EFFECTIVENESS OF AZITHROMYCIN IN COVID-19: THE PANDEMIC ERA

P.Nithyakala *, Merlin Jose, B.Monica, R.Muthuselvi, Nair Anagha Unnikrishnan
Swamy Vivekanandha College of pharmacy, Tiruchengode, Tamilnadu, India

*Author for Correspondence
Ms. P. Nithyakala, M.Pharm., (MBA).,
Assistant Professor,
Dept. of Pharmacy Practice,
Swamy Vivekanandha College of pharmacy, Tiruchengode,
Tamilnadu-635 205
Email: nithi29kala@gmail.com

ABSTRACT

The outbreak related to severe acute respiratory syndrome (SARS-COV-2) was first detected and reported in Wuhan-china in December 2019 and declared as a pandemic by the world health organization (WHO) on March 11, 2020. Also commonly known simply as the coronavirus, it comes under the family Coronaviridae. The covid-19 epidemic has changed the global focus of health care and also created an unpredictable crisis in every aspect of the healthcare system all over the world. Patients with covid-19 were treated with board spectrum antibiotics with unknown efficacy because covid-19 patients frequently need to prolong hospitalization and respiratory support. The nature and rationale for antibiotics prescribing in patients suspected to covid 19 are not well established. The study investigates the role of Azithromycin therapy and its impact on prognosis along with the appropriateness of azithromycin and also usefulness and its benefits. Antibiotics have been used in hospitals empirically to treat patients with covid 19 due to overlapping clinical and radiological features of secondary bacterial respiratory tract infection. The macrolide antibiotic azithromycin has been one of the recommended therapy against covid-19. Azithromycin (500 mg 0.D, followed by 250 mg OD for 2-5 days) has great assess on lung tissue and wide range of antibacterial efficacy, Conceivable antiviral action against covid-19. The covid-19 patient can lead to a steep increase in antibiotics use during the era of pandemic and as a result a potential increase in antimicrobial resistance rate.

KEYWORDS: COVID-19, AZITHROMYCIN, ANTIBIOTICS, SECONDARY BACTERIAL INFECTION, ANTIVIRAL EFFECTS

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1. INTRODUCTION

Coronavirus disease (COVID-19) is an infectious disease caused by the SARS-CoV-2 virus. Symptoms may appear after 2-14 days of the incubation period. Persons infected by the covid-19 virus may exhibit no symptoms, or illnesses ranging from mild to moderate to serious illness. Anyone can have mild to severe symptoms. People with these symptoms may have COVID-19. Symptoms like fever and chills, cough, shortness of breath, fatigue, muscle or body aches, headache, loss of taste or smell, Sore throat, Congestion or runny nose, nausea or vomiting, and diarrhea

Management of covid-19 in adult patient with mild or moderate symptoms are achieved using

first line treatment of Hydroxychloroquine 200mg 8 hourly for 10 days per oral route with combination to azithromycin 500mg one day and later 250mg for four days per oral, doxycycline 100mg for five days per oral can also be given with the combination to Hydroxychloroquine. furthermore second line treatment are chloroquine phosphate 500mg 12hour for 5 days in combination with azithromycin 500mg for one day , then 250mg for four day per oral, in addition to doxycycline 100mg for five days per oral is also given.

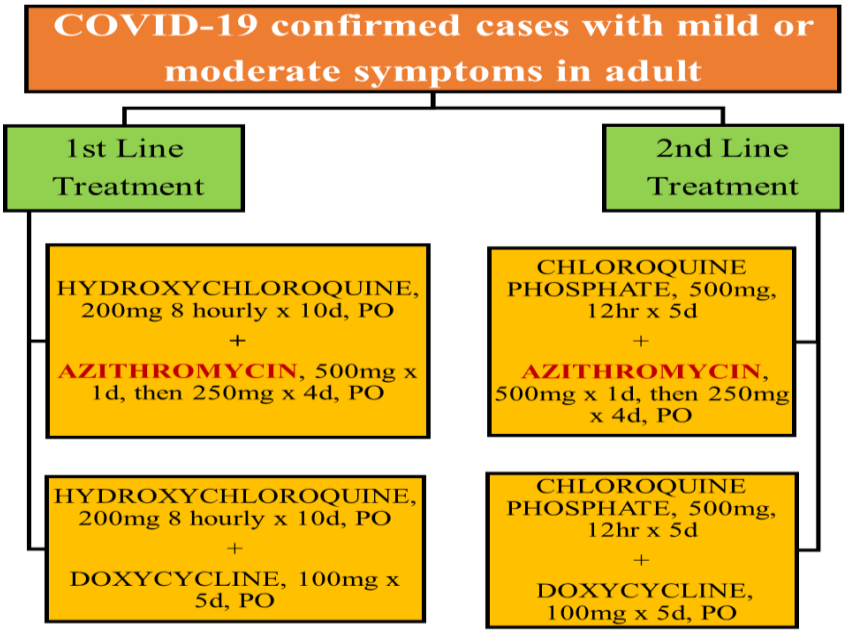

Figure 1: A brief architecture of Management to covid-19 adult patients with mild to moderate symptoms

The figure 1 shows the description depicted to covid-19 adult patients with mild to moderate symptoms

2.REVIEW ON:

This review laconically states the effectiveness of azithromycin in covid-19 in the pandemic era.

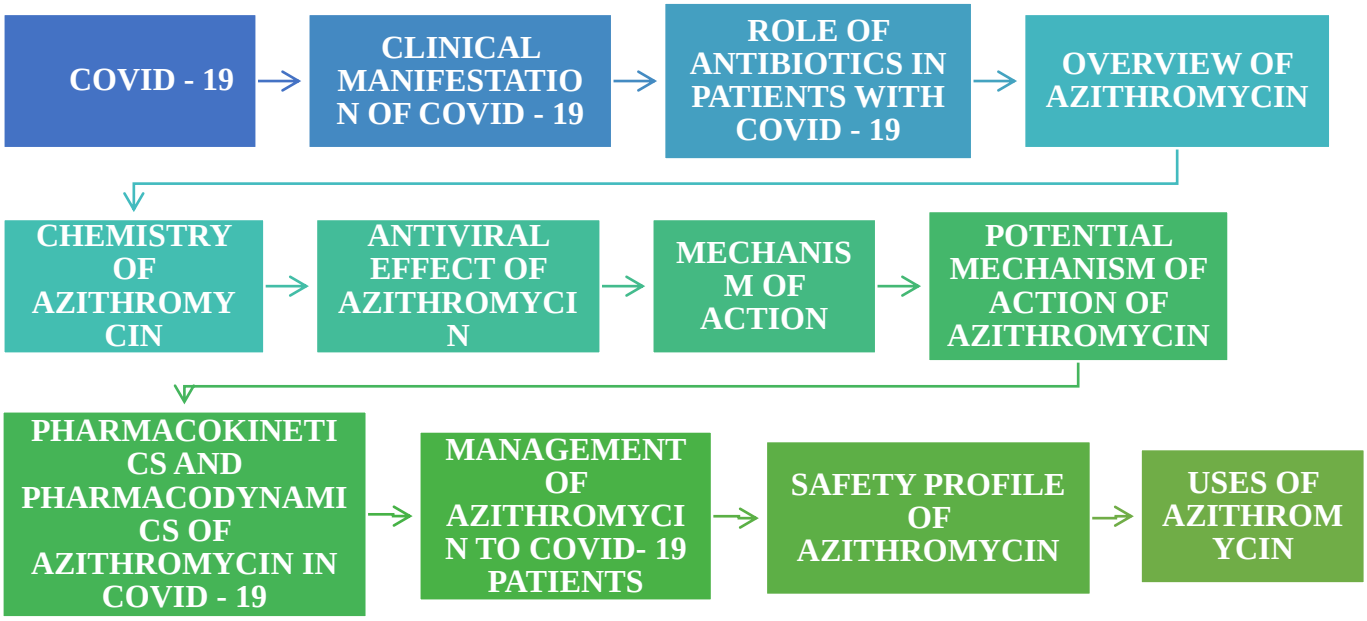

Fig 2: Architecture of Review article

These are several topics discussed under the review and briefly mentioned as flow chart in figure 2

2.1 **COVID-19**

An outbreak related to severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), was first evolved and reported in Wuhan-china in December 2019. The covid-19 epidemic is evolving rapidly, and the outbreak was declared a pandemic by the world health organization (WHO) on March 11. COVID-19 pandemic is considered as a sixth public health emergency in international concern. [11]

Coronavirus (CoV) is a positive-sense single-stranded RNA (ssRNA) virus with an envelope. It belongs to the order Nidovirales of the family Coronaviridae of the genus Coronavirus. The new type of coronavirus was produced by recombinant mutation of this virus in different hosts, will break out in the human population. The length of the coronavirus genome is 27–32 kb, which is that the largest RNA virus.[60]

The COVID-19 pandemic has sparked an unpredictable public health crisis all over the world. It has prompted numerous countries to implement lockdowns to mitigate the spread of the virus and to scale back the burden on health systems[12]. Many industries were affected and a lot of people were quarantined due to the spread of COVID-19, and this resulted in the fact that the life quality of humans is drastically affected. COVID-19 disease caused a lot of mortalities [1]. According to the latest update from Johns Hopkins coronavirus Resource Center, covid nearly infected over 179 million people and killed over 3.8 million worldwide.[10]

2.2CLINICAL MANIFESTATIONS OF COVID-19

SARS-CoV-2 is commonly spread by respiratory droplets, although spread by contact with contaminated fomites also occurs, as does transmission by aerosols in certain circumstances.[13]Patients mainly suffered from different symptoms like fever, dry cough, and fatigue which is mild in about 80% of cases, but the severity of the case may progress to develop respiratory distress or respiratory failure and hence the need for intensive care unit (ICU) will be increased.[15] COVID-19 infection usually presents as a respiratory syndrome, most commonly with fever and

cough.[16,17] Fever has been reported in up to 99% of people at some time during their illness [18]. Other common symptoms are cough, dyspnea, fatigue, anorexia, anosmia, myalgia, and sometimes confusion. Diarrhea may occur in up to 10% of patients[19]. Symptoms reported less frequently (< 5% of cases) include sore throat, rhinorrhea, headache, chest pain, dizziness, abdominal pain, and nausea.[16, 17]

2.3ROLE OF ANTIBIOTICS IN PATIENT WITH COVID-19

The role of antibiotics in the treatment of covid-19 is not adequately defined no criteria have been established for antibiotic treatment, duration, and type[2]. Three-quarters of patients with COVID-19 receive antibiotics. Antibiotic use is common within the inpatient setting. Covid-19 hospitalized patients receive at least 1 antibiotic during their hospital stay [3].The rationale for antibiotic prescribing in patients with suspected COVID-19 is not well established [20]. Broad-spectrum antibiotics are being widely used in patients with COVID-19. Many deaths are imputable by secondary bacterial infections. Thus, antibiotics appear to be an important defense against mortality in Covid-19 patients.[4] Secondary infections in COVID-19 patients are known to be associated with negative health outcomes[5]. Secondary bacterial infections are a significant cause of morbidity and mortality in the previous pandemic [56]. Despite the clinical importance of secondary bacterial infections, their contribution to COVID-19 severity and mortality is still not well established [14].Understanding the proportion of COVID-19 patients with acute respiratory bacterial co-infection, and the culprit pathogens are crucial for treating patients with COVID-19 and to help ensure responsible use of antibiotics and to minimize negative consequences of overuse.[21]

2.4OVERVIEW OF AZITHROMYCIN:

Azithromycin, a macrolide derivative and the first of the fifteen azalide ring family of antibiotics, exhibits broad activity against a wide range of gram-positive and gram-negative bacteria and other atypical pathogens[92.] Macrolides generally have a good tolerability profile. This class of drugs is primarily used to treat local and systemic infections, including infections of the skin, eyes, respiratory tract, gastrointestinal tract, and genital tract [93]. Antibiotics have significant antiviral activity [48, 47,55,57,64]. Azithromycin is considered one of the safest macrolides but this is controversial. Azithromycin is considered one of the safest macrolides but there is conflicting information about the risk of arrhythmias [80].They work by inhibiting bacterial growth by inhibiting protein synthesis. Azithromycin has in vitro activity against Ebola and Zika viruses and prevents serious viral respiratory infections. Besides extended antimicrobial coverage due to their anti-inflammatory and immunomodulatory effects, they have been used as adjuvant therapy for the treatment of respiratory viral infections [22]. AZM has been shown to have significant antiviral properties. Unlike CQ or HCQ, antiviral activity has been demonstrated in vitro and / or in vivo against various viruses such as Ebola, Zika, respiratory syncytial virus, H1N1 influenza virus, enterovirus, and rhinovirus [23].Many SARS-CoV-2 treatment regimens have been used in recent months, some of which include macrolide antibiotics, especially AZI, along with other medications. These studies are mainly based on several previous reports of the concomitant use of macrolides in other respiratory infections in patients with pneumonia.

2.5CHEMISTRY OF AZITHROMYCIN:

Azithromycin (9-DEOXO-9A-ASA 9A-methyl-9 A-homerythromycin) is derived from Erthuromycin in alternative alternate methyl nitrogen, with replacement of carbonate 9A, in addition to expanding the loop of 15 members [96]. This difference leads to structural for the internal reaction block in hemiketal, allowing acid degradation in the ethereal of neutral calcinosis assembly as an important pathway. In contrast, the reaction of the inner drought of Ratherycin is a capacity of activation temperature of 15.6 kilea / center [94]. In general, these results with a 300-fold growth in

azithromycin acids stabilized than erythromycin [90].

2.6ANTIVIRAL EFFECT OF AZITHROMYCIN:

Azithromycin is also thought to have antiviral properties that may act synergistically with antiviral drugs. Preclinical examinations have shown that these macrolide anti-microbial may have antiviral impacts against Zika, rhino, and Ebola [53,61,64,77]. However, no specific antiviral effect has been established in patients with COVID-19. Clinical studies of the use of azithromycin in patients with pneumonia caused by respiratory viruses are controversial. In a multicenter, open-label, randomized clinical trial in influenza A patients, combination therapy with oseltamivir and azithromycin (2 g / day, sustained release) was associated with improvement in some influenza-related symptoms, although no difference was found in inflammatory cytokines [66]. The exact mechanism is unknown. Nonetheless, a few instruments have been proposed for the putative antiviral properties saw in AD. The maturation and functioning of endosomes require an acidic environment. AZ is a weak base and preferentially accumulates intracellularly in endosomal and lysosomal vesicles, which can raise pH and block endocytosis and/or viral genetic secretion from lysosomes, thereby limiting viral replication.[24, 86] An acidic environment is also required for the disclosure of enveloped viruses such as influenza and HIV [91], and a similar mechanism may exist for coronaviruses, including enveloped viruses. This mechanism has also been proposed for the antiviral effects of HCQ and chloroquine (CQ) [25, 26]. Indeed, evidence suggests that AZ is more harmful for acidification than CQ [86].The putative antiviral effect of AZ may also be mediated by a global enhancement of the host pathway mediated antiviral (IFN) response during migration. Evidence suggests that AZ has the ability to reduce viral replication by inducing pattern recognition receptors, IFNs, and IFN stimulating genes. [47, 62, 77] AZ also acts directly on bronchial epithelial cells to support and improve lung function by decreasing mucus secretion [58]. In particular, for SARS-CoV-2, recent quantum mechanical models suggest a potential role for AZ, virus entry through a binding interaction between the SARS-CoV-2 spike protein and the receptor for the host protein ACE2 (angiotensin converting enzyme). Protein. Destruction of -2) protein; [27]

2.7MECHANISM OF ACTION:

The mechanism by which azithromycin exhibits its antiviral activity is still unknown. However, many mechanisms have been proposed. It has been suggested that azithromycin may inhibit endosome acidification during viral replication and infection.[86] As a weak base, azithromycin accumulates in the endosomal vesicles and increases the pH value. The processes of acidification and cleavage of endosomes are necessary for viral replication and infection. Another possible target for azithromycin is the stripping step during viral infection [22]. Again, this stage of the virus life cycle requires an acidic environment. In addition, due to its anti-inflammatory and immunomodulatory effects, azithromycin has been proposed as an alternative for patients with viral infections and inflammations [28]. Azithromycin reduces the production of pro-inflammatory cytokines such as interleukin-8 (IL-8), IL-6, tumor necrosis factor alpha (TNF-α), and matrix metalloproteinase (MMP) [23]. It also reduces oxidative stress and modulates T-helper function [63].

2.8POTENTIAL MECHANISM OF ACTION AZITHROMYCIN:[6]

SARS-CoV-2 Binding: Increasing the pH of trans-Golgi tissue can alter hACE2 glycosylation. Azithromycin mimics ganglioside due to its volume and chemical properties similar to GM1.

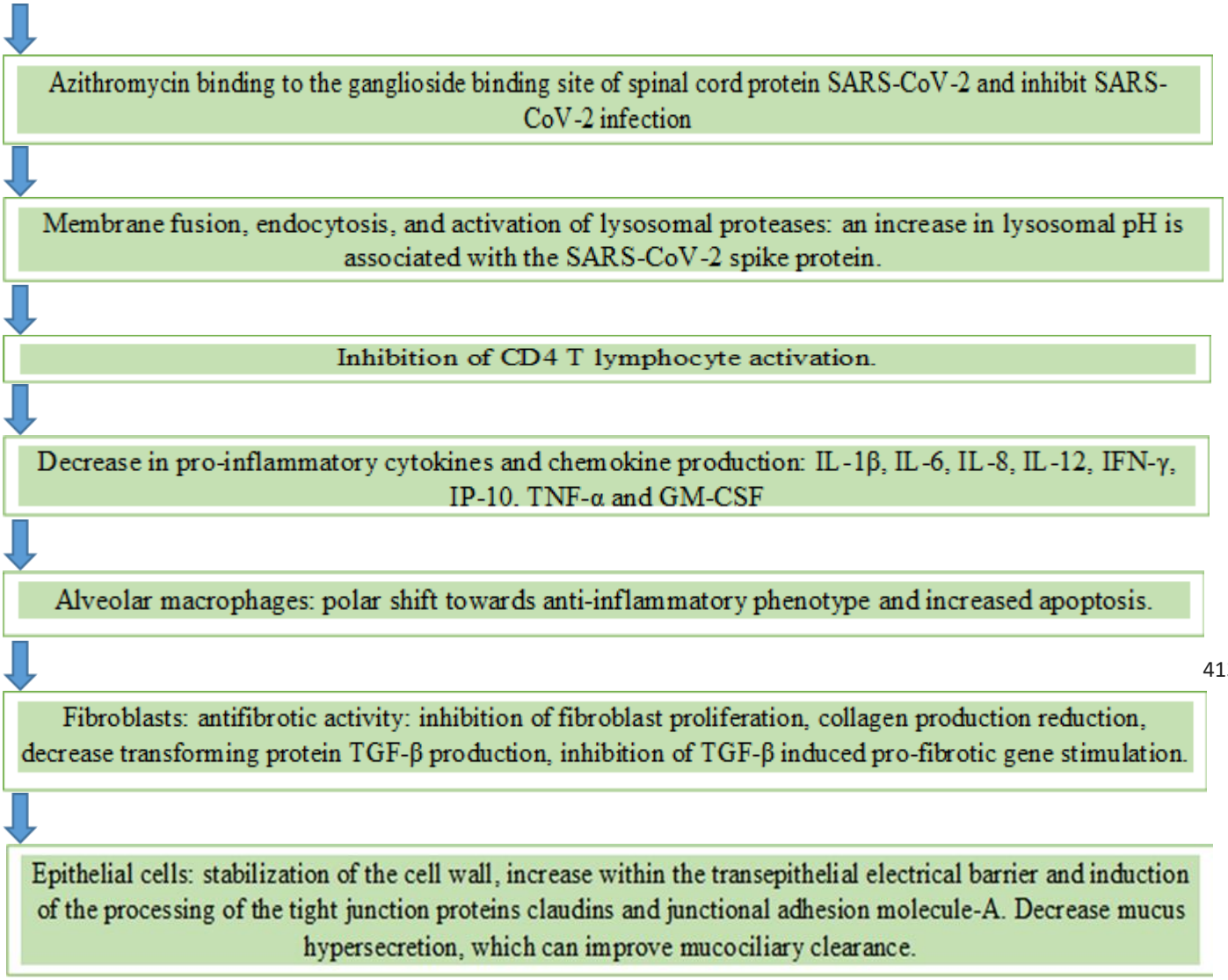

Figure 3: Flowchart on potential mechanism of action of azithromycin in treatment with covid -19

Azithromycin can act by binding SARS-CoV-2 to cells in the airways. Elevated pH due to intracellular accumulation can disrupt the trans-Golgi network (TGN) and lysosomal function[29, 73]. The authors hypothesized that this increase in TGN pH could alter glycosylation of hACE2 and other proteins [73]. Another direct antiviral mechanism of action of these macrolides has been theorized using molecular dynamics simulations [23]. Azithromycin mimics ganglioside due to its volume and chemical properties similar to GM1. Since the spinal cord protein SARS-CoV-2 has a ganglioside binding site, azithromycin can bind to this site and inhibit SARS-CoV-2 infection. This will prevent the viral anglioside proteins from reaching the host plasma membrane, which are involved in the pathogenesis of SARS-CoV-2 [23]. In addition, azithromycin can affect protein / CD147 interaction or CD147 expression [30]. An increase in the lysosomal pH of azithromycin can complicate the fusion process by altering the endocytosis process and the function of lysosomal proteases (cathepsins or purines) [29, 31, 32, 73]. It has been shown that 100M azithromycin can normalize overexpression and activation of Furina [73]. Given that SARS-CoV-2 has been shown to have a furin-like cleavage site in vertebrate proteins, reducing the activation of furin by azithromycin may prevent

SARS-CoV-2 from entering human epithelial cells.[33, 73]

2.9 PHARMACOKINETICS AND PHARMACODYNAMICS OF AZITHROMYCIN IN COVID 19:

The pharmacokinetics of AZ are well known. After oral administration, AZ is rapidly absorbed, has a long serum half-life (68 hours) and a large volume of distribution (31 L / kg).[88] AZ is absorbed by leukocytes at about 300 times higher concentrations than plasma [78]. The concentration of AZ is higher in infected tissues than in the plasma because leukocytes accumulate at the site of infection. Azithromycin accumulates in epithelial cells, fibroblasts, lymphocytes, and alveolar macrophages, where it can reach concentrations from 400 to 1000 times higher than in blood serum [31]. Chemotactic drug delivery further increases local drug concentrations as blood phagocytes and other cells migrate to infected and inflamed tissues and release accumulated azithromycin[31,86] . Therefore, azithromycin has a long elimination half-life of 68-79 hours [86]. This drug has good lung permeability and a stable drug concentration[67,86] , and after taking 500 mg once a day (OD) for 3 days Cmax 0.72-0.83 g / ml and 8.993-9.13 d for bronchial lavage. ml. Lung tissue[67, 85]. After a single oral administration of 500 mg, the highest concentrations are 1.2–2.18 µg / ml in the epithelial mucosa and 194 µg / ml in alveolar macrophages. [34, 95]

The pharmacodynamics of AZ is that the latter two are metabolized in the liver by interaction with cytochrome P450 CYP3A4, which is involved in various drug interactions. They are effective against certain microorganisms and have both bacteriostatic and bactericidal action, depending on their concentration and specific sensitivity to bacteria. The main pharmacodynamics target is the bacterial ribosome, which is considered one of the most conservative and complex cellular mechanisms. Bacterial ribosomes are made up of two separate subunits (small 30S and large 50S) that combine to form the 70S ribosome, which is prepared for the extended stage of protein synthesis. Thus, macrolides achieve antimicrobial activity by inhibiting bacterial protein synthesis through reversible binding to the 50S subunit of the 70S bacterial ribosome and blocking further protein translation.[59, 87]

2.10MANAGEMENT OF AZITHROMYCIN TO COVID -19 PATIENT:

The antibacterial macrolides azithromycin has a unique and exciting profile when looking for a drug remedy for covid-19[35]. Azithromycin is an FDA-authorized drug for the control of infections. Lately, it changed into repurposed for control of covid-19. In a clinical trial involving multiple patients, clearance of the novel virus was higher when patients were treated with azithromycin and hydroxychloroquine compared with hydroxychloroquine alone [9]. One in vitro study found azithromycin alone to be effective against SARS-Cov2, while another study found it to be effective only when combined with hydroxychloroquine[36]. Azithromycin increases the effectiveness of hydroxychloroquine in reducing viral load [8]. Viral clearance was observed in 12.5% 0f one patient who did not receive hydroxychloroquine and viral clearance was 70% with hydroxychloroquine alone. And viral clearance was 100% in patients treated with hydroxychloroquine with azithromycin. Patients without contraindications received 200 mg of hydroxychloroquine orally three times a day for 10 days in combination with 500 mg of azithromycin on the first day and then 250 mg daily for the next 4 days [37]. However, the optimal dose for viral infections is not yet known. In community-acquired pneumonia (CAP) IDSA guidelines recommend different treatments depending on the severity; for outpatients, 500mg once a day is recommended and 250 mg thereafter for 3 to 5 days and 500 mg once a day for 5 days for severe patients[49]. A recovery study evaluating the potential role of azithromycin in Covid-19 studied 500 mg once daily every 10 days. [6] For patients with pneumonia with NEWS score ≥ 5, broad-

spectrum antibiotic ceftriaxone was added to hydroxychloroquine and azithromycin.[89]

2.11SAFTEY PROFILE:

Azithromycin has a low risk of serious side effects and is considered safe[89]. The most common adverse events are from the gastrointestinal tract (nausea and abdominal pain), the central and peripheral nervous system (headache or dizziness), hepatotoxicity, and the development of antimicrobial resistance [31]. The use of macrolide azithromycin has been associated with cardiovascular events, especially in patients at increased cardiovascular risk [65, 68, 71,72,74,83]. Azithromycin can cause cardiac arrhythmias due to prolongation of the QT interval[79]. Although this likely increases the risk of arrhythmias and myocardial infarction, azithromycin does not have the significant drug interactions seen with other macrolide antibiotics. Therefore, in terms of cardiac activity, it is the safest of all macrolide antibiotics[81].

In hospitalized patients, the utilization of hydroxychloroquine and azithromycin has been associated with a better incidence of cardiac adverse events. this mix has been related to a better risk of QTc prolongation, ventricular arrhythmia, TdP (with an incidence of 0.4%), fibrillation, heart block, or systole [38, 39, 40, 41, 54]. within the only randomized controlled clinical test published so far in hospitalized patients with COVID-19, the utilization of hydroxychloroquine and azithromycin or hydroxychloroquine alone was related to a better risk of adverse events, QTc prolongation, or arrhythmia than azithromycin alone or standard of care [42]. The combined drugs are safely and successfully utilized in the treatment of patients with malaria [50, 69].

2.12USES OF AZITHROMYCIN:

Azithromycin (AZ) is a second-generation, broad-spectrum tissue macrolide that is primarily used to treat bacterial infections of the respiratory, intestinal, and urinary tract, such as community-acquired pneumonia and chlamydia34, 43, 51. The anti-inflammatory and immunomodulatory properties of azithromycin, along with its ability to prevent pulmonary fibrosis and maintain epithelial integrity, may play a role in modulating hyper inflammation in Covid-196,44.AZ is a macrolide antibiotic used primarily to treat upper and lower respiratory tract infections. It has been effective against some gram-positive, gram-negative, and atypical bacteria by binding to 50s ribosome subunits and suppressing protein synthesis 7. Azithromycin is also used as an immunomodulatory agent for various respiratory diseases such as cystic fibrosis, bronchiectasis, and bronchiolitis obliterans after lung transplantation, and asthma 82, 84. Azithromycin therapy has also been performed in a number of randomized trials to reduce the incidence of pulmonary exacerbations and improve the quality of life of patients with chronic obstructive pulmonary diseases (COPD) 75, 76. Azithromycin is receiving more and more attention because of its complementary nature of host defense responses through immunomodulatory effects in chronic inflammatory diseases 52, 70. Azithromycin has been shown to be effective against Zika and Ebola viruses 53 and is more likely to fight SARS-COV 2 in vitro45. Azithromycin also suppresses protein synthesis and experimentally reduces viral replication and inflammation, possibly because cytokines and viruses are composed of proteins and use cellular ribosomes to translate proteins 46.

CONCLUSION:

Azithromycin, A lifesaver amidst the pandemic for many lives. The review mainly focuses on the role of Azithromycin therapy and its impact on prognosis along with the appropriateness of azithromycin, its usefulness, and benefits. The clinical trials with a limited number of patients demonstrated a higher clearance of the novel virus when the patients were treated with Azithromycin. Azithromycin is mainly used for treating the secondary infections caused during covid-19.

It can be concluded that the role of antibiotics in the treatment of covid-19 is not

adequately defined and no criteria have been established for antibiotic treatment, duration, and type. Hence the antibiotics should be prescribed in the covid-19 patients only if necessary or for the treatment of secondary infections. However, based on evidence regarding clinical, preclinical, and some preliminary results in Covid-19 conveys that, azithromycin could have potential in the fight against this new disease.

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