Promising Effects of Atorvastatin on Outcomes of Patients with Severe COVID-19, A Retrospective Cohort Study

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Abstract

Purpose: Considering the anti-inflammatory effect of atorvastatin and the role of medical comorbidities such as hypertension and coronary artery disease on prognosis of the COVID-19 patients, we aimed to assess the effect of atorvastatin add-on therapy on mortality due to COVID-19. Methods: We conducted a retrospective cohort study, including patients who were hospitalized with confirmed diagnosis of severe COVID-19. Baseline characteristics and related clinical data of patients were recorded. Clinical outcomes consist of in hospital mortality, need for invasive mechanical ventilation and hospital length of stay. COX regression analysis models were used to assess the association of independent factors to outcomes. Results: Atorvastatin was administered for 421 out of 991 patients. The mean age was 61.640±17.003 years. Older age, higher prevalence of hypertension and coronary artery disease reported in patients who received atorvastatin. These patients had shorter hospital length of stay (P=0.001). Based on COX proportional hazard model, in hospital use of atorvastatin was associated to decrease in mortality (HR=0.679, P=0.005) and lower need for invasive mechanical ventilation (HR=0.602, P=0.014). Conclusions: Atorvastatin add-on therapy in patient with severe COVID-19 was associated with lower in hospital mortality and reduced the risk of need for invasive mechanical ventilation which support to continue the prescription of the medication.

Title: Promising Effects of Atorvastatin on Outcomes of Patients with Severe COVID-19, A Retrospective Cohort Study

Running Title: Atorvastatin for Severe COVID-19 Patients

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Methods: We conducted a retrospective cohort study, including patients who were hospitalized with confirmed diagnosis of severe COVID-19. Baseline characteristics and related clinical data of patients were recorded. Clinical outcomes consist of in hospital mortality, need for invasive mechanical ventilation and hospital length of stay. COX regression analysis models were used to assess the association of independent factors to outcomes.

Results: Atorvastatin was administered for 421 out of 991 patients. The mean age was 61.640±17.003 years. Older age, higher prevalence of hypertension and coronary artery disease reported in patients who received atorvastatin. These patients had shorter hospital length of stay (P=0.001). Based on COX proportional hazard model, in hospital use of atorvastatin was associated to decrease in mortality (HR=0.679, P=0.005) and lower need for invasive mechanical ventilation (HR=0.602, P=0.014).

Conclusions: Atorvastatin add-on therapy in patient with severe COVID-19 was associated with lower in hospital mortality and reduced the risk of need for invasive mechanical ventilation which support to continue the prescription of the medication.

Keywords

Atorvastatin, COVID-19, Mortality, Mechanical Ventilation, SARS-Cov-2, Prognosis.

What is already known about this topic?

Previous studies showed that, patients who used statins may have decreased rate of mortality due to COVID-19. Results about the effect of statins on other outcomes including need for mechanical ventilation and hospital length of stay were inconsistent.

What does this article add?

In our large-scale retrospective cohort study, we examined the effect of atorvastatin, as a lipophilic statin, on outcomes of patients with severe to critical form of COVID-19. In addition to decrease in mortality, we observed lower risk of need of invasive mechanical ventilation associated with atorvastatin administration and also shorter hospital length of stay in patients who received atorvastatin.

Introduction

The COVID-19 pandemic is still growing around the world and more than 90 million cases around the world with over 2 million deaths, have been identified[1]. Immune dysregulation and cytokine release associated with SARS-Cov-2 infection are considered as an important cause of mortality in this population and it could induce hyperinflammatory state, vasculitis, and cardiovascular events[2-4].

In previous studies, the anti-inflammatory role of statins in the reduction of cytokines, in some conditions other than infectious diseases, has been confirmed[5,6]. Also, studies have been shown that patients who have received atorvastatin, had a better prognosis in viral and bacterial pneumonia [7,8]. In some studies, it is hypothesized that decreasing the synthesis of cholesterol by statins and depletion of cell membrane cholesterol content, could disturb the entry of the virus into the cells[9]. SARS-COV-2 also generates multi pro-inflammatory cytokines by activating Toll-like receptors (TLRs) on T lymphocytes [10]. This TLR-MYD88-NFκB pathway promotes cytokine release. Statins also block this pathway; inhibit T cell activation and proliferation, so they have immunomodulatory effects[11].By considering the effect of underlying conditions

such as hypertension, diabetes, cardiovascular diseases, and hyperinflammation associated with COVID-19, statins could affect the prognosis of the patients who have been hospitalized due to COVID-19[12-14]. Therefore, we aimed to assess the effect of atorvastatin use, in the outcomes of the patients with severe to critical COVID-19.

Patients and Methods

Study design and patient selection

In this retrospective cohort study, all adult patients (age [?]18 years old)who were hospitalized due to severe to critical COVID-19, from March 2020 to July 2020, in the Imam Hossein medical center affiliated to Shahid Beheshti University of Medical Sciences, Tehran, Iran, were evaluated[15]. Patients without positive reverse transcriptase-polymerase chain reaction (rt-PCR) results were excluded and data from patients with a diagnosis of COVID-19 based on rt-PCR were included. The study was conducted based on the declaration of Helsinki and the institutional review board committee approved the study.

Data Collection

For each patient, demographic and laboratory data including past medical and drug history, outcomes, baseline complete blood count and inflammatory markers including C-reactive protein (CRP), erythrocyte sedimentation rate (ESR), ferritin and lactate dehydrogenase (LDH), and liver function tests were recorded. Also, vital signs on admission and selected pharmacotherapy for management of COVID-19 besides, the administration of atorvastatin and other cardiovascular medications including Angiotensin-Converting Enzyme Inhibitors (ACEIs), Angiotensin Receptor Blockers (ARBs), and beta-blockers, were documented. Atorvastatin use was defined as the administration of the medication on 1st day of admission.

Outcomes

In hospital mortality was defined as the primary outcome for the study. The need for invasive mechanical ventilation including ventilation via endotracheal or tracheostomy tubes and length of hospital stay are considered as the secondary outcomes.

Statistical Analysis

Statistical analysis was performed by STATA software version 14 (StataCorp, Texan, USA). All included patients stratified as they received atorvastatin or not during hospitalization. The parametric or non-parametric distribution of the quantitative data was analyzed using the Kolmogorov-Smirnov test. Data description of parametric quantitative variables reported as means ± standard deviation and non-normally distributed data reported as median (interquartile range=IQR). Qualitative variables reported as frequency (percentage). Continues variables compared using independent t-test or Mann-Whitney U test for normally and non-normally distributed data in bivariate analysis, respectively. Categorical variables analyzed using Chi-square or Fisher's exact test (in the situation in which more than 25% of the categories had frequencies below five). A P-value of less than 0.05 is considered significant.

The crude association between atorvastatin administration and occurrence of outcomes including the need for invasive mechanical ventilation and in-hospital mortality was performed using the univariate COX proportional hazards regression model. For the selection of the best predictors, variables with a P-value of less than 0.2are considered to be analyzed in multivariable COX regression analysis using a stepwise selection approach. Confounders were selected based on the recommendation of previously published epidemiological studies that reported the probable prognostic value of underlying conditions and also medications that were being used [16]. This included age, gender, body mass index (BMI) in demographics, hypertension, diabetes mellitus, coronary artery disease, chronic respiratory conditions, malignancies, immunocompromised, chronic kidney disease in comorbidities. Also, we adjusted the model for using beta-blockers and ACEIs or ARBs [17,18]. the model was adjusted for the medications which were used to treat COVID-19. Patients with negative time to event removed from the analysis. A 95% confident interval of hazard ratio was reported. The proportional hazard assumption for COX analysis was tested using scaled Schoenfeld residuals and the P-value

of 0.05 or more considered as no serious violations of the proportional hazards assumption.

Results

Nine hundred and ninety-one patients were included in the study. The mean age was 61.640±17.003 and 544 (54.89%) and 447 (45.11%) of the patients were male and female, respectively. Four hundred and twenty-one patients (42.48%) received atorvastatin whereas five hundred and seventy (57.52%) did not. Of those who received atorvastatin, 169 (40.14%) were taking the medication prior to hospital admission and atorvastatin was initiated for the rest of the patients on the first day of hospital admission.

Regarding demographics, patients who received atorvastatin were older (P<0.001), but no significant differences were observed in gender distribution and BMI between the two groups. Considering comorbidities, except for diabetes and CKD which were more prevalent in patients who did not receive atorvastatin (P<0.001), others including hypertension(P<0.001), coronary artery disease (P<0.001), and malignancy (P=0.012) were significantly higher in the group of patients who received atorvastatin. From laboratory data collected at baseline, C reactive protein was significantly higher in the group of patients who received atorvastatin (P=0.040). Patients who did not receive atorvastatin had a higher baseline erythrocyte sedimentation rate, serum creatinine, and urea levels compared to those who did not. Except for hydroxychloroquine (P=0.005) and corticosteroids (P=0.007), there were no significant differences between the two groups in medications used to treat COVID-19. Baseline demographics, clinical and laboratory data are presented in **Table 1** .

Based on the crude analysis, no significant differences observed in mortality rate between two groups (26.84% vs 25.09%, P=0.221). Patients who received atorvastatin had a significantly lower hospital length of stay (P<0.001). Also, this group had a lower but non-significant need for mechanical ventilation (P=0.563). Results for primary and secondary outcomes are represented in **Table 2** .

In unadjusted COX proportional analysis, atorvastatin was associated with a decreased in-hospital mortality (0.820[0.639-1.054]) and need for mechanical ventilation (0.709[0.486-1.034]). Stepwise COX regression proportional hazard ration analysis revealed that atorvastatin is associated with reduced risk of in-hospital mortality (0.679[0.517-0.890]) and the need for mechanical ventilation (0.602[0.401-0.903]), independently. From demographics, age, obesity, coronary heart disease, and malignancy included in the multivariable analysis to evaluate the need for invasive mechanical ventilation. Also, utilization of beta-blockers, ACEIs/ARB, atorvastatin, corticosteroid, hydroxychloroquine, and lopinavir/ritonavir were analyzed. In the stepwise model for the analysis of survival, age, hypertension, coronary heart disease, malignancy, and medication i.e., beta-blockers, ACEIs/ARB, atorvastatin, corticosteroid, hydroxychloroquine, and lopinavir/ritonavir remained in the multivariable model. The Association of factors with mortality and the need for invasive mechanical ventilation in COX proportional analysis is represented in **Table 3.**

Discussion

In our retrospective cohort study, among 991 patients suffering severe to criticalCOVID-19, atorvastatin which were administered for 421 of the patients was associated with a significant decrease in mortality (HR=0.679), the need for mechanical ventilation (HR=0.602), and hospital length of stay. Very little was found in the literature about the role of statins in the management of patients with COVID 19. In line with our study, data from the largest cohort study from China by Zhang et al, demonstrated that in-hospital use of statins improved survival among COVID-19 patients (HR=0.58). In this retrospective study, which included 1219 patients who used a statin, 28-day all-cause mortality risk was 5.2% and 9.4% in the statin and none statin users, respectively[19]. The lower mortality rate in this study compared to our results could be due to including moderate cases in the study by Zhang et al. which were not included in our study. Another study enrolled 71 patients with a pre-existing chronic cardiovascular disease, and in accordance with our findings, the mortality rate of patients who received statins was lower compared to the group of patients without statins (21.4% vs. 34.5%; p<0.05), and in their subgroup analysis, it is reported a significant reduction in mortality in the patients who were taking atorvastatin compared to non-statin users and patients who were taking other statins (P=0.025)[20]. In another retrospective cohort study, which compared intensive-care unit (ICU) admission, invasive mechanical ventilation rate, and death between statin users and non-statin users,

ICU admission was lower in the statin group but other outcomes were not different between the two groups[21]. Another retrospective multicenter cohort study showed a significant association between statin intake in 31 subjects and the absence of symptoms during COVID-19 with an odds ratio of 2.91, nevertheless, there were no effects on serious clinical outcomes[22].

Based on the result from our study which is in accordance with the previously performed studies, reduced need for mechanical ventilation as two important measures for pulmonary function, we could say that atorvastatin administration strongly reduces the disease severity by inhibition of the inflammatory process during the disease course. Also, these effects alongside to reduction in mortality rate which was statistically significant, make the medication an important choice of add-on therapy. Based on the significance of the mechanisms involved in the beneficial effect of the atorvastatin in the course of COVID-19, and the clinically proven efficacy, we could consider it in the treatment of patients who suffer from a severe form of the disease. It is important to note that, we studied the effect of the atorvastatin on the outcome of the patients as add-on therapy and we should not forget about the importance of early antiviral agents administration as potent inhibitors of the viral replication which could reduce the hospital length of stay[23], the role of potent anti-inflammatory agents such as corticosteroids and interleukin pathways inhibitors on mortality and severity in the treatment of the COVID-19 [24-27].

By considering the result of the study, we should be aware of the limitation we are facing in this study. First, this study was performed by a retrospective method which makes further randomized controlled trials emerge. Second, although we adjusted potential confounders to reduce the study results bias, it could be possible that some unmeasured factors such as prehospital used medication, the socioeconomic situation could interfere with the results. Third, we could expect that the result could be affected by the data from other institutions and a multicentric designed prospective study may be needed. Fourth, as we included data of the hospitalized patients with the severe form of the disease, extrapolation of the results to non-hospitalized patients with moderate disease severity may not be possible.

Conclusion

In conclusion, we found that atorvastatin therapy has positive effects on the course of hospitalization in patients with severe COVID-19. Mostly these effects were seen in important outcomes of these patients i.e., mortality rate, duration of hospitalization, and needs for mechanical ventilation due to COVID-19. Prospective randomized controlled trials are to be recommended to confirm the effect of statins on patients with viral infections, especially severe COVID-19.

Authorship:

MHA, Study concept and design, Acquisition of data, Critical revision of the manuscript for important intellectual content, Study supervision; OM, Statistical analysis, Drafting of the manuscript, Technical support, Acquisition of data; HAT, Drafting of the manuscript, Technical support; HA, Drafting of the manuscript, Statistical analysis, Critical revision of the manuscript for important intellectual content; Elham Pourheidar, Drafting of the manuscript, Critical revision of the manuscript for important intellectual content, technical support; Firouze Hatami, Drafting of the manuscript, technical support; Mohammad Mahdi Rabiei, Drafting of the manuscript, technical support; Mohammad Sistanizad, Study concept and design, Acquisition of data, Drafting of the manuscript, Statistical analysis, Administrative, , and material support, Critical revision of the manuscript for important intellectual content, Study supervision.

Authors disclosure

The authors declare no conflict of interest

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Table 1. Patient Demographics and Related Clinical and Laboratory Findings

Characteristics	*Characteristics*	*Total (n=991)*	*Received Atorvastatin (n=421)*	*Not-received Atorvastatin (n=570)*	*P-value*
Age (years)	*Age (years)*	61.640±17.003	65.46±14.94	58.82±17.88	<0.001
Sex	Male (%)	544 (54.89)	225 (53.44)	319 (55.97)	0.431
	Female (%)	447 (45.11)	196 (46.56)	251 (44.03)	
Body Mass Index (kg/m^2)	*Body Mass Index (kg/m^2)*	27.051±4.854	27.34±26.49	26.81±4.74	0.119
Vital Signs	*Systolic Blood Pressure (mmHg)*	117.59±20.71	118.55±19.65	116.95±21.49	0.219
	Diastolic Blood Pressure (mmHg)	74.69±27.19	74.70±11.76	74.71±34.58	0.985
	Pulse Rate (beats/min)	89.55±15.71	89.01±15.83	89.94±15.41	0.538
	Respiratory Rate (breath/min)	20.64±7.92	20.80±10.69	20.51±5.06	0.670

Characteristics	*Characteristics*	*Total (n=991)*	*Received Atorvastatin (n=421)*	*Not-received Atorvastatin (n=570)*	*P-value*
	O_2 Saturation (%)	88.29±7.82	88.35±7.04	88.25±8.38	0.924
Comorbidities	*Hypertension (%)*	407 (41.07)	233 (55.34)	174 (30.53)	<0.001
	Diabetes (%)	303 (30.58)	117 (27.79)	186 (32.81)	<0.001
	Coronary Artery Disease (%)	194 (19.58)	133 (46.08)	61 (10.70)	<0.001
	Chronic Kidney Disease (%)	102 (10.29)	37 (8.79)	65 (11.40)	<0.001
	Malignancy (%)	42 (4.24)	32 (7.60)	10 (1.75)	0.012
	COPD/Asthma [14]	87 (8.78)	38 (9.03)	49 (8.60)	0.813
Baseline Laboratory Data	*WBC (cell/micL)*	6.90 (4.63)	7.20 (4.80)	6.60 (4.40)	0.020
	Lymphocyte (cell/micL)	821.75 (1588.10)	828.00 (1596.00)	821.50 (1587.20)	0.780
	Hemoglobin (g/dL)	12.41±2.08	12.30±2.17	12.28±2.14	0.898
	INR	1.20±0.48	1.22±0.52	1.08±0.20	0.239
	PT	13.09±5.09	13.26±5.30	12.94±4.96	0.415
	PTT	28.25±12.79	27.39±10.87	28.93±14.22	0.126
	Lactate Dehydrogenase	645.00 (403.00)	643.00 (404.00)	659.00 (525.25)	0.282
	Ferritin	621.30 (964.00)	579.10 (812.10)	750.95 (1134.40)	0.508
	C-reactive Protein	54.00 (53.10)	55.30 (53.30)	51.50 (51.65)	0.040
	Erythrocyte Sedimentation Rate	52.74±28.41	48.20±29.01	60.17±26.12	0.021
	Creatine Phosphokinase	130.00 (211.00)	130.00 (206.00)	136.00 (264.00)	0.203
	Serum Creatinine	1.40 (1.20)	1.40 (1.20)	1.45 (1.08)	<0.001
	Serum Urea	50.00 (45.00)	48.20 (41.90)	52.30 (55.88)	<0.001
	Procalcitonin	0.73 (1.85)	0.49 (1.31)	1.16 (2.41)	0.873
	D-dimer	799.20 (2434.00)	709.00 (1257.00)	1712.50 (3756.75	0.365
	Aspartate Aminotrans-ferase	26.00 (27.00)	25.00 (25.40)	29.60 (38.13)	0.470
	Alanine Aminotrans-ferase	37.00 (29.50)	40.00 (26.40)	34.40 (39.78)	0.490

Characteristics	*Characteristics*	*Total (n=991)*	*Received Atorvastatin (n=421)*	*Not-received Atorvastatin (n=570)*	*P-value*
Medication Used to Treat COVID-19	*Hydroxychloroquine*	553 (55.80)	213 (89.67)	340 (59.65)	0.005
	Lopinavir/Ritonavir	557 (56.21)	236 (56.06)	321 (56.32)	0.935
	Corticosteroid	287 (28.96)	141 (33.49)	146 (25.61)	0.007
	Interferon Beta 1a	372 (37.54)	170 (40.38)	202 (35.44)	0.112
	Remdesivir	46 (4.64)	21 (4.99)	25 (4.39)	0.656
	Favipiravir	40 (4.04)	23 (5.46)	17 (2.98)	0.050

Table 2. Primary and Secondary Outcomes

Variable	Variable	*Total (n=991)*	*Received Atorvastatin (n=421)*	*Not-received Atorvastatin (n=570)*	*P-value*
Need for Mechanical Ventilation (%)	Need for Mechanical Ventilation (%)	144 (14.53)	58 (13.78)	86 (15.09)	0.563
Hospital Length of Stay (days) [Range]	Hospital Length of Stay (days) [Range]	6.00 (6.00) [1-80]	6.00 (5.00)	7.00 (6.00)	<0.001
In-hospital Outcome (%)	Death	256 (25.83)	113 (26.84)	143 (25.09)	0.221
	Recovery	735 (74.17)	308 (73.16)	427 (74.91)	

Table 3. Association of Factors with Outcomes in COX Proportional Hazard Regression Model

Variable	Crude HR*, 95% CI	P-value	Adjusted HR*, 95% CI	Adjusted HR*,
In Hospital Mortality	In Hospital Mortality	In Hospital Mortality	In Hospital Mortality	In Hospital Mo
Age (years)	1.034[1.025-1.043]	<0.001	1.036[1.026-1.045]	1.036[1.026-1.0
Gender	1.197[0.930-1.541]	0.162		
Obesity	0.982[0.957-1.009]	0.188		
Hypertension	1.535[1.199-1.965]	0.001	1.227[0.916-1.644]	1.227[0.916-1.6
Diabetes	0.982[0.755-1.277]	0.890		
Coronary Heart Disease	1.331[1.004-1.764]	0.047	0.980[0.719-1.337]	0.980[0.719-1.3
Chronic Kidney Disease	1.002[0.688-1.459]	0.992		
Malignancy	1.370[0.784-2.396]	0.269	1.706[0.961-3.031]	1.706[0.961-3.0
Chronic Respiratory Disease	1.194[0.962-1.482]	0.107		
Immunosuppressive disorders	1.205[0.674-2.152]	0.530		
Smoking	0.932[0.667-1.302]	0.679		
Beta Blocker	1.375[1.052-1.794]	0.020	1.327[0.981-1.795]	1.327[0.981-1.7
ACEIs/ARB	1.067[0.808-1.407]	0.647	0.754[0.553-1.029]	0.075
Atorvastatin	0.820[0.639-1.054]	0.121	0.679[0.517-0.890]	0.679[0.517-0.8
Corticosteroid	1.205[0.930-1.561]	0.159	1.245[0.941-1.649]	1.245[0.941-1.6

Variable	Crude HR*, 95% CI	P-value	Adjusted HR*, 95% CI	Adjusted HR*,
Hydroxychloroquine	0.814[0.635-1.045]	0.106	0.813[0.629-1.051]	0.813[0.629-1.0
Lopinavir/Ritonavir	1.220[0.945-1.574]	0.128	1.250[0.951-1.641]	1.250[0.951-1.6
Remdesivir	0.815[0.456-1.457]	0.489		
Favipiravir	0.739[0.430-1.273]	0.276		
Mechanical Ventilation	Mechanical Ventilation	Mechanical Ventilation	Mechanical Ventilation	Mechanical Ven
Age (years)	1.019[1.007-1.028]	0.001	1.026[1.014-1.038]	1.026[1.014-1.0
Gender	1.259[0.868-1.825]	0.225		
Obesity	0.994[0.969-1.029]	0.744	1.390[0.903-2.140]	1.390[0.903-2.1
Hypertension	1.190[0.781-1.811]	0.418		
Diabetes	1.141[0.779-1.672]	0.499		
Coronary Heart Disease	1.115[0.750-1.657]	0.592	0.704[0.422-1.174]	0.704[0.422-1.1
Chronic Kidney Disease	0.750[0.405-1.390]	0.361		
Malignancy	1.652[0.768-3.552]	0.199	1.963[0.894-4.312]	1.963[0.894-4.3
Chronic Respiratory Disease	1.470[0.838-2.577]	0.179		
Immunosuppressive disorders	0.924[0.340-2.508]	0.877		
Smoking	1.008[0.624-1.629]	0.972		
Beta Blocker	1.639[1.110-2.418]	0.013	2.071[1.334-3.217]	2.071[1.334-3.2
ACEIs/ARB	0.823[0.545-1.242]	0.252	0.670[0.426-1.054]	0.670[0.426-1.0
Atorvastatin	0.709[0.486-1.034]	0.074	0.602[0.401-0.903]	0.602[0.401-0.9
Corticosteroid	1.507[1.034-2.196]	0.033	1.445[0.962-2.170]	1.445[0.962-2.1
Hydroxychloroquine	0.711[0.489-1.033]	0.073	0.707[0.482-1.036]	0.707[0.482-1.0
Lopinavir/Ritonavir	1.367[0.934-2.000]	0.108	1.357[0.904-2.037]	1.357[0.904-2.0
Remdesivir	0.944[0.414-2.152]	0.892		
Favipiravir	1.577[0.859-2.893]	0.141		

*Hazard ratio

The model was fitted based on the Schoenfeld residual test for the evaluation of the proportional hazard assumption with P=0.253, P=0.218, respectively.