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A review on cardio-hepatic toxic macrolide: Azithromycin

Aparna Sadhu
Assistant Teacher (Life Sciences), Lowa Dibakar Vidyamandir High School, West Bengal, India

Dipsikha Manna
Department of Physiology, Faculty, Belur Sramajibi Swasthya Prakalpa Samity, Belur, Howrah, West Bengal, India

Susmita Datta
Department of Microbiology, Faculty, Belur Sramajibi Swasthya Prakalpa Samity, Belur, Howrah, West Bengal, India

Sarmishtha Chatterjee
Department of Anatomy and Physiology, Vice Principal, Belur Sramajibi Swasthya Prakalpa Samity, Belur, Howrah, West Bengal, India
Corresponding author email: sarmishthaobesity@gmail.com

***Abstract*---**Drug-induced cardio-hepatic toxicity is the foremost cause of heart and liver damage, with the use of antimicrobial-agent. Most patients, although recuperate after discontinuing the offending-agent, severe cases may consequence in progressive disease. Azithromycin is a rare cause of idiosyncratic drug-induced cardiac and liver injury. This semi-synthetic macrolide has a substantial potency against both gram-positive and gram-negative organisms due to the presence of a nitrogen atom in its ring. A search was performed in PubMed, Scopus, Google Scholar and Research Gate. Azithromycin divulges a lower number of interactions with proteins, whereas, QTc prolongation with torsades de pointes (Tdp) and polymorphic ventricular tachycardia are communally occurred in cardiovascular system, due to dysregulation of intracellular [Ca^{++}] via the Na^{+}-Ca^{++} exchanger activity, leading to delayed after depolarizations. In addition azithromycin-induced liver injury was more cholestatic in nature, with an ALT/ALP ratio of <2 ULN, contributing vanishing bile duct syndrome. This review hereafter revealed the adverse effect of azithromycin in relation with cardio – hepatic toxicity.

***Keywords*---**Azithromycin, Macrolide, QT interval, DILI, Hepatotoxicity.

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Introduction

Macrolide derived from *Streptomyces erythreus*, a type of soil-borne bacteria, are bacteriostatic antibiotic. It is a diverse class of hydrophobic compounds exemplified by a macrocyclic lactone ring and discriminated by variable side chains (Lenz et al., 2021). Macrolide has a broad spectrum of activity against many gram-positive bacteria (cocci) (LiverTox, 2012). The mode of action of macrolide is to bind to the large subunit of rRNA and slab the 'tunnel' through which the mounting peptide chain exits (Swayze et al., 2007). Macrolides are widely used as antimicrobial agents due to their anti-inflammatory, excellent tissue penetration, prolonged tissue persistence and prokinetic properties (Kryfti et al., 2013, Suresh et al., 2013, Dhar et al., 2021). Along with microbicidal properties, macrolides are also tied with immunomodulatory action to suppress hyper-immunity and inflammation for decreasing in bacterial virulence and biofilm formation as well as reduction of mucus hypersecretion. These non-microbicidal actions of macrolides are apparented in a period of several weeks and are bordered to the 14 to 15 member macrolides, such as erythromycin, clarithromycin, and azithromycin etc. (Kryfti et al., 2013, Dhar et al., 2021). According to US National Library Medicine, currently available macrolides are able to tolerate orally and widely used to treat mild-to-moderate contagions. However, it is reported that, several macrolides have been linked to liver as well as cardiovascular toxicity (Viluksela et al., 1996, Vial et al., 1997, Chitturi and Farrell, 2001, Zang et al., 2022, Kutlin et al., 2002, Rao et al., 2014, Farang et al., 2021, Wu et al., 2023). Macrolides can exhibit toxic bioactivity, which may be a root of the adverse side effects monitored in response to the administration of macrolide drugs (Zang et al., 2021, Lenz et al., 2021). Modulation of host immune responses may be the reason behind the toxicity (Parnham et al., 2014, Lenz et al., 2021).

Azithromycin, like other macrolide antibiotics such as erythromycin and clarithromycin, is bacteriostatic against many gram-positive bacteria as well as it is more active than erythromycin against several gram-negative bacteria too (LiverTox, 2012). This is a wellknown semisynthetic macrolide (Cambell, 2022). Azithromycin is typically given in moderate-to-severe infections, generally well tolerated, but side effects in addition to severe adverse reactions are observed, including nausea, abdominal pain, dyspepsia, headache, dizziness, rashes, diarrhea, hepatotoxicity, severe hypersensitivity, cardiovascular in tolerance etc (Moy et al., 2015, Zang et al., 2022, Wu et al., 2023) shown in Figure 1. The focus of this review hereafter was to state the adverse effects of a semisynthetic microlide, named azithromycin in relation with liver and cardiovascular system.

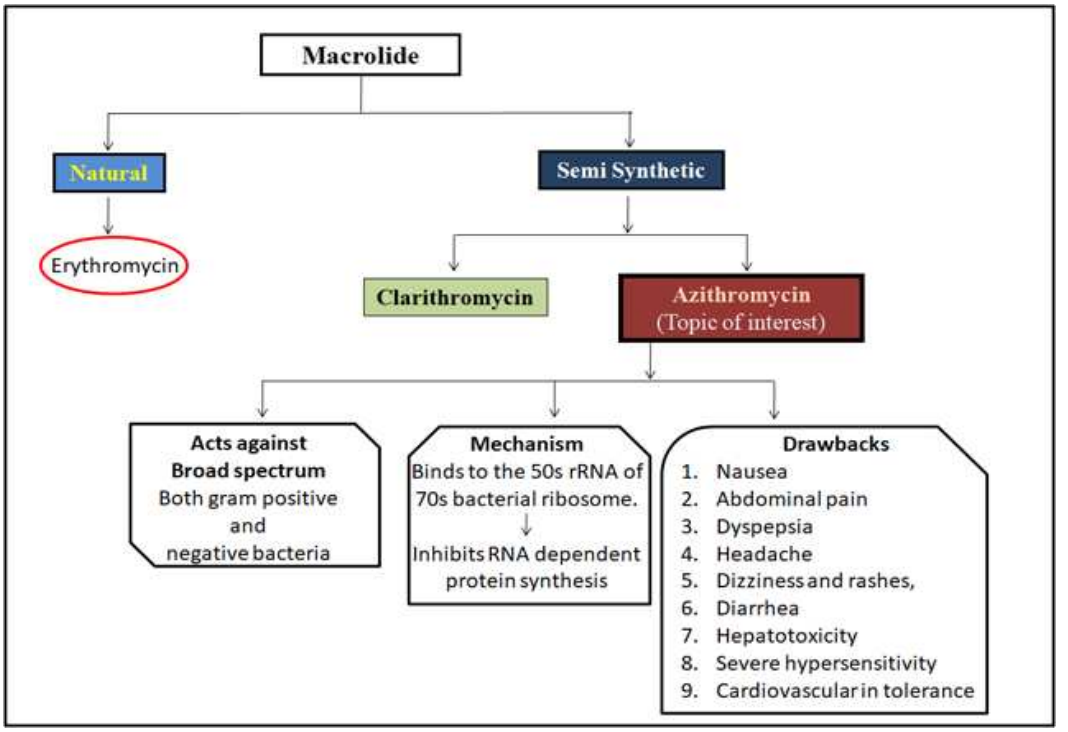

Figure 1. Classification of macrolides with special emphasis on azithromycin

Azithromycin

Azithromycin, a part of the azalide subclass of macrolide, contains a 15 membered ring with a methyl substituted nitrogen (Fohner et al., 2017). According to pharmacokinetic properties, azithromycin is more stable at low pH, resulting in a longer serum half-life and enhanced concentrations in tissues compared to erythromycin (Zuckerman et al., 2011). As a result of the better constancy at low pH, azithromycin has an oral bioavailability of 37% (Tsai et al., 2015, Fohner et al., 2017). Consequently, the pharmacodynamic property of azithromycin shows significantly augmented potency against gram-negative bacteria.

Macrolides are lipophilic and are widely allocated in blood and tissues (Zuckerman et al., 2004, Tsai et al., 2015, Fohner et al., 2017). Once in the bloodstream, macrolides preferentially bind alpha-1-acid glycoprotein (AGP) encoded by the gene orosomucoid 1 (ORM1). The binding protein institutes in the highest concentration after albumin (Tsai et al., 2015). Erythromycin is 70–80% bound to AGP in the plasma. However, azithromycin is 93% unbound in the plasma, but only 16% unbound in liver tissue (Sugie et al., 2004, Fohner et al., 2017). Azithromycin concentrates in phagocytes, which then transport the drug to the site of infection (Parnham et al., 2014). According to Zuckerman et al (2004), concentrations of azithromycin are 800 times in phagocytes which are doubled from erythromycin, found in the serum. Azithromycin accumulated in the liver, are 50 times higher than in the serum (Sharma and Mullangi, 2013, Derendorf 2020). After 2-3 hours, peak plasma concentrations are attained. Due to its wide tissue dispersion, azithromycin has a lengthy half-life (2-4 days) (Lalak and Morris, 1993, Idkaidek et

al., 2014). These elevated levels may result in cholestasis and damage to the bile ducts as well as cardiovascular injury (Chandrupatla et al., 2002, Martinez et al., 2015, Ray et al., 2012, Giudicessa and Ackerman, 2012).

Dose and mode of administration

Azithromycin is accessible for both oral and intravenous administration. Sandman and Iqbal (2024) stated that the usual dose is 250 mg or 500 mg, specified once daily for 3 to 5 days. In severe infections, a higher dose is exploited. Oral formulations comprise tablets (250 mg, 500 mg), packets (1 gram dissolved in ¼ cup or 60 ml of water) and suspension for reconstitution (100 mg/5 ml, 200 mg/5 ml). Dosing can be administered with or without food. Intravenous (IV) azithromycin is available in a 500 mg solution for reconstitution. It should be infused over at least 60 minutes. Azithromycin administration should not be via intramuscular injection or IV bolus. The ophthalmic solution (1%) is available in a 2.5 ml bottle which is used in bacterial conjunctivitis (Drew et al., 1992). Azithromycin demonstrates excellent tissue penetration and intracellular accretion (Sandman and Iqbal, 2024).

Adverse effects

Azithromycin is usually regarded as a safe antimicrobial mediator. Nevertheless, there are adverse effects of azithromycin in regards with cardio-hepatic toxicity (Ioannidis et al., 2001, Sandman and Iqbal, 2023).

Cardiac damage

There is escalating evidence that cytochrome P450 (CYP) plays a role in the onset, progression and prognosis of cardiovascular disease, particularly, heart failure (Elbekai and Kadai, 2006, Aspromonte et al., 2014, Ong et al., 2017). Azithromycin has been shown to be a weak substrate for CYP3A4 (cytochrome P450 family 3 subfamily A member 4) and to neither induce nor inhibit CYP3A4 activity (He et al., 2009). Only about 6% of azithromycin is recovered in the urine, with most being excreted unaltered in the bile, through both multidrug resistance-associated protein-2 (MRP2) (encoded by the gene ATP- binding cassette sub-family C member 2, ABCC2) and ATP- binding cassette sub-family B member 1 (ABCB1) (Tsai et al., 2015, Fohner et al., 2017). Sugie et al. (2004) stated that MRP2 is considered to play a smaller role in excretion of azithromycin into the bile than ABCB1. Henceforth, it is revealed that azithromycin divulges a lower number of interactions with proteins, likely is less affected by genetic variation and has enhanced activity against gram negative bacteria due to higher tissue concentrations (Fohner et al., 2017). However, azithromyocin can cause QTc prolongation and has been associated with torsades de pointes (Tdp) and polymorphic ventricular tachycardia (Kezerashvili et al., 2007, Huang et al., 2007, Ray et al., 2012, Chorin et al., 2020). TdP, a rare polymorphic ventricular tachycardia, is considered by a gradual amend in the amplitude and twisting of the QRS complexes around the isoelectric line on an electrocardiogram (Drew et al., 2010). TdP is associated with QTc prolongation, which is the heart-rate–attuned lengthening of the QT interval. QT prolongation is one of the most infamous adverse drug reactions leading to sudden cardiac death (Yap et al., 2003). Drug-induced prolonged depolarisation (a prolonged QT interval)

of the heart can predispose a patient to develop this life-threatening arrhythmia (Li et al., 2017). Azithromycin is proarrhythmic (Ray et al., 2012, Yang et al., 2017), which led us to hypothesize that it would increase the risk of sudden cardiovascular toxicity and cardiac death. After administration of azithromycin, cardiac Na^+ current, upsurges intracellular [Na^+] and subsequently endorse dysregulation of intracellular [Ca^{++}] via the Na^+-Ca^{++} exchanger activity, leading to delayed after depolarizations (DADs) and triggered arrhythmias (Mitchell et al., 1998, Dzhura et al., 2000, Yang et al., 2017). This is the hallmark of catecholaminergic polymorphic ventricular tachycardia (CPVT). However, arrhythmias can lead to complications with cardiomyopathy in which high SGOT activity is observed (Kallip and Payne 1960). The whole aspect is graphically documented in Figure 2.

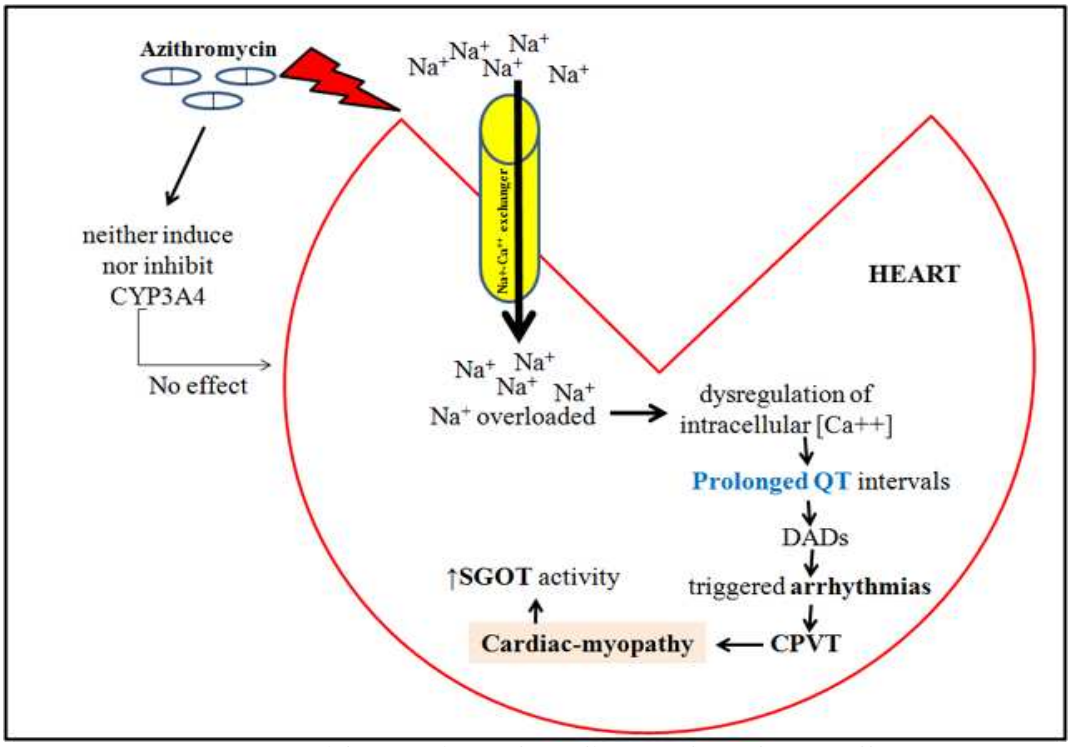

Figure 2. Azithromycin and cardiovascular adverse effect

Hepatotoxicity

Drugs are an imperative cause of liver injury and manifestations may array from asymptomatic elevation of liver enzymes to fulminant hepatic failure (Das, 2011). Drug-induced hepatotoxicity is an acute or chronic reaction to a natural or manufactured compound (Fisher et al., 2015, Francis and Navarro, 2022). The two types of hepatotoxic mechanisms are intrinsic (dose-dependent) and idiosyncratic (more unpredictable) (Chalasani et al., 2015, Katarey and Verma, 2016, Francis and Navarro, 2022). Quantitative systems toxicology (QST) is a discipline of pharmacology, hunts for to comprehend and ultimately envisage the toxic effects of drugs by integrating computational and experimental methods (Bloomingdale et al., 2017, Woodhead et al., 2019). Drug induced liver injury (DILI), a QST model of liver

injury, incorporates the results from *in vitro* mechanistic toxicity assays with estimations of *in vivo* exposure and known biochemistry to realise biochemically induced hepatotoxicity (Howell et al., 2012, Shoda et al., 2014, Woodhead et al., 2017, Woodhead et al., 2019). DILI is a diagnosis of segregation, relying on obtaining a detailed history along with extensive blood work, hepatobiliary imaging and a liver biopsy (Lewis 2013, Liang and Ramdass, 2022). Hepatotoxicity mechanisms represent in DILIsym comprises oxidative stress, mitochondrial dysfunction and bile acid transport inhibition (Yang et al., 2015). Identification of the type of DILI is imperative to detect whether it is hepatocellular, cholestatic or mixed to narrow down differential diagnoses (Chalasani et al., 2014). Hepatocellular DILI has a ratio of the serum alanine aminotransferase (ALT) and alkaline phosphatase (ALP) ≥ 5 upper limit of normal (ULN), cholestatic DILI has a ratio < 2 ULN, and mixed DILI has a ratio between 2 and 5 ULN (Francis and Navarro, 2022). These are mechanistically connected to cell death and transaminase elevation (Yang et al., 2015, Woodhead et al., 2019).

Azithromycin persuades liver injury (hepatocellular or cholestatic in nature) usually occurs within 1-3 weeks after drug instigation (Martinez et al., 2015, Park et al., 2020). Azithromycin-induced liver injury was more cholestatic in nature, with an ALT/ALP ratio of <2 ULN (Chalasani et al., 2014, Han et al., 2017, Park et al., 2020, Francis and Navarro, 2022). This semisynthetic macrolide is a rare cause of cholestatic liver injury and an inaccessible cause of vanishing bile duct syndrome (VBDS) owing to rapidly progressive nature, with complete irreversible ductopenia within only 20 days (Devarbhav, 2012, National Institute of Diabetes and Digestive and Kidney Diseases, 2012, Dawkins et al., 2023). VBDS is pigeonholed by progressive ductopenia as well as portal tract fibrosis via immune, toxic and idiosyncratic mechanisms, with complete small bile duct destruction leading to cirrhosis (Bessone et al., 2021). Moreover, prompt recognition of the adverse effect of azithromycin is hyperbilirubinemia due to underlying DILI (Dawkins et al., 2023). This semisynthetic macrolide henceforth is associated with an asymptomatic elevation of liver transaminases (Wong et al., 2021). Typically, azithromycin can cause cholestatic hepatitis, as well as hepatocellular injury with jaundice too (Lockwood et al., 2010, LiverTox, 2012, Wong et al., 2021).

The rationale behind azithromycin tempted hepatotoxicity depends on the basis of the structural characteristics. The structure–toxicity relationship combined with *in silico* ADMET (absorption, distribution, metabolism, excretion and toxicity data) parameters evaluation and structure based computations can be used to predict drug impurity toxicity (Han et al., 2019, Zhang et al., 2022). According to Zhang et al (2022), the structure of impurities of azithromycin has mainly changed in the side chain (C5 position) of the lactone rings. The construction of impurities F, L and H are different only in the nitrogen (N)-linked substituents on the side chain group at C5 position. The N-linked substituents in impurity F is an electron-withdrawing aldehyde group from N atom, while the N-connected substituents in impurity H and impurity L are electron-donating groups, leading to different charges of N atoms. The charge of N atoms on the side chain group at C5 position of azithromycin analysed by *in silico* ADMET predictions (Zhang et al., 2022), henceforth are the main culprit to provoke type two DILI, cholestatic hepatotoxicity which may upshot in the elevation of transaminase, leading to cirrhosis and jaundice, depicted in Figure 3.

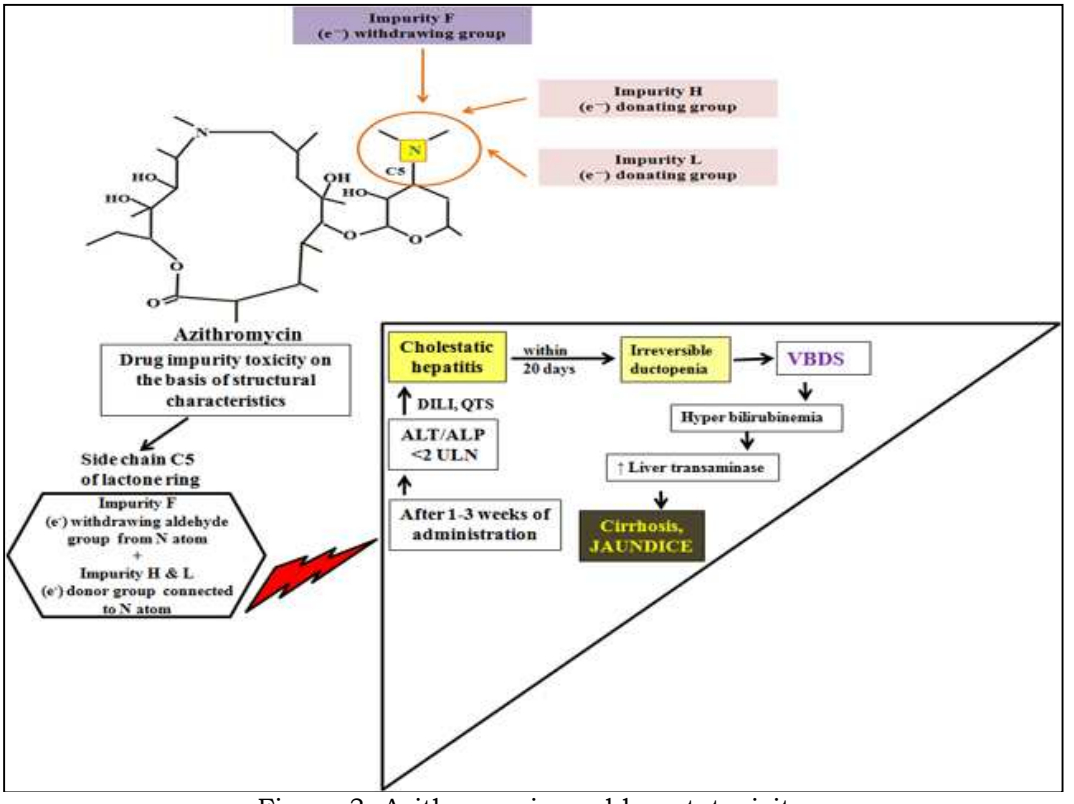

Figure 3. Azithromycin and hepatotoxicity

Conclusions

In summary, this review comprehended that azithromycin has enhanced activity against gram negative bacteria owing to the higher tissue concentrations. All documents evaluate the adverse effect of azithromycin in relation with cardio – hepatic toxicity. QTc prolongated DADs is the outcome in cardiovascular toxicity. Hepatotoxicity due to extensive structural impurities of this semisynthetic macrolide antibiotic will endow with a theoretical basis for quality consistency assessment and manufacturing process. A multidisciplinary collaborative approach with clinicians, pharmacists and nursing is entailed for superiority of overall therapeutic success to focus on the antimicrobial stewardship leading to proactively optimizing medication effectiveness and safety.

Conflicts of Interest

No potential conflicts of interest were disclosed.

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References

Aspromonte, N., Monitillo, F., Puzzovivo, A., Valle, R., Caldarola, P., Iacoviello, M. (2014). Modulation of cardiac cytochrome P450 in patients with heart failure. Expert Opin Drug Metab Toxicol, 10 (3), 327-339

Bessone, F., Hernández, N., Tanno, M. E., Roma, M.G. (2021). Drug-Induced Vanishing Bile Duct Syndrome: From Pathogenesis to Diagnosis and Therapeutics. Semin Liver Dis, 41 (03), 331-348

Bloomingdale, P., Housand, C., Apgar, B J. F., Millard, jL., Mager, D. E., Burke, J. M., Shah, D. K.(2017). Quantitative systems toxicology. Curr Opin Toxicol, 4, 79-87

Cambell, K. B. (2022). Chapter 10 – Antimicrobial agents and torsades de pointes, Editor (s): James E. Tisdale, Torsades de Pointes, Academic Press, 231-266

Chalasani, N. P., Hayashi, P. H., Bonkovsky, H. L., Navarro, V. J., Lee, W. M., Fontana, R. J. (2014). ACG Clinical Guideline: the diagnosis and management of idiosyncratic drug-induced liver injury. Am J Gastroenterol, 109, 950–966

Chalasani, N., Bonkovsky, H. L., Fontana, R., Lee, W., Stolz, A., Talwalkar, J., Reddy, K. R,., Watkins, P. B., Navarro, V., Barnhart, H., Gu, J., Serrano, J. (2015). United States Drug Induced Liver Injury Network. Features and Outcomes of 899 Patients With Drug-Induced Liver Injury: The DILIN Prospective Study. Gastroenter, 148 (7), 1340-52.e7

Chandrupatla, S., Demetris, A. J., Rabinovitz, M. (2002). Azithromycin-induced intrahepatic cholestasis. Dig Dis Sci, 47, 2186–2188

Chitturi, S., Farrell, G. C. (2001). Drug-induced cholestasis. Semin Gastrointest Dis, 12, 113-124

Chorin, E., Wadhwani, L., Magnani, S., Dai, M., Shulman, E., Nadeau-Routhier, C., Knotts, R., Bar-Cohen, R., Kogan, E., Barbhaiya, C., Aizer, A., Holmes, D., Bernstein, S., Spinelli, M., Park, D. S., Stefano, C., Chinitz, L. A., Jankelson, L. (2020). QT interval prolongation and torsade de pointes in patients with COVID-19 treated with hydroxychloroquine/azithromycin. Heart Rhythm, 17 (9), 1425–1433.

Das, B. K. (2011). Azithromycin induced hepatocellular toxicity and hepatic encephalopathy in asymptomatic dilated cardiomyopathy. Indian J Pharmacol, 43 (6), 736–737

Dawkins, M., Fishkin, T., Gavriel Berman, G., Wang, A., Saidman, J., Partiula, B. (2023). Severe Azithromycin-Induced Liver Injury With Vanishing Bile Duct Syndrome Necessitating Liver Transplantation. . AIM Clinical Cases, 2, e230251

Derendorf, H. (2020). Excessive lysosomal ion-trapping of hydroxychloroquine and azithromycin. International Journal of Antimicrobial Agents, 55 (6), 106007

Devarbhavi, H. (2012). An update on drug-induced liver injury. J Clin Exp Hepatol, 2, 247-259

Dhar, R., Talwar, D., Singh, V., Dumra, H., Rajan, S., Jindal, S.K. (2021). Expert recommendations on the role of macrolides in chronic respiratory diseases. Lung India, 38 (2), 174-182

Drew, B. J., Ackerman, M.J., Funk, M., Gibler, W. B., Kligfield, P., Menon, V., Philippides, G. J., Roden, D. M., Zareba, W. (2010). Prevention of torsade de pointes in hospital settings: a scientific statement from the American Heart

Association and the American College of Cardiology Foundation. Cir, 121 (8), 1047–1060

Drew, R. H., Gallis, H. A. (1992). Azithromycin--spectrum of activity, pharmacokinetics, and clinical applications. Pharmacotherapy, 12 (3), 61-73

Dzhura, I., Wu, Y., Colbran, R., Balser, J., Anderson, M. (2000). Calmodulin kinase determines calciumdependent facilitation of L-type calcium channels. Nature Cell Biol, 2,173–177

Elbekai, R. H., El-Kadi, A. O. S. (2006). Cytochrome P450 enzymes: central players in cardiovascular health and disease. Pharmacol Ther, 112 (2), 564-587

Farag, N. E., El-Kherbetawy, M. K., Ismail, H. M., Abdelrady, A. M., Toraih, E. A., Abdelbasset, W. K., Lashine, R. M., EL-dosoky, M., Abed, S. Y., Ibraheem, K. M., Fawzy, M. S., Zaitone, S. A. (2021). Differential Effect of Three Macrolide Antibiotics on Cardiac Pathology and Electrophysiology in a Myocardial Infarction Rat Model: Influence on Sodium Nav1.5 Channel Expression. Pharmaceuticals, 14, 597

Fisher, K., Vuppalanchi, R., Saxena, R. (2015). Drug-Induced Liver Injury. Arch Pathol Lab Med, 139 (7), 876-887

Fohnera, A. E., Sparreboomb, A., Altmana, R. B., Klein, T. E. (2017). PharmGKB summary: macrolide antibiotic pathway, pharmacokinetics/pharmacodynamics. Pharmacogenet Genomics, 27 (4), 164–167

Francis, P., Navarro, V. J. (2022). Drug-Induced Hepatotoxicity. In: StatPearls [Internet]. Treasure Island (FL): StatPearls Publishing

Giudicessa, J. R., Ackerman, M. J. (2012). Azithromycin and risk of sudden cardiac death: Guilty as charged or falsely accused? Cleveland Clinic Journal of Medicine, 8 (9), 539-544

Han, B., Sheng, Y., Wang, L., Feng, H., Hou, X., Li, Y. (2017). Intrahepatic cholestasis of pregnancy or azithromycin-induced intrahepatic cholestasis. Med (Baltimore), 96 (52), e9346

Han, Y., Zhang, J., Hu, C. Q., Zhang, X., Ma, B., Zhang, P. (2019). In Silico ADME and Toxicity Prediction of Ceftazidime and its Impurities. Front Pharmacol, 10, 434. 10.3389/fphar.2019.00434

He, X. J., Zhao, L. M., Qiu, F., Sun, Y. X., Li-Ling, J. (2009). Influence of ABCB1 gene polymorphisms on the pharmacokinetics of azithromycin among healthy Chinese Han ethnic subjects. Pharmacol Rep, 61, 843-850

Howell, B. A., Yang, Y., Kumar, R., Woodhead, J. L., Harrill, A. H., Clewell, H. L., Andersen, M. E., Siler, S. Q., Watkins, P. B. (2012). In vitro to in vivo extrapolation and species response comparisons for drug-induced liver injury (DILI) using DILIsymTM: a mechanistic, mathematical model of DILI. J Pharmacokinet Pharmacodyn, 39, 527-541

Huang, B., Wu, C., Hsia, C., Yin Chen, C. (2007). Azithromycin-induced torsade de pointes. Pacing Clin Electrophysiol, 30, 1579–1582

Idkaidek, N. M., Naji Najib, N., Salem, I., Jilani, J. (2014). Physiologically-Based IVIVC of Azithromycin. Am J Pharmacol Sc,i 2 (6), 100-102

Ioannidis, J. P., Contopoulos-Ioannidis, D. G., Chew, P., Lau, J. (2001). Meta-analysis of randomized controlled trials on the comparative efficacy and safety of azithromycin against other antibiotics for upper respiratory tract infections. J Antimicrob Chemother, 48 (5), 677-689

Kallip, T., Payne, M. A. (1960). High Serum Transaminase Activity in Heart Disease: Circulatory Failure and Hepatic Necrosis. Cir, 21 (5), 646 – 660

Katarey, D., Verma, S. (2016). Drug-induced liver injury. Clin Med (Lond), 16 (6), s104-s109

Kezerashvili, A., Khattak, H., Barsky, A., Nazari, R. (2007). Azithromycin as a cause of QT-interval prolongation and torsade de pointes in the absence of other known precipitating factors. J Interven Car Electrophysiol, 18 (3), 243-246

Kryfti, M., Bartziokas, K., Papaioannou, A. I., Papadopoulos, A., Kostikas, K. (2013). Clinical effectiveness of macrolides in diseases of the airways: Beyond the antimicrobial effects. Pneumon, 26, 33-46

Kutlin, A., Roblin, P. M., Hammerschlag, M. R. (2002). Effect of prolonged treatment with azithromycin, clarithromycin, or levofloxacin on Chlamydia pneumoniae in acontinuous-infection model. Antimicrob Agents Chemother, 46, 409–412

Lalak, N. J., Morris, D.L. (1993). Azithromycin clinical pharmacokinetics. Clin Pharmacokinet, 25, 370-374

Lenz, K. D., Klosterman, K. E., Mukundan, H., Kubicek-Sutherland, J. Z. (2021). Macrolides: From Toxins to Therapeutics. Toxins, 13, 347

Lewis, J. H. (2013). Drug-Induced Liver Injury Throughout the Drug Development Life Cycle: Where We Have Been, Where We are Now, and Where We are Headed. Perspectives of a Clinical Hepatologist. Pharm Med, 27, 165–191

Li, M., Ramos, L. G. (2017). Drug-Induced QT Prolongation And Torsades de Pointes. P T, 42 (7), 473–477

Liang, R., Ramdass, A. (2022). Azithromycin-Induced Liver Injury in an Asthma Exacerbation Patient With Autoimmune Features. Cureus, 14 (5), e25447

LiverTox. (2012). Clinical and Research Information on DrugInduced Liver Injury. Bethesda (MD): National Institute of Diabetes and Digestive and Kidney Diseases, Macrolide Antibiotics. https://www.ncbi.nlm.nih.gov/books/NBK547852/

Lockwood, A. M., Cole, S., Rabinovich, M. (2010). Azithromycin-induced liver injury. Am J Health Syst Pharm, 67, 810-814

Martinez, M. A., Vuppalanchi, R., Fontana, R. J., Stolz, A., Kleiner, D. E., Hayashi, P. H., Gu, J., Hoofnagle, J. H., Chalasani N. (2015). Clinical and Histologic Features of Azithromycin-Induced Liver Injury. Clinical Gastroenterology and Hepatology, 13, 369–376

Mitchell, G. F., Jeron, A., Koren, G. (1998). Measurement of heart rate and Q-T interval in the conscious mouse. Am J Physiol, 274, H747–H751

Moy, B. T., Dojki, F. K., Scholes, J. V., Hoffman, M. G. (2015). Azithromycin-induced cholestatic hepatitis. Conn Med, 79, 213–215

Ong, C. E., Pan, Y., Mak, J. W. (2017). The roles of cytochromes P450 in vascular biology and cardiovascular homeostasis. Int J Clin Exp Med, 10 (1), 1624-1636

Park, H. J., Seo, K. II., Yong, C. II. (2020). Liver transplantation for azithromycin-induced severe liver injury. Korean J Transplant, 34 (4), DOI:10.4285/kjt.20.0017

Parnham, M. J., Haber, V. E., Giamarellos-Bourboulis, E. J., Perletti, G., Verleden, G. M., Vos, R. (2014). Azithromycin: mechanisms of action and their relevance for clinical applications. Pharmacol Ther, 143(2), 225-245

Rao, G. A., Mann, J. R., Shoaibi, A., Bennett, C. L., Nahhas, G., Sutton, S. S., Jacob, S., Strayer, S. M. (2014). Azithromycin and levofloxacin use and increased risk of cardiac arrhythmia and death. Ann Fam Med, 12, 121–127

Ray, W. A., Murray, K. T., Hall, K., Arbogast, P. G., Stein, C. M. (2012). Azithromycin and the Risk of Cardiovascular Death. N Engl J Med, 366 (20), 1881-1890

Sandman, Z., Iqbal, O. A. (2024). Azithromycin. In: StatPearls [Internet]. Treasure Island (FL): StatPearls Publishing

Sharma, K., Mullangi, R.(2013). A concise review of HPLC, LC-MS and LC-MS/MS methods for determination of azithromycin in various biological matrices. Biomed Chromatogr, 27 (10), 1243-1258

Shoda, L., Woodhead, J. L., Siler, S. Q, Watkins, P. B., Howell, B. A. (2014). Linking physiology to toxicity using DILIsym®, a mechanistic mathematical model of drug-induced liver injury. Biopharm Drug Dispos, 35, 33-49

Sugie, M., Asakura, E., Zhao,Y. L., Torita, S., Nadai, M., Baba, K., Kitaichi, K., Takagi, K., Takagi, K., Hasegawa, T. (2004). Possible Involvement of the Drug Transporters P Glycoprotein and Multidrug Resistance-Associated Protein Mrp2 in Disposition of Azithromycin. Antimicrobial Agents and Chemotherapy, 48 (3), 809–814

Suresh, B. K., Kastelik, J., Morjaria, J. B. (2013). Role of long term antibiotics in chronic respiratory diseases. Respir Med, 107, 800-815

Swayze, E. E., Griffey, R. H., Bennett, C. F. (2007). 2.26 -Nucleic Acids (Deoxyribonucleic Acid and Ribonucleic Acid). Comprehensive Medicinal Chemistry II, 2, 1037-1052

Tsai, D., Jamal, J. A., Davis, J., Lipman, J., Roberts, J. (2015). Interethnic differences in pharmacokinetics of antibacterials. Clin Pharmacokinet, 54 (3), 243-260

Vial, T., Biour, M., Descotes, J., Trepo, C. (1997). Antibiotic-associated hepatitis: update from 1990. Ann Pharmacother, 31, 204-220

Viluksela, M., Vainio, P. J., Tuominen, R. K. (1996). Cytotoxicity of macrolide antibiotics in a cultured human liver cell line. J Antimicrob Chemother, 38, 465-473

Wong, K. M., Hosseinnejad, K., Palaparty, P., Ravakhah, K. (2021). Azithromycin-Induced Liver Injury in Legionnaires' Disease. Cureus, 13 (9), e17856

Woodhead, J. L., Brock, W. J., Roth, S. E., Shoaf, S. E., Brouwer, K. L. R., Church, R., Grammatopoulos, T. N., Stiles, L., Siler, S. Q., Howell, B. A., Mosedale, M., Watkins, P. B., Shoda, L. K. M. (2017). Application of a mechanistic model to evaluate putative mechanisms of tolvaptan drug-induced liver injury and identify patient susceptibility factors. Toxicol Sci Off J Soc Toxicol, 155, 61-74

Woodhead, J. L., Yang, K., Oldach, D., MacLauchlin, C., Fernandes, P., Watkins, P. B., Siler, S. Q., Howell, B. A. (2019). Analyzing the mechanisms behind macrolide antibiotic-induced liver injury using quantitative systems toxicology modeling. Pharm Res, 36, 48

Wu, Y., Bi, W. T., Qu, L. P., Fan, J., Kong, X. J., J, C. C., Chen, X. M., Yao, F. J., Liu, L. J., Cheng, Y. J., Wu, S. H. (2023). Administration of macrolide antibiotics increases cardiovascular risk. Front Cardiovasc Med, 10, 1117254. doi: 10.3389/fcvm.2023.1117254

Yang, Y., Nadanaciva, S., Will, Y., Woodhead, J. L., Howell, B. A., Watkins, P. B., Siler, S. Q. (2015). MITOsym®: A Mechanistic, Mathematical Model of Hepatocellular Respiration and Bioenergetics. Pharm Res, 32, 1975–1992

Yang, Z., Prinsen, J. K., Bersell, K. R., Shen, W., Yermalitskaya, L., Sidorova, T., Luis, P. B., Hall, L., Zhang, W., Du, L., Milne, G., Tucker, P., George Jr, A. L., Campbell, C. M., Pickett, R. A., Shaffer, C. M., Chopra, N., Yang, T., Knollmann, C. B., Roden, D. M., Murray, K. T. (2017). Azithromycin Causes a Novel Proarrhythmic Syndrome. Circ Arrhythm Electrophysiol, 10 (4), doi:10.1161/CIRCEP.115.003560

Yap, Y.G., Camm, A. J. (2003). Drug-induced QT prolongation and torsades de pointes. Heart, 89 (11), 1363–1372

Zhang, H., Zou, J., Yan, X., Chen, J., Cao, X., Wu, J., Liu, Y., Wang, T. (2021). Marine-Derived Macrolides 1990–2020: An Overview of Chemical and Biological Diversity. Mar. Drugs, 19, 180

Zhang, M. Q., Zhang, J. P., Hu, C. Q. (2022). A Rapid Assessment Model for Liver Toxicity of Macrolides and an Integrative Evaluation for Azithromycin Impurities. Front Pharmacol, 13, 860702

Zuckerman, J. M. (2004). Macrolides and ketolides: azithromycin, clarithromycin, telithromycin. Infect Dis Clin North Am, 18 (3), 621–649

Zuckerman, J. M., Qamar, F., Bono, B. R. (2011). Review of macrolides (azithromycin, clarithromycin), ketolids (telithromycin) and glycylcyclines (tigecycline). Med Clin North Am, 95 (4), 761-791