Original Article

Effect Of Rosuvastatin In The Protection Against Azithromycin Induced Cardiotoxicity In Covid-19 Patients: A One-Year Prospective Study

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Abstract

Background Azithromycin is a widely used broad-spectrum antibiotic that was recently used in the treatment protocol of COVID-19 but its cardiac side effects became a more prominent concern. Rosuvastatin is a synthetic statin that showed anti-inflammatory, antioxidant and autonomic nervous system regulatory effects in addition, there is increasing evidence supporting that it could play a beneficial role in patients with COVID-19. **Objective** To evaluate the protective effect of Rousvastatin against Azithromycin-induced cardiotoxicity in Covid-19 patients. **Patients and Methods** This is a prospective study that was conducted on adult patients diagnosed with COVID-19 who were admitted to isolation centres in Minia Governorate, Egypt for the period of one year (June 2021 to May 2022). The study included a total of 80 COVID-19 patients who were divided into 2 groups (n=40 each), group (I) "Azithromycin group" that included patients received Azithromycin (500 mg/day for 5 days) orally and group (II) "Azithromycin + Rosuvastatin group" that included patients received Azithromycin by oral route as group (I) plus Rosuvastatin 20 mg/day orally. All included cases were subjected to full history taking, clinical examination and laboratory investigations and after treatment, the outcome measures were reported and compared. **Results** No significant differences were observed between groups regarding demographic and baseline characteristics. Also, the two groups were comparable with no significant differences in pulse rate, blood sugar, CBC, electrolyte elements, liver enzymes, and kidney function (a slight reduction was noticed in group II). While, Ferritin level was significantly lower in group (II) compared to group (I), (830 ± 72.5 vs. 865 ± 69.5, p=0.03). No significant differences were observed among groups as regards Troponin level (p=0.56) "Only one case was positive in group (I)". Both groups were almost comparable without significant differences in both stages of infection and mortality (p=0.38 and 1.0, respectively). **Conclusion** Rosuvastatin did not have a significant role in the protection of Azithromycin-induced cardiotoxicity, it slightly ameliorates the biochemical and stress markers alterations of Azithromycin. Further larger studies are warranted for investigating this issue.

Keywords: Rosuvastatin, Azithromycin Induced Cardiotoxicity, Covid-19.

INTRODUCTION

Coronavirus disease 2019 (COVID-19) is the highly contagious viral illness caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), has had a catastrophic effect on the world's demographics resulting in more than 3.8 million deaths worldwide and it emerging as the most consequential global health crisis since the era of the influenza pandemic of 1918 ***(Wang et al., 2020)***. COVID-19 involving many organs including the cardiovascular system and the cardiovascular involvements, such as myocardial injury, myocarditis, acute myocardial infarction, dysrhythmias, and heart failure, have been reported in the COVID-19 patients ***(Afshar et al., 2021)***. Also, others added that cardiovascular involvement may occur through various mechanisms and include respiratory failure, hypoxemia due to progressive cardiac load, direct myocarditis or cardiomyopathy, indirect effects of the systemic inflammatory response, and drug interaction ***(Wiersinga et al., 2020)***.

Azithromycin (AZ) is a widely used broad spectrum macrolide antibiotic and the sole member of the azalide subclass, it is derived from erythromycin and it has an aza-methyl substitution (insertion of a nitrogen atom) in the macrolide ring ***(NCBI, 2021)***. Azithromycin has anti-inflammatory and antiviral properties and that has been hypothesized to have activity against SARS-CoV-2 ***(Oliver and Hinks, 2021)***. The anti-inflammatory effects of azithromycin may reduce cytokine levels that may help prevent progression to tissue damage and severe COVID-19, especially if administered early in the disease course

(Oldenburg et al., 2021). Azithromycin cardiac side effects became a more prominent concern, some studies have identified QT interval prolongation and torsade de pointes as possible side effects from azithromycin treatment ***(Kim and Welch, 2014)***. Rosuvastatin is a fully synthetic HMG-CoA reductase inhibitor, it is a lipid-lowering drug that belongs to the statin class of medications which are used to lower the risk of cardiovascular disease and manage elevated lipid levels by inhibiting the endogenous production of cholesterol in the liver ***(Luvai et al., 2019)***. Rosuvastatin showed a variable range of activities such as anti-inflammatory, antioxidant, ion channel stabilizing, and autonomic nervous system regulatory effects ***(Hasan and Kow, 2020)***. Increasing evidence supports the use of statins in patients with COVID-19 ***(Castiglione et al., 2020)***. Therefore, the current study attempts to evaluate the protective effect of rousvastatin against Azithromycin Induced Cardiotoxicity In Covid-19 patients.

Patients and methods

This is a clinical prospective study that was conducted on adult patients of both sexes diagnosed with COVID-19 who were admitted to isolation centers in Minia Governorate, Egypt during the period of one year (June 2021 to May 2022). The study included a total of 80 COVID-19 patients who were divided into 2 groups (n=40 each) as follows: Group (I) Azithromycin group that included patients received Azithromycin (500 mg/day for 5 days) orally ***(Gautret et al.,2020)*** and group (II) Azithromycin + Rosuvastatin group that included patients received Azithromycin by oral route as group (I) plus Rosuvastatin 20 mg/day orally ***(Di Napoli et al., 2005)***. Adult patients (18 years up to 60 years) of both sexes with a positive covid-19 test result confirmed by RT-PCR, patients received azithromycin (500 mg/day for 5 days) for treatment of COVID-19 infection. Exclusion criteria were; proarrhythmic electrolyte abnormalities, a documented history of Brady arrhythmias, QT prolongation, torsade de pointes and use of antiarrhythmic drugs.

All included cases were subjected to full history taking, clinical examination and laboratory investigations were taken on admission and after treatment including complete blood picture, random blood sugar, electrolyte elements, liver and kidney functions, Ferritin, D-dimer and C-reactive protein and Troponin. The outcome measures were reported after the end of treatment.

Statistical methods

Data analyses were performed using SPSS software (version 20, IBM, NY, USA) ***(IBM Corp., 2011)***. Number and percentage (N, %) were used to describe categorical variables while numerical variables were described by the mean and standard deviation (Mean ± SD) and range. As regards the comparison between groups, Chi-square or Fischer's exact tests were used for categorical data and T-test or Mann-Whitney U test was used for continuous data however, Paired T-test was used for the comparison between before and after treatment in each group for continuous data. $P \leq .05$ was considered statistically significant.

Results

No significant differences were noticed between groups regarding age, sex, smoking, diabetes, hypertension and also coronary artery disease (Table, 1). Regarding the clinical and laboratory data, the two groups were comparable with no significant differences in pulse rate, blood sugar and electrolyte elements (a slight reduction was noticed in group II). Also, no significant differences were observed between groups in complete blood picture and liver enzymes (ALT and AST), and kidney function (urea and createnine). While Ferritin mean was significantly lower in group (II) that received Azithromycin + Rosuvastatin compared to group (I) that received Azithromycin only (830 ± 72.5 vs. 865 ± 69.5, p=0.03) however, insignificant reduction was observed in this group in CRP and D-dimer values (Table, 2). No significant differences were observed between groups as regards Troponin level (p=0.56) "Only one case was positive in group (I)", (Figure 1). Regarding the outcome, both groups were almost comparable without significant differences in both stages of infection and mortality (p=0.38 and 1.0, respectively), (Table, 3).

Table (1) Comparison among groups regarding demographic and baseline data.

Variable	Groups		P. value (Sig.)
	Group (I) AZ (n = 40)	Group (II) AZ+RS (n = 40)	
Age (years)	50.1 ± 4.9	49.1 ± 4.3	0.33^{NS}
Sex (M/F)	26/14	21/19	0.26^{NS}
Smoking (+ve)	17	11	0.16^{NS}
Diabetes	12	17	0.15^{NS}
Hypertension	11	17	0.16^{NS}
Coronary artery disease	0	0	1.0^{NS}

T-test and Chi-square tests were used $p \geq 0.05$= NS (Non significant).

Table (2) Comparison among groups regarding clinical and laboratory data**.**

Variable	Groups		P. value (Sig.)
	Group (I) AZ (n = 40)	Group (II) AZ+RS (n = 40)	
Pulse rate (BPM)	75.3 ± 4.9	74.9 ± 4.8	0.71^{NS}
RBS (mg/dl)	188.4 ± 90.9	164.1 ± 64.1	0.17^{NS}
K (mmol/L)	4.18 ± 0.47	4.17 ± 0.56	0.93^{NS}
Na (mmol/L)	137.0 ± 8.74	135.5 ± 7.54	0.41^{NS}
Ca (mg/dl)	7.91 ± 0.40	7.82 ± 0.38	0.31^{NS}
Hb (g/dl)	11.7 ± 1.58	12.0 ± 1.26	0.35^{NS}
TLC (10^9/L)	13.42 ± 5.59	11.50 ± 3.35	0.07^{NS}
Lymphocytes (%)	10.51 ± 2.82	10.20 ± 2.25	0.59^{NS}
Platelets (/mcL)	230 ± 70.1	261 ± 84.5	0.09^{NS}
T. Bilerubin (mg/dl)	1.11 ± 0.11	1.09 ± 0.11	0.42^{NS}
ALT (U/L)	25.2 ± 5.3	25.3 ± 5.5	0.93^{NS}
AST (U/L)	30.0 ± 6.2	29.3 ± 6.5	0.62^{NS}
Urea (mg/dl)	28.8 ± 3.4	28.3 ± 3.2	0.50^{NS}
Createnine (mg/dl)	1.01 ± 0.18	0.96 ± 0.22	0.26^{NS}
Ferritin (NG/ML)	865 ± 69.5	830 ± 72.5	**0.03***
CRP (mg/L)	108.1 ± 7.9	105.8 ± 7.5	0.19^{NS}
D-Dimer	2.46 ± 1.92	2.28 ± 1.70	0.66^{NS}

T-test was used $p \geq 0.05$= NS (Non significant) * $p < 0.05$ (significant)

Table (3) Comparison among groups regarding outcome**.**

Variable		Groups		P. value (Sig.)
		Group (I) AZ (n = 40)	Group (II) AZ+RS (n = 40)	
Stage of infection	**Mild**	4 (10.0%)	1 (2.5%)	0.38^{NS}
	Moderate	28 (70.0%)	30 (75.0%)	
	Severe	8 (20.0%)	9 (22.5%)	
Mortality	**Cured**	39 (97.5%)	39 (97.5%)	1.0 ^{NS}
	Died	1 (2.5%)	1 (2.5%)	

Chi-square test was used p≥ 0.05= NS (Non significant)

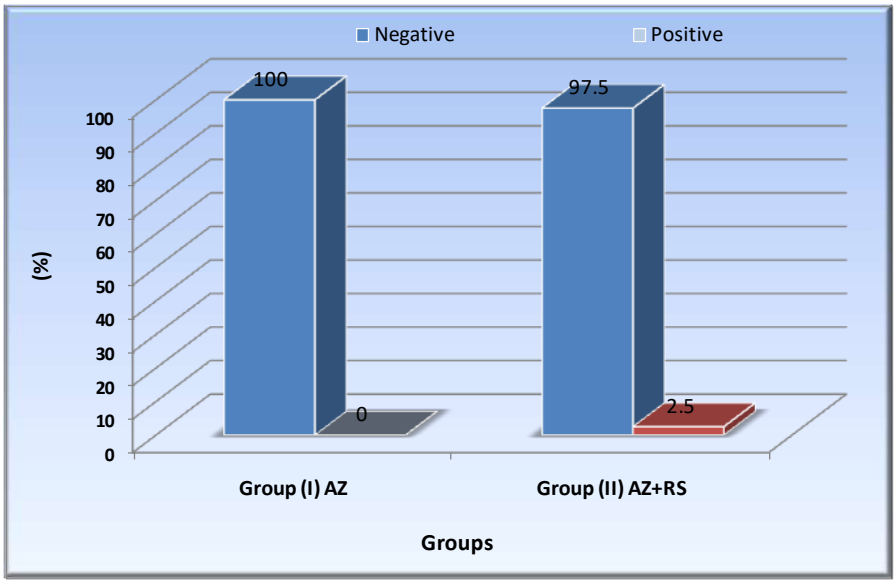

Figure (1) Troponin level between groups

Discussion

Coronavirus disease-2019 pandemic has created a great challenge in multiple realms throughout the world but is particularly significant for health systems, it is one of the threatening pandemics in history involving many organs, including the cardiovascular system ***(Afshar et al., 2021)***. Azithromycin is a widely used broad-spectrum antibiotic that was recently used in the treatment protocol of COVID-19 but its cardiac side effects became a more prominent concern. Increasing evidence supports the use of statins in patients with COVID-19 ***(Bifulco and Gazzerro, 2020 & Castiglione et al., 2020)***. Accordingly, the National Institutes of Health COVID-19 Treatment Guidelines recommend that patients with COVID-19 who are prescribed statins for the treatment or prevention of cardiovascular disease should continue statin therapy ***(Wiersinga et al., 2020)***. This study attempts to evaluate the protective effect of Rousvastatin against Azithromycin Induced Cardiotoxicity In Covid-19 patients. To the best of our knowledge, very little data were available about the effect of Rousvastatin on Azithromycin Induced Cardiotoxicity in Covid-19 patients.

The current results showed that Rousvastatin decreased significantly Ferritin level while, it had a slight "insignificantly" effect on Troponin level and did not affect the outcome in terms of stage of infection and mortality rate after treatment. Similar to our findings, A recent meta-analyses included 9 studies with a total of 3,449 patients on the association between statin use

and COVID-19 found that statin use did not improve the severity outcome (OR=1.64; 95% CI 0.51–5.23) or the mortality rate from COVID-19 (OR =0.78; 95% CI 0.50–1.21) ***(Hariyanto and Karniawan, 2020)***.

A recent study by ***Mansour et al., (2021)*** studied the protective effect of Rosuvastatin on Azithromycin induced cardiotoxicity in a rat model. They found that Rosuvastatin significantly ameliorates ECG changes, biochemical, and oxidative stress markers alterations of Azithromycin. Also, the histological evaluation from Azithromycin group showed marked areas of degeneration, myofibers disorganization, inflammatory infiltrate, and hemorrhage. In addition, immunohistochemical evaluation showed significant increase in both Caspase 3 and Tumor necrosis factor (TNF) immune stain. Also, Rosuvastatin treated group showed restoration of the cardiac muscle fibers in H&E and Immunohistochemical results.

The rat models showed that Azithromycin produces oxidative stress, inflammation, and apoptosis of the myocardial tissue and this causes ECG changes, myocardial infarction, and death ***(Atli et al., 2015)***. also, Rousvastatin prevents of cardiovascular diseases and has strong anti-oxidative and anti-inflammatory properties ***(Kanno et al., 2018)***. Furthermore, it has been reported that Rousvastatin had mild anticoagulant effect with a potential to decrease the risk of thrombus formation in the veins, arteries, and microvessels, which individually or jointly are considered the primary causes of the frequently fatal respiratory and cardiovascular failures in COVID-19 patients ***(Undas et al., 2014)***.

It has been reported that lactate dehydrogenase (LDH) is one of the cardiac biomarkers, it is released from the damaged myocardium into the blood caused by Azithromycin via inducing ischemia ***(Atli et al., 2015)***. ***El-Shitany et al., (2016)*** and ***Mansour et al., (2021)*** found a significant decrease in LDH level in the group of patients received Azithromycin + Rousvastatin compared to the group received Azithromycin only. In addition, similar results revealed Rosuvastatin ability to increase antioxidant activities and reduce lipid peroxidation, which prevents cardiac tissue damage ***(Yu et al., 2018)***. In a recent study by ***Gaitan-Duarte et al., (2022)***, the found that the combined use of Rousvastatin+Colchicine reduces the risk of 28-day mortality and the need for invasive mechanical ventilation in hospitalized patients with pulmonary compromise from COVID-19. This study has some limitations. Of these, the relatively small sample size.

Conclusions

This study concluded that Rosuvastatin did not have a significant role in the protection of Azithromycin-induced cardiotoxicity, it slightly ameliorates the biochemical and stress markers alterations of Azithromycin. Further larger studies are warranted for investigating this issue.

Ethical considerations The study protocol and all procedures were approved by the ethical committee of the Faculty of Medicine, Minia University. Verbal consent was taken from the patient him/herself or his/her relatives before getting involved in the study. The steps, the aims, the potential benefits and hazards, all were discussed with the patient or his relatives. The study project was registered on clinical trail under the registration number of NCT03202407.

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Conflict of interest None.

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