal pharyngitis (Hooton, 1991).

Resistance

Azithromycin-resistant strains include streptococci, staphylococci, and some Haemophilus influenzae strains. Resistance mechanisms to macrolide mediated by plasmids include (Goodman & Gilman, 1997):

1) Methylation of the bacterial ribosomal receptor, resulting in reduced antibiotic affinity for the 23S subunit;

2) Enzymatic inactivation of the antibiotic (via esterases produced by Enterobacteriaceae);
3) Decreased permeability of the cell wall to the drug (S. Epidermidis).

Resistance can also be of chromosomal origin (mutations that alter the ribosomal protein). Resistance is common among staphylococci and streptococci and is often cross-resistant with other macrolides.

Pharmacokinetics

Following oral administration, azithromycin is rapidly absorbed from the gastrointestinal tract.

The presence of food in the stomach influences drug absorption depending on the pharmaceutical formulation employed (reduced absorption with capsules; unchanged absorption with tablets) (Martindale, 1999). In the presence of a full stomach, the capsule tends to disintegrate more slowly, thereby exposing azithromycin, which is acid-labile, to the acidic stomach environment for a longer period. Azithromycin loses the sugar molecule to which it is bound, cladinose, and is thus degraded to de-cladinose-azithromycin (DCA) (Curatolo et al., 2011).

Biodisponibility: 37-40%.

Peak plasma concentration: 0.24 mcg/ml (500 mg).

Time to peak plasma concentration: 2-3 hours.

AUC (Area Under the Curve): 2.1 mcg/h/L (500 mg).

Serum protein binding: 7-50%.

Volume of distribution: 23-31 L/kg.

Azithromycin distinguishes itself from other macrolides due to its extensive tissue distribution, where it achieves higher concentrations than in plasma, making plasma levels less relevant as an efficacy indicator. It also exhibits a high concentration in cells, including phagocytes. It appears that the antibiotic accumulates in tissue fibroblasts, acting as natural drug depots, which subsequently release it to phagocytes. Minimal concentrations are found in the liver and the central nervous system, when meninges are not inflamed. After oral administration of a 500 mg dose of azithromycin, the concentration in ovarian tissue was found to be 2.7 mcg/g, in uterine tissue 3.5 mcg/g, and in the fallopian tubes 3.3 mcg/g.

Azithromycin undergoes no hepatic metabolism (Luke et al., 1996).

It does not inhibit CYP3A activity.

Clearance: 18 ml/min/kg.

Renal clearance: 6-11.4 L/h (100-190 ml/min).

Half-life: 68 hours. Due to the high tissue concentration of azithromycin, the drug's plasma half-life can extend up to 4 days (Clin. Pharmacokinet., 2000).

The primary route of excretion is through feces and bile (metabolites). Only a small amount (6%) is excreted in urine, with 4.5% excreted within a week after oral administration and 12.2% within a week after intravenous administration.

In elderly patients (67-80 years old), the AUC value increases by 25% compared to young patients (29-39 years old). Additionally, AUC and renal clearance parameters

are inversely proportional. This suggests that dose adjustment may be necessary in the presence of renal insufficiency (Clin. Pharmacokinet., 2000).

In patients with hepatic cirrhosis (Child-Pugh class A and B classification), AUC values, half-life, and renal clearance remain relatively unchanged.

Classification

Chemical formula

$C_{38}H_{72}N_2O_{12}$

Molecular weigh

749.0

ATC code

J01FA10

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