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Therapeutic potential of Azithromycin in the management of Covid-19-A review

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Abstract

Severe acute respiratory syndrome-CoV-2 (SARS-CoV-2) virus causes highly contagious condition known as COVID-19 disease which has mild to severe symptoms such as weakness, headache, fever, cough, hypoxia with acute respiratory distress syndrome leadingto multiple organ failure and death. This highly contagious disease is now became the most challenging health problem worldwide. The antibiotics are widely used among hospitalized patients for the management of Covid-19. However a number of studies are still required for the determination of use of antibiotics for the management of Covid-19 patients as significant deaths are reported due to secondary infections and emergence of drug resistant pathogens.Azithromycin is an azalide and very useful for the management of Covid-19 due to its great therapeutic potential. However,there are side effects associated with the use of this antibiotic alone or in combination with other drugs. There are also possible chances of the emergence of antimicrobial resistance among the patients infected with SARS-CoV-2 virus due to the extensive use of antibiotics with threat of transmission of drug resistant pathogens. In this review, the therapeutic potential of azithromycin for the management of Covid-19 patients has been discussed along with clinical evidences about its efficacy alone or in combination with other drugs with possible side effects in the Covid-19 patients.

Introduction

A novel corona virusalso known as severe acute respiratory syndrome-CoV-2 (SARS-CoV-2), was first detected in China in December 2019. This virus causes highly contagious condition known as COVID-19 disease which has mild to severe symptoms such as weakness, headache, dizziness, fever, cough, hypoxia with acute respiratory distress syndrome and multiple organ failure (Kaymakci et al., 2020). Corona virus is very small in size with single stranded RNA as a genetic material containing crown like spikes on its external surface(Zhong et al., 2003).The corona virus was named SARS-CoV-2 by the International Committee on Taxonomy of Viruses (ICTV) and has mortality rate of more than 9% in many countriesworldwide(Cui et al., 2019; Lai et al., 2019).The antibiotics are widely used among hospitalized patients for the management of Covid-19 disease. However a

number of studies are still required for the determination of antibiotic usage for the management of Covid-19 patients as significant death rate is observed among them due to the incidence of secondary infections and emergence of drug resistant pathogens (Chedid et al., 2021). Azithromycin is an azalide and belongs to a subclass of macrolide antibiotics and inhibits bacterial growth by interfering with bacterial protein synthesis (Bakheit et al., 2014).Recent studies revealed that azithromycin has antiviral effects against a number of viruses causing respiratory tract infections. Therefore, this antibiotic could be effective in the management of Covid-19 and other respiratory tract infections.However, there is very less clinical data is availableregarding use of azithromycin alone or in combination with other drugs in the treatment of respiratory tract infections as a number of possible adverse effects are associated with the use of this drug(Vitiello and Ferrara, 2021).There are possible chances of emergence of antimicrobial resistance among the Covid-19 patients due to extensive use of antibiotics (Adebisi et al., 2021).Recent clinical trials have raised safety concerns about the use of azithromycin and other drugs due to their arrhythmogenic potential (Sultana et al., 2020). This review aims to discuss the therapeutic potential of azithromycin for the management of Covid-19 patients. Also, clinical evidence about the efficacyof azithromycinalone or synergetic use has been discussed with possible side effects to the Covid-19 patients (Gouvea dos Santos, 2020).

Potential treatment strategies for Covid-19

There is lack of effective treatment option available despite of the extensive research undergoing against novel SARS-CoV-2 virus infection. This highly contagious and

dangerous disease is now became the most challenging health problem in the world. Currently, the management of this disease is restricted to use of preventive and control measures and the work on the development of an effective treatment option for this disease is still ongoing. However, several drugs which are in use for the treatment of other diseases have been tried based on their pharmacological and clinical knowledge (Gouvea dos Santos, 2020). Viral infections are difficult to treat as compared to bacterial infections due to their unique properties. Viruses generally use host cell's machinery for the preparation of viral proteins which are required for its replication thus it is very difficult to target virus without possessing any adverse effect to the host cells. Replication of genetic material is one of the

important steps of viral multiplication. A better understanding of molecular mechanisms,anti viralagentsmay be developed which can target the various proteins which are helpful inthe replication of virus (Magden et al., 2005).There are various classes of antiviral agents viz; chloroquine, ivermectin, nitazoxanide, hydroxychloroquine, lopinavir, remdesivir, tocilizumab along with supporting agents such as vitamin C, vitamin D, azithromycin and promising vaccines which can be used in the prevention, control and treatment of novel corona virus infection (Gouvea dos Santos, 2020). Several workers havealso suggested the use ofRNA-dependent RNA polymerase (RdRp), which regulates viral replication, as a potential treatment agent for this viral infection(Aftab et al., 2020).The identification of important proteins which help in the viral replication and followed by their blocking could also be an u viral proteins which help in replication and hen blocking them could also be an effective way to control this disease(Raethong et al., 2020).Monoclonal antibodies can be produced from the viral components obtained from the covid patients. However, the monoclonal antibodies obtained from murine model may lead to lesser immunity in the patients (Berger et al., 2002). Many researchers areworking to develop potential antibodies which can neutralize the virus and may prove effective in the treatment of the disease [8]. The novel therapeutic treatment strategies such as RNA interference can also be used to develop antiviral agents. In this process, RNA molecules are used to inhibit viral gene expression and protein synthesis by neutralizing targeted mRNAs (Uludag et al., 2020).The miRNAs and siRNAs can be designed as per the genetic and morphological structure of SARS CoC-2 virus (Kalhori et al., 2021). Also, the selective gene silencing technology can be used to turn off the vital proteins (Khanna et al., 2015). The effective treatment strategy can also be designed by identification of cell surface receptors and designing complementary

receptor molecules for blocking of viral spike proteins and binding sites(Wallset al., 2020).The possible potential treatment strategies for COVID-19 have been represented in Table-1

Table-1 Potential treatment strategies against SARS-CoV-2 virus

Sr. No.	Possible treatment strategy	Mechanism	References
1	Vital viral proteins	Blocking of critical viral enzymes needed for replication	(Raethong et al., 2020).
2	Monoclonal antibodies	Blocking and neutralizing virus.	(Berger et al., 2002; Jahanshahlu et al., 2020).
3	Inhibition of replication of virus	Converting viral proteins which regulates replication into non-functional proteins	(Magden et al., 2005; Aftab et al., 2020).
4	RNA interference and Gene silencing	Silencing of viral targets using siRNA, siRNA molecules and selective gene silencing	(Uludag et al., 2020;Kalhori et al., 2021; Khanna et al., 2015).
5	Blocking of viral binding sites	Blocking binding of virus to cell surface receptors	(Walls et al., 2020)
6	Antiviral drugs, supporting agents and vaccines	Prevention, control and treatment of novel corona virus infection	(Gouvea dos Santos, 2020).

Use of antibiotics in the management of Covid-19

The antibiotics are widely used among hospitalized Covid-19 patients. However a number of studies are still required for the determination of antibiotic usage for the management of Covid-19 patients as significant death rate is observed in these due to incidence of secondary infections and significant emergence of drug resistance (Chedid et al., 2021).Some of Covid-

19 patients may develop bacterial coinfection therefore, a number of antibiotics such as azithromycin, ampicilin, gentamicin, ciprofloxacin, amoxicillin, cefriazone, amoxicillin-clavulanic acid, cefepime, vancomycin, meropenem are widely recommended for the management of Covid-19(Adebisi et al., 2021).The broad spectrum antibiotics are used in the hospitalized Covid-19 patients. A study revealed the widespread broad-spectrum antibiotic use in patients with COVID-19. Combinational therapy of β-lactams and macrolides or fluoroquinolones was also reported. However, piperacillin/tazobactam was most commonly used antibiotic drug combination among ICU patients (Beovic et al., 2020).Bendala Estrada and co-workers (2021), analyzed the use of antibiotics among hospitalized Covid-19 patients as per the data obtained from a semi-Covid-19 registry. In this study, it has been observed that there was high death rate among the patients receiving antibiotics. However, macrolides had higher survival rate. The antibiotic usage was high among the patients despite the few incidence of bacterial co-infection (Bendala Estrada et al., 2021). There are possible chances of emergence of antimicrobial resistance globally among the patients infected with SARS-CoV-2 virus due to extensive use of antibiotics with spread of drug resistant pathogenic strains (Adebisi et al., 2021).It is important to monitor the antimicrobial drug resistance from time to time in acute care settings. The health and community care system may be characterized based on the data collected. The useful information may be used to update or develop health care strategies to counter antimicrobial drug resistance (Rawson et al., 2020).

Azithromycin as useful antibiotic

Azithromycin is an azalide and belongs to a subclass of macrolide antibiotics. This is obtained from erythromycin and inhibits bacterial growth by interfering with the protein synthesis. It inhibits bacterial protein synthesis via binding with 50S subunit of the bacterial ribosome which leads to inhibition of translation of mRNA (Bakheit et al., 2014). Besides this, azithromycin has a number of other pharmacological effects including its immunostimulatory effects due to which it can be applied in the treatment of inflammatory conditions such as asthma and chronic obstructive pulmonary disease.As per several studies, azithromycin may also minimize viral load by inhibiting viral replication and ability to express antiviral genes (Khezri et al., 2021). Azithromycin is used to treat a number of bacterial infections such as middle ear infections, typhoid and bronchitis. It is also found effective in the treatment of sexually transmitted infections such as nongonococcal urethritis, chlamydia, and cervicitis (Bakheit et al., 2014).

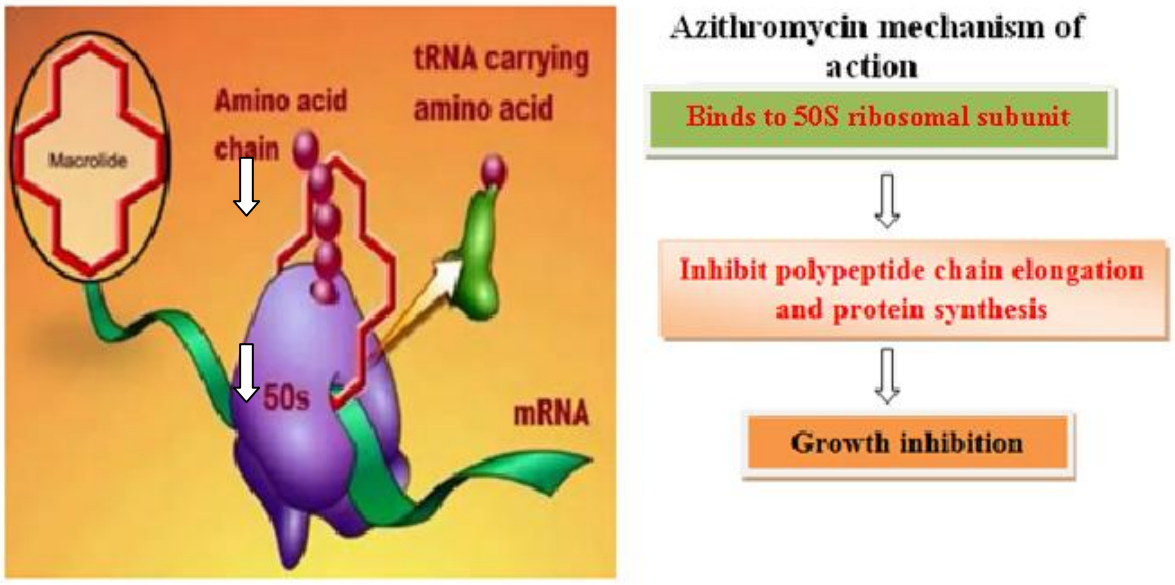

Fig-1 Mode of action of azithromycin

Azithromycin binds to 50S ribosomal subunit and inhibit bacterial growth by suppressing protein synthesis (Fig-1). It also inhibits bacterial quorum sensing mechanism and biofilm formation. It accumulates in higher concentrations in infection sites and clear plasma. It has good safety record with minimum patient risk (Parnham et al., 2014).

Therapeutic potential of azithromycin for COVID-19 patients

The emergence of incidences of novel corona virus infections has created huge demand for the rapid effective drugs worldwide. Azithromycin is a macrolide antibiotic which is well known for its immunomodulatory and antiviral effects. COVID 19 is an urgent tissue damaging disease leading to hyper inflammatory condition due to extensive secretion of cytokines (Khezri et al., 2021). Recent studies demonstrate that azithromycin had antimicrobial activity against a number of viruses which affects respiratory tract. Therefore, this antibiotic could be effective in the treatment of Covid-19 and other respiratory tract infections. However, there is very less clinical evidence is available on the effectiveness of azithromycin alone or in combination in the treatment of respiratory tract infections due to possible adverse effects. In some studies, cases of azithromycin-induced malignant

arrhythmias have been observed. (Vitiello and Ferrara, 2021). The efficacy of hydroxychloroquine and azithromycin combination tested for the treatment of COVID-19. As

per molecular dynamics, simulations, it has been demonstrated that this drug combination acts synergistically to prevent the attachment of virus to the host cells. The azithromycin has similarity with the GM1's sugar moiety which acts as cofactor for attachment of viruses. Azithromycin interacts with ganglioside binding domain of the Covid virus. It has been demonstrated that both the drug acts as competitive inhibitors of corona SARS-CoV-2 virus and prevents the attachment of virus to the host cells (Fantini et al., 2020). The *in vitro* studies have demonstrated that azithromycin has various immunomodulatory effects as it has ability to produce pro inflammatory cytokines such as IL-8, IL-6 and TNF alpha. In addition to these, it also helps to reduce oxidative stress along with stimulation of T-helper cells. It can be concluded on the basis of clinical and preclinical data evidence that this antibiotic as great potential to combat this novel disease (Pani et al., 2020).An outbreak of SARS-CoV-2 lead to highly infectious viral pneumonia which could be treated with antibiotics. It is more challenging to select an appropriate antibiotic for the treatment of this condition. Azithromycin is known to have good access to lung tissues with good synergistic antibacterial effect with other drugs (Ali et al., 2021).

Clinical evidences on the efficacy of azithromycin alone or in combination for treatment of Covid-19

There are very less authentic clinical evidences on the beneficial effects of azithromycin in the treatment of Covid-19 due to risks associated with it.It has been observed that this drug increased the mortality and length of stay rates when given in combination withhydroxychloroquine due to the associated cardiac side effects (Lighter and Raabe, 2020). In vitro studies have demonstrated that hydroxychloroquine has food antiviral activity than azithromycin and thus it may be good option for the treatment of Covid-19. However, the results of clinical trials are not so encouraging. According to human fusion field method, it has been found that the zinc sulphate is major agent for curing Covid-19 patents. Aspirin has shown some improvements in kidney functions of the patients than azithromycin(Wenjun, 2020). As per preclinical and clinical evidences, azithromycin have shown potential against Covid-19. However, some clinical evidences have revealed that azithromycin has controversial outcomes when used in combination with hydroxychloroquine. Based on French clinical trial, both the drugs shown potential side effects when used synergistically

(Pani et al., 2020). The efficacy of azithromycin for hospitalized Covid -19 patents was evaluated in a randomized phase 2 multicenter clinical trial on 284 patients admitted in fifteen centers across Belgium. The patients which were hospitalized in Covid wards were selected for the study when they were symptomatic and tested positive through CT scan or PCR test within last 72 hrs. The group of patients were given azithromycin 500mg during the first five consecutive days after their inclusion in the study. The trial was aimed to investigate the urgent need and impact of drugs such as azithromycin against Covid-19 (Gyselinck et al., 2021). There is limited evidence about the effect of azithromycin or clarithromycin regimen for Covid-19. A randomized trial including three groups of Covid-19 patients were selected to understand the addition of treatment regimen of both the drugs. Azithromycin 500mg/24h was given to 107 patients, 99 patients were given clarithromycin 500mg/12h for seven days, whereas 99 patients were included in control group and were given standard treatment only. All the groups were symptomatic and their clinical and biochemical evaluations were assessed by performing various tests. The results demonstrated significant improvements in the patients treated with azithromycin and clarithromycin and conversion to early negative PCR test. Overall, it has been observed that clarithromycin and azithromycin could be beneficial for early control of fever and conversion to mild Covid-19 (Rashad et al., 2021).In a similar study, 84 patients suspected with Covid-19 from Toledo, Spain were treated with antihistamines and azithromycin. All the patients were found seropositive for Covid-19. This study suggests that both this drug combination may be useful for the treatment in selected cases and may prevent the severe form of the disease (Morán Blanco et al., 2021).In another study, out of 239 patients which were treated with azithromycin, 29 were matched with equal number of patients kept in control group. In this matched subcohorts, no significant changes were observed in using azithromycin. However, among unmatched cohorts, the prolonged hospital stay associated to azithromycin use. Despite of small sample size was included, there was no clinical benefit was found in use of azithromycin in terms of prolonged hospital stay and improvement in lung function after 48 h of treatment (Rodríguez-Molinero et al., 2020).The main clinical evidence about the beneficial effects of azithromycin alone or in combination with other drugs such as hydroxychloroquine of chloroquine in the treatment of Covid-19 received from French open non randomized clinical trial conducted on 42 hospitalized patients who were infected with the virus over 14 days. These patients were given hydrochloroquine 600mg daily with azithromycin (500mg on first day and 250mg for next four days). It has been observed that 100% of the patients were found free from viral load after six days when both the drugs were used as compared to hydroxychloroquine alone (57.1%). However this study had some methodological issues(Gautret el al., 2020).

Impact of Aztihromycin treatment regimen on Covid-19 patients

There is no clear cut clinical evidence about the efficacy of azithromycin for the Covid-19 patients except its antimicrobial effect in bacterial super infection. As per CAP treatment guidelines from scientific societies, it has been suggested that broad spectrum antibiotic should be used preferably to treat bacterial superinfection and not to use macrolide alone as first line treatment option. However, the arrhythmogrnic potential of azithromycin is lower in comparison to other antibiotics in the macrolide group (Cutroneo et al., 2020). In the Covid-19 patients, antibiotics are used due to their anti-inflammatory, anti-modulating and antiviral effects. However, the use of some antibiotics for the treatment of Covid-19 is quite controversial and acceptable widely (Bakheit et al., 2014).This pandemic has created the demand of the medicines which could improve the prognosis of the disease and azithromycin is one of them. There is less data on the antiviral and an immunomodulaory activity of this antibiotic is available specifically in patients infected with SARS-CoV-2 virus. Since recent clinical trials has raised serious safety concerns about the use of azithromycin and other drugs such as hydrochloroquine due to their arrhythmogenic potential. World health organization has not recommended the use of azithromycin as treatment drug for Covid-19. However, some country's national organizations has different stand about its use (Sultana et al., 2020). As the Hippocratic Oath given to medical personnel states that patients should not be harmed, therefore, physicians should not prescribe azithromycin for Covid-19 patients until sufficient data is obtained from randomized controlled trials (Lighter and Raabe, 2020).Also, the major scientific communities including the drug regulatory agencies and public health organizations have not recommended the use of azithromycin as treatment drug for Covid-19 patients. Even world health organization has not issued any document about the safety and effectiveness of this drug. However, the Italian drug agency has also not recommended the use of hydroxychloroquine and azithromycin drug combination for Covid-19 patients until the incidence of bacterial superinfection (AIFA, 2020).

Possible side effects of azithromycin in patients with Covid-19

Many clinical personnel have raised the serious concern about the cardiovascuibut many clinicians raise concerns regarding cardiovascular risk associated with the antibiotic use in the patients (Ali et al., 2021). The clinical trials revealed that treatment regimen of hydroxychloroquine and azithromycin could be beneficial for Covid-19 patients with some cardiovascular side effects. As per a study on 161 RT-PCR positive patients, there was decrease in the sign and symptoms of the Covid-19 with the application of

hydroxychloroquine and azithromycin treatment regimen. The commonly occurring side effects were stomach pain, hypoglycaemia, itching, skin rash, arrhythmia and conjunctivitis. However these side effects are manageable (Abbas et al., 2020).Azithromycin is in use for Covid-19 patients despite of less clinical evidence available in support. Therefore there is great threat of associated side effects and emergence of antimicrobial drug resistance. Kamel and co-workers (2021), analyzed the efficacy and safety of azithromycin in Covid-19 patients by suing randomized controlled trials. Their results demonstrated that azithromycin cannot be recommended to Covid-19 patients as long term treatment regimen due to lack of efficacy and risk of development of antibiotic drug resistance (Kamel et al., 2021). In a UK based randomized clinical trial, the results do not suggest the routine use of azithromycin for the recovery of hospitalized patients with suspected Covid-19. However, there is frequent use of azithromycin among Covid-19 patients despite of increased risk of antibiotic resistance (Principle trial collaborative group, 2021).

Summary

A novel corona virus strain, also known as severe acute respiratory syndrome-CoV-2 (SARS-CoV-2), was first detected in 2019 and causes highly contagious disease condition COVID-19. The antibiotics are widely used among hospitalized Covid-19 patients for the management of infection. Significant death rate is observed due to incidence of secondary infections. Azithromycin inhibits bacterial growth by interfering with the protein synthesis and recently known to have significant antiviral properties against the viruses which cause respiratory tract infections. However, there is very low clinical data is available about the efficacy and safety of this drug alone or in combination to be used as treatment regimen for Covid-19 patients due to associated adverse effects. Also, there are possible chances of emergence of antimicrobial resistance due to extensive use of antibiotics with possible spread of drug resistant pathogenic strains.

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