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Research Article

The Potential Role of Azithromycin Once Weekly as a Novel Prophylaxis in Ambulatory People Who are at High Risk for Covid-19 Infection

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Abstract: Viruses targeting respiratory tract have significant impact on pulmonary function. Coronavirus disease 2019 (COVID-19) is one of the newly emerged respiratory tract viral infection. Pandemic COVID-19 has caused significant impact on clinical and economic consequences all over the globe. As the process of developing a new drug or a vaccine takes from months to years, it is a pressing need to look for an already existing drug that has the potentiality to work in a prophylactic manner in ambulatory peoples who are at high risk of developing SARS-COV-2. Prevention of the disease is a better option than treating it. World Health Organization WHO recommends prevention strategies like distancing, home isolation, people education, and wearing gloves and mask for suspected COVID-19 patients. COVID-19 has devastating impacts on clinical and economy. Healthcare team and individuals that help in delivery of care to patients all are at high risk for infection. It has rapid human-human horizontal transmission. An idea of using Azithromycin (an approved inveterate drug) in a specific dose and special designed regimen as a prophylaxis for SARS-COV-2 rather than treatment has emerged to light. In this review we will demonstrate the reasons behind the selection of Azithromycin rather than other antibiotics, its advantage that has made it a reasonable candidate to be given as a prophylactic agent against the virulent COVID-19, and its potential mechanism as anti-inflammatory and immune-modulatory agent in reducing the probability of COVID-19 in infecting ambulatory people who are at serious risk.

Keywords: Ambulatory high risk people; Azithromycin once weekly; COVID-19; Clinical and economic impacts.

INTRODUCTION

The prevalence of the pandemic COVID-19 is increasing day by day as the number of cases worldwide has exceeded a million as of 5th of April 2020, and it is affecting a total number of 205 countries and territories (World o meter. 2020). In fact with the absence of an approved vaccine or antiviral medication that can stop the spread of COVID-19 despite the several trials of repurposing antiviral drugs, has pushed a need of finding an already existing drug for both treatment and prophylaxis (Dong, L. *et al.*, 2020). The key to reduce the incidence of infections and deaths caused by COVID-19, is by detecting the category of people that are actually at high risk who aren't under clinical supervision, and who have several concomitant comorbidities such as diabetes, asthma, kidney diseases, serious heart conditions, liver disease, sever obesity(BMI>40) and elderly people (__2020. People Who Are at Higher Risk for Severe Illness | Coronavirus | COVID-19). Therefore, administering an immune-modulator and anti-inflammatory prophylactic drug to these people who are in the ambulatory setting is preferred, economically feasible and cost effective especially if using a drug with affordable prices and high potentialities as Azithromycin. An article has demonstrated several scenarios which can be used to decrease the burden on health system especially in less developed countries with high population density using a specialized modelling technique (McKibbin, W. J., & Roshen, F. 2020).

Surprisingly, Azithromycin is not a regular antimicrobial agent, its mechanism as immune-modulator and anti-inflammatory on the long term has been studied widely in the literature and was conducted under numerous clinical trials, also as any immune-modulator drug can impose its action either via up-regulating the immune system or down-regulate it, most of the studies have found that antimicrobials as

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Azithromycin tend to down-regulate the immune-response thus help in the cytokine storm that is a fatal outcome of COVID-19 that can induce severe respiratory distress syndrome which will lead to hospitalization and further fatal outcomes due to hospital stay (Ruh, C. *et al.,* 2017; & Conti, P. *et al.,* 2020). Generally, macrolide antibiotics have received a variety of clinical indications rather than just restricting its role as an antimicrobial agent, as the interest in this has begun since 1980s, many clinical trials has experimented its immune-modulatory and anti-inflammatory activity in chronic airway related diseases such as COPD, Asthma, Cystic fibrosis and that has shown a great success, so it is relevance to suggest the using of Azithromycin in a prophylactic dose against SARS-COV-2 as it is an airborne virus, that mainly affects the respiratory system and causes pneumonia like symptoms (Gray, G. C. *et al.,* 1998; & Arias, P., & Armesto, J. 2011).

Azithromycin broad spectrum antibacterial agent is commonly used in respiratory tract infection treatment and prophylaxis. Azithromycin reaches and highly accumulate in number of cells like; polymorphonuclear leukocytes (PMN), peripheral blood mononuclear cells (PBMC) and fibroblasts. Fibroblasts are distributed all over the tissues. Accumulation of azithromycin in White Blood Cells, direct effect on neutrophils reduces inflammatory cell migration and modification of activation and differentiation of monocytes, all may explain the immunomodulatory effect. It has been demonstrated that azithromycin, in the air way, decreases the influx of monocytes, stimulates macrophages activation and decrease pro-inflammatory cytokines. Azithromycin 15 membered lactone ring containing nitrogen makes it more bioavailable, longer half-life and of higher stability over the 14-membered ring Erythromycin, Clarithromycin and Roxithromycin. The common adverse effect of azithromycin are generally gastrointestinal disturbances (Zarogoulidis, P. *et al.,* 2012; Tamaoki, J. 2004; & Schögler, A. *et al.,* 2015).

We need to explain the points that has made Azithromycin as a potential candidate against SARS-COV-2, first the ability of Azithromycin to down-regulate the release of pro-inflammatory mediators from lung epithelial cells such as Granulocyte macrophage colony-stimulating factor (GM-CSF) that is responsible for neutrophils infiltration, IL-8 which exacerbate tissue remodeling, IL-6 which increase neutrophils attraction and TNF-alpha, so the reduction of these mediators helps in attenuation of airway inflammation (Cramer, C. L. *et al.,* 2013; & Murphy, D. M. *et al.,* 2008). Second, Azithromycin possess an anti-viral activity that is not present in other macrolides as Erythromycin and Telithromycin, as it increases the expression of Interferon (INF) gamma and beta which are responsible for their antiviral activity (Gielen, V. *et al.,* 2020). Third, it is important to highlight the long half-life that Azithromycin possess that allows for once weekly administration in addition to its good oral bioavailability, high accumulation in cells especially in phagocytes as 200 folds greater than serum levels, and it lacks the inhibitions of CYP3A4 enzyme unlike Clarithromycin so less drug-drug and drug-food interactions (McMullan, B. J., & Mostaghim, M. 2015). We propose the use of Azithromycin as a prophylactic agent over other macrolides due to the above mentioned reasons, in addition to the decreased overall mortality when using it over other macrolides (Fleet, J. L. *et al.,* 2013).

DISCUSSION

Azithromycin, a semi synthetic second generation macrolide (azalide) antibiotic with 15-membered lactone ring which is resistant to beta-lactamase produced by bacteria, it exhibits its mechanism of action by inhibiting bacterial protein synthesis and binding to the 50s subunit of the bacterial ribosome therefore inhibits its assembly. Moving to its remarkable pharmacokinetic properties that made it superior to other antibiotics including its acid stability allowing for oral administration, large volume of distribution estimated from 23-31L/Kg and low serum levels which allows it to accumulate in tissues and cells specially macrophages, and its long half-life which makes it legitimate for once weekly administration (Parnham, M. J. *et al.,* 2014; & Banjanac, M. *et al.,* 2012). In a clinical trial that was conducted to observe the pharmacokinetic properties for Azithromycin, none of the participants quit from the study and it turned out that azithromycin is well tolerated with few side-effects as mild gastrointestinal (gas/flatulence) and headache (Ballow, C. H. *et al.,* 1998), another comparative clinical trials have shown the better tolerability of Azithromycin over Erythromycin in the term of side-effects, also to be superior to that of Cefaclor, Doxycycline or Amoxicillin (Brogden, R. N., & Peters, D. H. 1994). Regarding the black box warning against Azithromycin in prolonging the QT interval, it is important to note that arrhythmias tend to happen with coexisting risk factors, also it is suggested that QT prolongation isn't a specific predictor of cardiac adverse events and patients who are on medications that prolongs the QT interval who have developed torsade des pointes (TdP), have already subclinical QT prolongation. It was found that Azithromycin is the least macrolide to cause cardiac arrhythmias and when decreasing potassium levels it was found that Azithromycin didn't cause QT prolongation unlike Erythromycin and Clarithromycin. Over an 8 years study ended in 2011 it was estimated that 45% of the cases who had QT prolongation while taking macrolides used another drug that is probable to cause QT prolongation (Albert, R. K. *et al.,* 2014; Ohtani, H. *et al.,* 2000; & Elisabetta, P. E.R. 2013).

It is noteworthy to mention the antiviral properties of Azithromycin, as a clinical trial with p

value=0.0002 has shown the effect of Azithromycin against Rhinovirus as the administration of Azithromycin has decreased the virus load by 9 folds in bronchial cells and decreased the replication of Rhinovirus in nasal cystic fibrosis cells (more susceptible to Rhinovirus infection) by 4.8 folds compared to untreated cells and another mechanism for Azithromycin against the viral infection is by increasing the percentage of both Interferon beta type 1,3 and interferon gamma type 1 (antiviral proteins) which allows the epithelial to protect themselves against respiratory viruses, decreasing the cytokine production as TNF alpha (Schögler, A. *et al.,* 2015; & Menzel, M. *et al.,* 2016).

As a result that leads us to thinking of administering Azithromycin as a prophylactic agent in frequency of once weekly rather than daily dose, a randomized double blinded comparative study has taken place in 5 different Australian centers with 379 participant that have been recruited to compare the outcome of administering Azithromycin once weekly in 1200mg or daily dose of 250mg and participants were assessed every 1, 3 and6 months to measure lung functions outcomes the results were as following, there was no difference in the therapeutic outcome in both groups, no difference in the FEV1% for both groups, number of admission and the time for first exacerbation were less in the weekly group, change in the nutritional status and BMI were the same for both groups, there was improvement in physical domain regarding the weekly group, the decrease in CRP was higher in the daily group, improvement in the quality of life was the same for both groups, no difference between the reduction in having microorganisms between two groups, and the adverse events were higher in the weekly group manifested as nausea, vomiting and diarrhea due to the higher dose. Hence as the differences between the two groups are almost equal, it is preferred to use a once weekly regimen due to economic reasons and as Azithromycin has a long half-life in the sputum (delivered via PMNNs) estimated by 12 days and 10 days in neutrophils (McCormack, J. *et al.,* 2007; & Wilms, E. B. *et al.,* 2006).

A close scenario to high risk adult individuals under stress of pandemic COVID-19 is described in a double blinded, placebo controlled randomized clinical trial on adult young population who are at higher risk for respiratory infection due to high stress like military forces suggested that 1 gram per week azithromycin was of benefit in decreasing the respiratory infection frequency. The prophylactic therapy was well tolerated and compared to placebo the adverse effects were not more than the adverse effects in the placebo group. This can be extrapolated to ambulatory individuals at high stress and high risk for coronavirus respiratory infection. Another suggested role of azithromycin in acute respiratory distress syndrome ARDS in COVID-19 patients is reduction of mortality in this patient group. Alveolar injury leading to ARDS is reported in COVID-19 and requirement of intubation and mechanical ventilation. A prospective cohort study was conducted on moderate to severe ARDS patients of any etiology in intensive care unit ICU of a Japanese hospital. Patients were given adjunctive intravenous azithromycin and this resulted in rapid discontinuation of ventilator and enhancement of 90-day mortality (Kawamura, K. *et al.,* 2018; & Gray, G. C. *et al.,* 2001).

It is reported in both in-vivo and in-vitro plentiful evidence for macrolide anti-inflammatory and immunomodulatory effect. Also, it is reported that macrolides improves lung function and reduce air way hyper responses. There are series of studies that confirms the immunomodulatory effect of macrolides despite that, the solid mechanism of action is not completely understood. Moreover the economic situations related to the pandemic SARS-COV-2, burdens on health care systems and the cost of treating the disease versus prophylaxis should be weighed to decide the best approach that can help in the current situations. The economists have divided three states of the disease according to Markov model which are susceptible, actively infected, dead or recovered, and here it is crucial to prevent the transformation from susceptible to infected (Atkeson, A. 2020). An economic study was conducted based on clinical data of randomized control trial for administering Azithromycin as prophylaxis in HIV patients, it was found that macrolide prophylaxis is cost effective in increasing the amount of CD4 (T-helper) and restore immune functions (Taneja, N. K., & Tyagi, J. S. 2007).

CONCLUSION

In summary, the necessity to immunize high risk susceptible people to SARS-COV-2 requires the search of a suitable medication to work as a prophylactic agent, the suggestion of Azithromycin as once weekly dose is preferable in increasing the adherence and potentially minimize the propagation of SARS-COV-2. Azithromycin is used in prophylactic treatment for many respiratory disease to prevent complications like COPD and cystic fibrosis. So it may represent a good choice in COVID-19 prophylaxis in working individuals. The reason behind that is the immunity augmentation by azithromycin. Since the economic situations worldwide are on edge and the pressure on health care systems' resources is increasing day by day it is important to conduct clinical trials using a drug that has both immune-modulator and anti-inflammatory effects that could help in controlling the pandemic COVID-19. Further investigation of the immune modifying properties of azithromycin is required.

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