Actual Clinical Efficacy of Statin Therapy (Hmg-CoA Reductase Inhibitors) on the Course of SARS-Cov-2/COVID-19 Infection During the Domination Period of Alpha, Beta, Gamma and Delta Variants

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Article

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Abstract: Background/Objectives: To date, SARS Cov-2 virus has caused more than 775 million cases worldwide and led to 7 million deaths. The virus enters cells with the aid of the ACE2 receptor located in the airway epithelium, but also in endothelial cells lining the inner walls of vessels. Endothelial damage results in impaired blood flow and gas exchange. Statins have been shown to have a pleiotropic effects on the vascular epithelium. Aim of the study: Assessment of the efficacy and safety of statin therapy in patients with COVID-19. **Methods**: Two hundred and one COVID-19 patients hospitalized at the Jerzy Gromkowski Regional Specialist Hospital between March 2020 and December 2021 (i.e. during the period dominated by Alpha, Beta, Gamma and Delta variants). Patients were divided into three groups: (I) patients treated with statins prior to the admission to the hospital; (II) patients started on statins after admission due to Covid-19; (III) control patients with Covid-19, not treated with statins either prior to or during hospitalization. Met Statistica 13.1 calculations were used in the paper. Shapiro-Wilk, Kruskal-Wallis and ANOVA tests were also performed. **Results**: Out of the 201 patients total, group I comprised 66 patients with a mean age of 66.2 years; group II comprised 33 patients with a mean age of 75.3 years; and the control group comprised 97 patients with a mean age of 61.1 years. The groups characteristics did not show significant differences in terms of gender, place of hospitalization, percentage of Covid-19 vaccinations, number of convalescents. Death was observed in: 12% of patients in group I, 6% of patients in group II, and 6% of patients in group III. Body Mass Index (BMI) in group I was 31.3: a value significantly higher than the control group's 28.3, ($p<0.05$). The severity of Covid-19 assessed on admission in group I – 4.09 – was statistically higher than in the control group 3.52 ($p<0.05$). The number of pulmonary embolism incidents did not differ between groups. **Conclusions**: During the period dominated by Alpha, Beta, Gamma and then Delta variants, we found no statistically significant positive or negative effects of statin therapy on the duration of hospitalization, number of complications or percentage of deaths between the two studied groups of patients: those who received statins prior to hospitalization, and those who received statins during hospitalization.

Keywords: statins; SARS-Cov-2 infection; Covid-19

1. Introduction

Since the beginning of the epidemic to date, over 775 million cases of COVID-19 and over 7 million Covid-related deaths have been recorded in the world (data as of April 28, 2024). [1] Almost 6.7 million SARS-CoV-2 infections have been confirmed in Poland. [2] The seroprevalence studied in Europe and the United States indicates that the number of cases may be even ten times higher. Although the pandemic status of Covid-19 was canceled by the WHO on May 5, 2023, experts believe that SARS-Cov-2 still poses a significant epidemic threat. Currently, the dominant subvariants of the Omicron SARS-Cov-2 variant – although quite infectious – are definitely less pathogenic than the Alpha, Beta, Gamma and Delta variants, which dominate earlier. The SARS-Cov-2 virus enters

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host cells by connecting its surface fusion protein (S-spike) to the angiotensin-converting enzyme 2 (ACE2) receptor. [3] It has been shown that other proteins, although to a varying extent, facilitate the penetration of SARS-Cov-2 into the interior of cells. These proteins include: CD147, GRP78, ADAM17, serine proteases TMPRSS2 and TMPRSS4, furins, GRP70 protein, matrix metalloproteinase inducer. [4,5] ACE2 receptors are located on the epithelial cells of the respiratory tract, gastrointestinal tract, cardiomyocytes, bile duct epithelial cells, Sertoli cells, Leydig cells, myocytes, olfactory epithelial cells, glial cells and, what is particularly important, on endothelial cells lining the inner walls of vessels. [1] Endothelial damage in the course of Covid-19 results in blood flow disorders but also affects gas exchange in the lungs. Statins are drugs that lower blood cholesterol, have a complex pleiotropic effect on the vascular epithelium and, consequently, on the course of certain infections (e.g. influenza and pneumonia of various etiologies) and some autoimmune diseases (systemic lupus erythematosus, rheumatoid arthritis and others). [2,3] Hence the hypothesis that they may positively affect the course of SARS-Cov-2 infection. [4,6]

Objectives

The aim of the study was to assess the efficacy and safety of statin therapy in two group of patients with SARS-Cov-2/Covid-19: those who used statins chronically due to hypercholesterolemia prior to SARS-Cov-2/Covid-19 infection, and those who were started on statins upon admission to the hospital due to Covid-19, all in actual clinical practice, during the period of dominance of the most pathogenic SARS-Cov-2 variants: Alpha, Beta, Gamma and Delta.

2. Materials and Methods

The above study received the consent of the Bioethics Committee – ID no.: KB/42/2020. The sample group were 201 patients hospitalized for Covid-19 at the Jerzy Gromkowski Regional Specialist Hospital in Wrocław, I Department of Infectious Diseases, between March 2020 and December 2021, i.e. in the period dominated by the Alpha, Beta, Gamma and Delta SARS-Cov-2 variants. The inclusion criteria for the study were: a SARS-Cov-2 infection confirmed with RT-PCR and/or antigen test; age above 18 years; O2 saturation <94% at admission; presence of symptoms characteristic of coronavirus infection reported at admission. Information on comorbidities and hitherto treatment was collected for each patient; the course of Covid-19 and the therapies used (antiviral therapy, oxygen therapy, ventilation) were assessed. Then, the laboratory test results at admission and during hospitalization were analyzed. Patients were then divided into three groups: group I, including patients who received statins at the beginning of hospitalization (Atorvastatin 20 mg daily, p.o.); sample 2 (II), including patients who received statins prior to the hospitalization (Atorvastatin and Rosuvastatin in doses of 10-40 mg) and the therapy was continued during hospitalization due to Covid-19; control group (III), including patients who did not use statins prior to the admission and during hospitalization. The main elements assessed were: death, length of hospitalization, and presence of Covid-19 complications.

Statistical Analysis

Statistical analysis was performed using the Statistica 13.1 software (TIBCO, Inc., USA). For measurable variables, arithmetic means, medians, standard deviations, range of variability (extreme values), lower quartile and upper quartile were calculated. For qualitative variables, their frequencies (percentage) were calculated. All quantitative variables examined were tested with the Shapiro-Wilk test to determine the type of distribution. The comparison of quantitative variable results was performed using the Kruskal-Wallis test or one-way ANOVA analysis of variance – depending on whether the assumptions were met. Additionally, a post-hoc test was performed (Tukey's test and Dunn's test); correlations were checked using the Spearman's rank-sum test. An $\alpha = 0.05$ level was assumed for all comparisons.

 doi:10.20944/preprints202410.2297.v1

3. Results

The analysis covered a total of 201 patients. Group I comprised 35% (n=24) women and 65% (n=44) men, group II comprised 55% (n=18) women and 45% (n=15) men, and the control group III comprised 38% (n=37) women and 62% (n=60) men. In group I, 88% (n=60) of patients were discharged from the hospital in good condition, death was noted in 12% (n=8) of patients, in group II 94% (n=31) were discharged, death was noted in 6% (n=2) of patients, and in the control group III 94% (n=92) were discharged, death was noted in 6% (n=6) of patients. The majority of the subjects in each group were not vaccinated against SARS-Cov-2: 81% (n=55) in group I, 81% (n=26) in group II, 91% (n=89) in the control group III. The studied samples did not show statistically significant difference in terms of gender, place of hospitalization, vaccination against SARCoV-2 ($p>0.05$) or percentage of convalescents and deaths (Table 1), although the number of deaths was statistically insignificantly higher in group I.

Table 1. Characteristics of the studied groups.

		Group						P-value*
		Group I (n=68)		Group II (n=33)		Control group III (n=98)		
		n	%	n	%	n	%	
Gender	Female	24	35.3	18	54.5	37	38.1	0.16
	Male	44	64.7	15	45.5	60	61.9	
SARS-Cov-2 vaccination	No	55	80.9	26	81.3	89	90.8	0.14
	Yes	13	19.1	6	18.8	9	9.2	
Death/Discharge	**Death**	**8**	**11.8**	**2**	**6.1**	**6**	**6.1**	**0.38**
	Discharge	60	88.2	31	93.9	92	93.9	

n – number of patients; % - percentage of patients; *chi-squared test.

Table 2 presents the characteristics of the studied groups by age, BMI and length of hospitalization. The mean age in group I was 66.2 years (min-max: 38.0-89.0 years; SD=11.7 years), in group II 75.3 years (min-max: 46.0-92.0 years; SD=10.7 years), and in the control group 61.1 years (min-max: 23.0-99.0 years; SD=16.6 years). Statistically significant differences were shown between group I and II, and between group II and the control group ($p<0.05$) (Table 2). The mean BMI value in group I was 31.3 (min-max: 23.4-45.7; SD=5.5), in group II the mean was 29.0 (min-max: 21.4-45.5; SD=6.0), and in the control group III 28.3 (min-max: 17.3-41.7; SD=5.3), statistically significant differences were shown between group I and the control group III ($p<0.05$) (Table 1). Assessing the length of hospitalization, no statistically significant differences ($p>0.05$) were found between the studied groups of patients (Table 1).

Table 2. Characteristics of the studied groups by age, BMI and length of hospitalization.

	Group	$\bar{x}$	Me	Min	Max	Q1	Q3	SD	P-value* (main result)	P-value (multiple comparison)
Age [years]	Group I (n=68)	66.2	69.0	38.0	89.0	60.5	73.0	11.7	**<0.001***	Group I vs Group II: **p=0.007***;** Group I vs. Control group III: p=0.06*** Group II vs. Control group III: **p<0.001*****
	Group II (n=33)	75.3	76.0	46.0	92.0	70.0	82.0	10.7		
	Control group III (n=98)	61.1	63.0	23.0	99.0	48.0	72.0	16.6		
BMI	Group I (n=38)	31.3	31.3	23.4	45.7	26.3	35.4	5.5	**0.026****	

 doi:10.20944/preprints202410.2297.v1

	Group II (n=18)	29.0	27.0	21.4	45.5	25.0	31.8	6.0		Group I vs Group II: p=0.29****; Group I vs. Control group III: **p=0.017****; Group II vs. Control group III: p=0.89****
	Control group III (n=69)	28.3	28.4	17.3	41.7	25.1	31.9	5.3		
Length of hospitalization [days]	Group I (n=68)	11.5	9.5	1.0	43.0	6.0	14.5	7.3	0.85*	-
	Group II (n=33)	10.7	9.0	1.0	41.0	7.0	12.0	7.2		
	Control group III (n=98)	11.5	9.0	1.0	34.0	6.0	16.0	7.8		

$\bar{x}$ - mean; Me – median; Q1 – first quartile; Q3 – third quartile; Min – minimum value; Max – maximum value; SD – standard deviation; * Kruskal-Wallis test; **one-way ANOVA variance test; ***Dunn's test; ****Tukey's test

.Table 3 summarizes the WHO severity grade at admission and discharge in the studied groups. Statistically significant differences in the severity of Covid-19 assessed using the WHO severity grade were shown at admission for group I – that mean was 4.09 points (min-max: 2.0-7.0 points; SD=1.08 points) which was 0.57 points higher compared to the control group, where the mean was 3.52 points (min-max: 2.00-6.00 points; SD=1.09 points)($p<0.05$). Otherwise, there no statistically significant differences were observed in the scores obtained ($p>0.05$) (Table 3).

Table 3. Severity of Covid-19 at admission and discharge assessed using the WHO severity grade.

	Group	**$\bar{x}$**	**Me**	**Min**	**Max**	**Q1**	**Q3**	**SD**	**P-value* (main result)**	**P-value (multiple comparison)**
WHO grade – upon admission	Group I (n=67)	4.09	4.00	2.00	7.00	3.00	5.00	1.08	**0.005**	Group I vs Group II: p=0.08; Group I vs. Control group III: **p=0.003;** Group II vs. Control group III: p=0.96
	Group II (n=33)	3.58	3.00	2.00	6.00	3.00	4.00	1.23		
	Control group III (n=97)	3.52	3.00	2.00	6.00	3.00	4.00	1.09		
WHO grade – upon discharge	Group I (n=59)	2.29	2.00	2.00	6.00	2.00	2.00	0.81	0.62	-
	Group II (n=30)	2.17	2.00	1.00	5.00	2.00	2.00	0.65		
	Control group III (n=89)	2.17	2.00	1.00	6.00	2.00	2.00	0.80		

$\bar{x}$ - mean; Me – median; Q1 – first quartile; Q3 – third quartile; Min – minimum value; Max – maximum value; SD – standard deviation; * Kruskal-Wallis test; ** Dunn's test.

Statistically significant differences were demonstrated for HGB: the average result in group I was 14.3 g/dL (min-max: 10.3-18.8 g/dL; SD=1.7 g/dL) and was higher by 1.4 g/dL when compared to the average in group II – 12.9 g/dL (min-max: 8.9-15.4 g/dL; SD=1.6 g/dL) ($p<0.05$) (Table 6).

Statistically significant differences between groups were also shown for ALT activity ($p<0.05$), although the post-hoc test did not show any differences between individual groups ($p>0.05$) (table 6).

Statistically significant differences between groups were demonstrated for LDH activity ($p<0.05$) as well; post-hoc analysis showed differences between group I, where the mean result was 545.4 (min-max: 238.0-1950.0; SD=305.8), and group II, where the mean was 368.2 (min-max: 231.0-732.0; SD=132.8) ($p<0.05$). Analyzing the remaining selected laboratory parameters, no statistically significant differences ($p>0.05$) were found between the assessed groups (Table 6).

 doi:10.20944/preprints202410.2297.v1

Table 4. Selected results of blood laboratory tests in the studied sample groups.

	Group	$\bar{x}$	Me	Min	Max	Q1	Q3	SD	P-value* (main result)	P-value (multiple comparison)
CRP	Group I (n=68)	114.0	93.7	3.0	447.9	54.2	144.8	84.0	0.06	-
	Group II (n=31)	74.9	79.9	0.9	194.4	20.9	109.8	54.9		
	Control group III (n=94)	103.7	63.1	0.5	565.6	25.2	150.2	107.4		
HGB [g/dL]	Group I (n=68)	14.3	14.4	10.3	18.8	13.5	15.3	1.7	**0.001**	Group I vs Group II: **p<0.001;** Group I vs. Control group III: p=0.10; Group II vs. Control group III: p=0.06
	Group II (n=33)	12.9	13.2	8.9	15.4	11.9	14.2	1.6		
	Control group III (n=98)	13.7	14.0	6.5	17.2	12.7	15.0	1.9		
WBC	Group I (n=68)	7.0	6.6	2.6	16.1	4.8	8.6	3.0	0.43	-
	Group II (n=33)	7.8	7.1	3.0	16.0	5.4	9.2	3.1		
	Control group III (n=98)	7.7	6.7	0.0	45.6	4.8	8.9	5.3		
Total billirubin [mg%]	Group I (n=60)	0.67	0.60	0.20	1.40	0.50	0.80	0.27	0.64	-
	Group II (n=31)	0.67	0.50	0.30	1.90	0.40	0.90	0.38		
	Control group III (n=86)	0.74	0.60	0.10	4.80	0.40	0.80	0.61		
ALT [IU/ml]	Group I (n=68)	58.2	44.5	11.0	657.0	26.5	57.0	85.0	**0.044**	Group I vs Group II: p=0.33; Group I vs. Control group III: p=0.98; Group II vs. Control group III: p=0.37
	Group II (n=32)	35.0	28.6	7.0	122.0	15.7	46.0	24.7		
	Control group III (n=96)	55.9	37.5	8.0	752.0	23.0	64.0	80.9		
INR	Group I (n=68)	1.04	1.040	0.880	1.4	0.975	1.08	0.09	0.40	-
	Group II (n=32)	1.09	1.045	0.910	1.6	0.970	1.12	0.16		
	Control group III (n=96)	1.10	1.040	0.890	4.15	0.990	1.11	0.34		
D-dimers	Group I (n=67)	1840.1	954.0	309.0	14831.0	679.0	1826.0	2669.5	0.56	-
	Group II (n=32)	2674.6	848.0	400.0	53670.0	588.5	1197.5	9328.0		
	Control group III (n=95)	1342.9	957.0	227.0	5799.0	561.0	1702.0	1146.4		
Creatinine	Group I (n=68)	1.00	0.840	0.550	5.6	0.765	1.03	0.63	0.14	-
	Group II (n=33)	1.14	0.970	0.590	2.9	0.840	1.26	0.50		
	Control group III (n=97)	1.16	0.890	0.570	9.07	0.730	1.11	1.08		
Cholesterol	Group I (n=26)	143.5	142.4	80.4	190.1	128.0	160.2	27.7	0.56	-
	Group II (n=14)	164.5	135.6	90.9	551.0	113.6	162.3	115.2		
	Control group III (n=35)	154.8	148.0	78.0	238.6	122.7	187.2	42.5		
TGL	Group I (n=24)	183.7	169.2	70.2	455.0	127.4	219.8	87.7	0.07	-
	Group II (n=9)	119.5	102.5	68.6	189.0	96.1	142.3	39.5		
	Control group III (n=30)	154.2	150.1	47.3	334.4	104.2	179.4	67.8		
LDH	Group I (n=64)	545.4	452.5	238.0	1950.0	349.0	607.0	305.8	**0.005**	Group I vs Group II: **p=0.007;** Group I vs. Control group III: p=0.25; Group II vs. Control group III: p=0.12
	Group II (n=29)	367.2	319.0	231.0	732.0	278.0	429.0	132.8		
	Control group III (n=91)	477.4	410.0	175.0	1499.0	290.0	618.0	257.4		

$\bar{x}$ - mean; Me – median; Q1 – first quartile; Q3 – third quartile; Min – minimum value; Max – maximum value; SD – standard deviation; * Kruskal-Wallis test; ** Dunn's test.

Table 5 summarizes the basic medication used in the treatment of Covid-19. GSK was Yesen by 96% (n=65) of the subjects in group I, 82% (n=27) in group II and 84% (n=82) in the control group. Statistically significant differences were shown in the obtained results ($p<0.05$) (Table 5). In the case of antiviral therapy for SARS-COV-2, statistically significant differences ($p<0.05$) were shown as well. In group I, antiviral therapy was received by 18% (n=12) of patients, in group II 33% (n=11), and in

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the control group 36% (n=35). In the case of the remaining medication, no statistically significant differences were found (p>0.05) (Table 5).

Table 5. Medication used in the treatment of Covid-19.

		Group						P-value*
		Group I (n=68)		Group II (n=33)		Control group III (n=98)		
		n	%	n	%	n	%	
GSK (dexamethason 8mg daily)	No	3	4.4	6	18.2	16	16.3	**0.042**
	Yes	65	95.6	27	81.8	82	83.7	
Heparin	No	1	1.5	1	3.0	5	5.1	0.45
	Yes	67	98.5	32	97.0	93	94.9	
Antivirals, anti-SARS-Cov-2 (remdesivir. malnupirawir)	No	56	82.4	22	66.7	62	63.9	**0.032**
	Yes	12	17.6	11	33.3	35	36.1	
Immunomodulators (tocilizumab)	No	67	98.5	31	96.9	97	100.0	0.28
	Yes	1	1.5	1	3.1	0	0.0	

n – number of patients; % - percentage of patients; *chi-square test.

Table 6 summarizes the number of pulmonary embolism incidents in the studied groups and shows no statistically significant differences (p>0.05) in this regard (Table 6). Interestingly, when analyzing all sample groups as a whole, we did not observe other forms of vascular embolism.

Table 6. Pulmonary embolism incidents in individual groups.

		Group						P-value*
		Group I (n=68)		Group II (n=33)		Control group III (n=98)		
		n	%	n	%	n	%	
Pulmonary embolism	No	64	94.1	31	96.9	90	91.8	0.58
	Yes	4	5.9	1	3.1	8	8.2	

n – number of patients; % - percentage of patients; *chi-square test.

4. Discussion

In experimental models, statins have been shown to inhibit the activation of NK-kB secondary to hypoxia, which enhances the anti-inflammatory response. An abnormal anti-inflammatory response is crucial for the fate of a patient with Covid-19. In addition, statins – in a complex mechanism – increase the concentration of the soluble ACE2 receptor, which, by binding to SAS-Cov-2, blocks its fusion with cell membranes and thus indirectly limits the replication of this virus; they also demonstrate the ability to directly bind to the SARS-Cov-2 protease in a mechanism similar to protease inhibitors. Based on the above data, it seems justified to attempt to assess the actual clinical efficacy of statin therapy on the course of Covid-19. Regardless of the current availability of excellent anti-viral drugs and the activity of SARS-Cov-2 (at the moment Poland is experiencing problems with the availability of Paxlovid), making such assessments may be significant anyway, since we cannot foresee what subsequent variants or recombinants of the virus will become dominant after the Omicron variants. In a meta-analysis covering four retrospective studies – a total of 8990 patients – Kow et al. [7] showed a significant 30% reduction in the risk of fatal or severe course of COVID-19 in patients receiving statin therapy as compared to those not receiving it. However, most of these patients were treated for hypercholesterolemia or had coronary artery disease. The authors of that paper state that HMG-CoA reductase inhibitors can be safely used during the pandemic and can also bring benefits to patients.

Marvan et al. [8] worked with a group of patients who also had coronary artery disease and advanced atherosclerotic process (i.e. patients with a confirmed risk of a more severe course of Covid-

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19) and were treated with statins prior to admission to hospital due to Covid-19. These patients showed a slightly lower percentage of deaths and a lower number of thromboembolic complications. Similar conclusions were reached by the authors of the Inspiration-S study, also concentrating on patients with coronary artery disease, critically ill, treated with statins (Atorovastatin) [9], although the obtained results – unlike the results of the Kow meta-analysis – were not statistically significant. Our observations did not confirm the results of the clinical studies cited above and are generally consistent with the observations of Peymani et al. [10].

Observations confirm the safety of statin therapy in this group of patients, which is consistent with the observations of Kow et al. In contrast to the results of the study by Xu L et al., none of our Covid-19 patients on statin therapy demonstrated exacerbated rhabdomyolysis or significant liver damage that would discontinuation of statin therapy.[11]

Despite the lack of statistical significance in terms of length of hospitalization, number of complications and death rate between the analyzed sample groups, in group I the number of deaths was even statistically insignificantly higher compared to the control group and the group using statins prior to admission to the hospital due to Covid-19. Choi showed a beneficial effect of statin therapy on the death rate in patients using statins before admission [12], and Vehedian presented a reduction in the number of patients requiring mechanical ventilation. [13] It seems that the higher death rate in this group, however, was associated with a greater severity of the disease assessed using the WHO severity grade at the time of admission, higher LDH activity (which indicates advanced damage or a developing multi-organ failure) and less access to effective antiviral drugs.

5. Conclusions

Despite the positive effect of statin therapy on the course of some infectious diseases, confirmed by both basic research and clinical studies, the analysis performed by us on sample groups of patients infected in the period of dominance of the Alpha, Beta, Gamma and Delta SARS-Cov-2 variants, including patients who took statins prior to the Covid-19 diagnosis and patients started on statins after admission due to Covid-19, did not reveal a statistically significant positive or negative effect of statin therapy on the length of hospitalization, number of complications or the death rate

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Institutional Review Board Statement: The above study received the consent of the Bioethics Committee – ID no.: KB/42/2020.

Informed Consent Statement: "Informed consent was obtained from all subjects involved in the study.

Data Availability Statement: We encourage all authors of articles published in MDPI journals to share their research data. In this section, please provide details regarding where data supporting reported results can be found, including links to publicly archived datasets analyzed or generated during the study. Where no new data were created, or where data is unavailable due to privacy or ethical restrictions, a statement is still required. Suggested Data Availability Statements are available in section "MDPI Research Data Policies" at https://www.mdpi.com/ethics.

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