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Original Research

Adherence to Treatment with Oral Nucleoside/Nucleotide Analogs in Patients with Chronic Hepatitis B

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Abstract

Objectives: Adherence to antiviral treatment is important for treatment success and prevention of resistance. It was aimed to determine treatment adherence to nucleoside/nucleotide analogs and factors influencing on adherence.

Methods: The study included 168 patients who received oral nucleoside/nucleotide analog with diagnosis of chronic hepatitis for at least 1 year. Data regarding demographic characteristics and missed drug were collected using a survey, while list of medication within prior year were extracted from pharmacy registry and Medication Possession Rate (MPR) was calculated.

Results: There were 60 women (35.7%) and 108 men (64.3%) in the study. Mean age was calculated as 43.61±10.35 years. It was found that 29.2% of patients were non-adherent based on MPR (MPR<0.90). It was observed that adherence was improved on middle age. Treatment adherence was found to be higher in patients receiving medication due to disorders other than hepatitis B. It was found that there was no significant difference in adherence according to age, gender, occupation status, marital status, smoking or alcohol consumption habits, type of antiviral treatment, time and mode of drug intake, and biopsy finding at time of drug prescription. The most common cause was identified as forgetfulness for missed drug. Other common causes were inoccupation and alteration in daily routine.

Conclusion: In our study, the treatment adherence determined by MPR was 70.8%. This rate was lower than those reported for chronic hepatitis B in the literature. It is important to monitor and encourage treatment adherence in patients with chronic hepatitis B by clinicians.

Keywords: Adherence, Antiviral treatment, Chronic hepatitis B, Medication possession ratio, Nucleoside/nucleotide analogs

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Chronic hepatitis B infection is defined as serum HBsAg positivity for more than 6 months.[1] The HBV infection is an important public health problem worldwide, which accounts for more than 887,000 deaths annually. According to the World Health Organization, Turkey is at medium endemicity region for chronic HBV infection.[2,3]

Nucleoside analogs (NAs) are most widely used agents in the treatment of chronic hepatitis B.[3] Incompliance to antiviral treatment may lead drug resistance and treatment failure; thus, increased health-care costs due to unfavorable outcomes.

There is no a gold standard to measure adherence to medi-

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cation. Since viral load is affected by many factors other than adherence such as drug effectiveness, polypharmacy, drug resistance, treatment failure, and undetermined effects of disease, viral load alone cannot be used as a measure for treatment adherence.

Reasons such as forgetfulness, inattention, and sociodemographic factors can lead disruption in drug intake and different levels of drug intake process. Treatment adherence as attempted to be determined by surveys has potential to determine adherence-related obstacles and to measure drug intake behaviors in the patients. However, they do not always provide accurate outcomes. Treatment adherence by Medication Possession Rate (MPR) is one of the feasible methods due to easiness of calculation and interpretation.

In our study, treatment adherence and related factors were determined using a survey and MPR in patients with chronic hepatitis B who were receiving NA for at least 1 year.

Methods

The study included patients aged >18 years diagnosed as chronic hepatitis B infection and received treatment for at least 1 year who were Turkish speakers and had sufficient education level and willingness to complete survey. All participants gave written informed consent before participation.

The patients with comorbid diseases (dementia, severe psychiatric, or neurologic disorder) that may influence on results, pregnant women and those infected with other hepatitis viruses (hepatitis C virus, hepatitis D virus) or human immunodeficiency virus were excluded from the study.

The study included 168 patients presented between January 2018 and April 2018. We excluded 7 patients due to incomplete data and two patients declining to complete survey.

1. When a patient presented, list of drugs within prior 1 year were extracted from pharmacy registry, and MPR was calculated:

MPR= days of supply within prior 12 months (days)/12 months (365 days)

Based on findings of major studies on adherence to hepatitis B treatment, patients with MPR≥0.90 were defined as adherent, while those with MPR<90 were defined as non-adherent.[4,5]

2. A survey about demographic data and drug use were completed by patients. We used ACTG adherence baseline questionnaire from center for AIDS prevention studies (California University, San Francisco, AIDS Research Institute) after modification in our study, in which Turkish validation was proven.[6]
3. As self-reported feedback, patients were questioned whether they missed tablets within prior 4 day, 1 week, 1 month, and 3 months.
4. In addition, age, gender, educational and marital status, life standard, smoking or alcohol consumption, comorbid diseases, concurrent drug use, previous treatments, and time of drug intake were also questioned.

Results of HBV DNA testing and other laboratory evaluations were extracted from patient files.

As reimbursement for hepatitis B drugs requires biopsy in Turkey, liver biopsy is performed in all patients unless there is contraindication. Approval of the ethics committee was obtained on January 9, 2018, with the decision number of 1858.

Statistical Analysis

Statistical analysis was performed using IBM SPSS Statistics version 24.0 (IBM SPSS Statistics for Windows, Version 24.0, 2016; IBM Corp., Armonk, NY, USA). Pearson Chi-square test, Fisher's exact test, and Chi-square trend were used to compare categorical variables, while Mann–Whitney U-test was used to compare continuous variables between groups. P value < 0.05 was considered as statistically significant.

Results

Of 168 patients, 64.3% (n=108) were male. Mean age was 43.61±10.35 years (21–85 years). Table 1 presents demographic characteristics of patients.

Mean age at diagnosis was 33 years, while mean age at treatment onset was 36 years.

Of the patients, 52 were previously used different classes of antiviral agents; 32 patients (19%) had received IFN, while 16 patients (9.5%) had received LAM.

Biopsy results were available in 159 patients. In seven patients, the treatment was initiated without biopsy as there was contraindication for biopsy.

Table 2 presents current antiviral treatment and missed drug as reported in the survey.

It was found that 119 patients (70.8%) were found to be adherent, while 49 patients (29.2%) were non-adherent based on MPR.

It was seen that MPR adherence rate was significantly improved by advancing age (p<0.05).

It was found that there was no significant difference in treatment adherence according to occupational status; however, in paired comparisons among non-employed group, it was found that treatment adherence was significantly higher in retired individuals when compared to

Table 1. Demographic characteristics of the cases

	N	%
Age		
18-29 years old	14	8.3
30-39 years old	45	26.8
40-49 years old	62	36.9
50-59 years old	34	20.2
60 years and older	13	7.8
Mean±Sd (Median (Min.-Max.))	43.61±10.35	43 (21-85)
Gender		
Woman	60	35.7
Male	108	64.3
Education Status		
İlliterate	15	8.9
Primary Education	93	55.4
High School	35	20.8
University	25	14.9
Working Status		
Working	108	64.3
Not Working	60	35.7
In Shift		
Yes	31	28.7
No	77	71.3
Not Working		
Student	3	5.0
Retired	23	38.3
Housewife	34	56.7
Life Standard		
Lives alone	9	5.4
In a family setting	159	94.6
Marital Status		
The married	141	83.9
Single	22	13.1
Divorced	5	3.0
Cigaret		
Yes	48	28.6
No	86	51.2
Left	34	20.2
Alcohol		
Yes	7	4.2
No	138	82.1
Left	23	13.7
Additional disease		
Those with more than additional disease	50	29.8
Those who use more than one drug	16	11
A-Hypertension	20	11.9
B-Diabetes	18	10.7
C-Heart disease	9	5.4
D-Other	19	11.3
Additional medication use	48	28.6
A- Hypertension	21	12.5
B- Diabetes	14	8.3
C- Heart disease	8	4.8
D- Other	16	9.5
HAI		
Mean±Sd (Median (Min.-Max.))	7.16±2.49	7 (2-14)
Fibrosis		
Mean±Sd (Median (Min.-Max.))	2.31±0.71	2 (1-5)

HAI: Histologıcal activity index.

Table 2. Current drug information of the cases

	N	%
Time to take medicine		
Morning	56	33.3
Noon	19	11.3
Evening	93	55.4
Method of taking medication		
Hungry	36	21.4
Full	132	78.6
Drug skip		
In the last 4 days	34	20.2
Within the last 1 week	46	27.4
In the last month	74	44.0
In the last 3 months	92	54.8
Did you miss your medication last weekend (Saturday or Sunday)?		
Yes	27	16.1
No	141	83.9
Antiviral drug used		
Tenofovir	93	55.4
Entecavir 0,5 mg	47	28.0
Entecavir 1 mg	9	5.4
Lamivudine	14	8.3
Telbivudine	5	3.0

housewives ($p<0.05$). Table 3 presents distribution of demographic characteristics as well as smoking and alcohol consumption habits according to treatment adherence by MPR.

Table 4 presents distribution of comorbidities, additional drug use rates, medication times, medication administration patterns, and last weekend discontinuation rates according to MPR treatment compliance of the patients.

It was found that age, age at diagnosis and treatment onset, and HBV DNA inhibition were significantly higher in adherent group when compared to non-adherent group ($p<0.05$). In both groups, it was seen that there was a regression in actual AST, ALT, and AFP levels when compared to baseline, while actual AFP levels were significantly lower in MPR adherent group when compared to MPR non-adherent group ($p<0.05$). Table 5 presents age, age at diagnosis and treatment onset, time from diagnosis to treatment onset, treatment duration, biopsy results and mean actual AST, ALT, and AFP according to MPR treatment adherence.

The distribution of initial and current HBV DNA positivity rates according to MPR treatment compliance of the cases are shown in Table 6. HBV DNA inhibition was significantly higher in adherent group when compared to non-adherent group ($p<0.05$).

Table 3. Demographic characteristics and distribution of smoking and alcohol habits of the patients according to MPR treatment compliance

	MPR				X^2	P
	Treatment compatible		Treatment is incompatible			
	n	%	n	%		
Age						
18-29 years old	9	64.3	5	35.7	6.796	0.009
30-39 years old	25	55.6	20	44.4		
40-49 years old	45	72.6	17	27.4		
50-59 years old	30	88.2	4	11.8		
60 years and older	10	76.9	3	23.1		
Gender						
Woman	43	71.7	17	28.3	0.031	0.859
Male	76	70.4	32	29.6		
Education Status						
İlliterate	12	80.0	3	20.0	1.726	0.189
Primary Education	68	73.1	25	26.9		
High School	23	65.7	12	34.3		
University	16	64.0	9	36.0		
Working status						
Working	76	70.4	32	29.6	0.031	0.859
Not working	43	71.7	17	28.3		
Not Working						
Student	1	33.3	2	66.7	8.466	0.009
Retired	21	91.3	2	8.7		
Housewife	21	61.8	13	38.2		
In shift						
Yes	21	67.7	10	32.3	0.144	0.704
No	55	71.4	22	28.6		
Life Standard						
Lives alone	6	66.7	3	33.3	0.080	0.721
In a family setting	113	71.1	46	28.9		
Marital Status						
The married	101	71.6	40	28.4	0.829	0.683
Single	14	63.6	8	36.4		
Divorced	4	80.0	1	20.0		
Cigaret						
Yes	33	68.8	15	31.3	4.406	0.110
No		57	66,3	29	33.7	
Left	29	85.3	5	14.7		
Alcohol						
Yes	4	57.1	3	42.9	1.437	0.490
No	100	72.5	38	27.5		
Left	15	65.2	8	34.8		

Pearson Chi-Square, Fisher's Exact test, Chi-square trend analysis, Row percentage used; MPR: Medication Possession Rate.

In the self-reported adherence survey questioning prior 3 months, 71 patients reported (42.2%) that they did never miss drug, while 51 patients (30.3%) reported that they missed drug only once.

In non-adherent patients according to MPR, the most common cause of missed drug was forgetfulness (79.4%); followed by inoccupation, being outside of home and alteration in daily routine. Running out of drug (40.8%) was another cause for missed drug.

In the single logistic regression analysis performed for the variables thought to be effective on MPR compliance, age, age at diagnosis, age at onset of treatment, student and re-

Table 4. Distribution of co-morbidities, additional drug use rates, medication times, medication administration patterns and last weekwnd discontinuation rates according to MPR treatment compliance of the patients

	MPR				X^2	p
	Treatment compatible		Treatment is incompatible			
	n	%	n	%		
Additional disease						
There is	40	80.0	10	20.0	2.895	0.089
No	79	66.9	39	33.1		
A-Hypertension						
There is	18	90.0	2	10.0	4.037	0.045
No	101	68.2	47	31.8		
B-Diabetes						
There is	15	83.3	3	16.7	1.525	0.217
No	104	69.3	46	30.7		
C-Heart disease						
There is	8	88.9	1	11.1	1.501	0.287
No	111	69.8	48	30.2		
D-Other						
There is	13	68.4	6	31.6	0.060	0.806
No	106	71.1	43	28.9		
Additional medication use						
There is	40	83.3	8	16.7	5.082	0.024
No	79	65.8	41	34.2		
Time to take medicine						
Morning	40	71.4	16	28.6	3.565	0.168
Noon	10	52.6	9	47.4		
Evening	69	74.2	24	25.8		
Method of taking medication						
Hungry	30	83.3	6	16.7	3.465	0.063
Full	89	67.4	43	32.6		
Did you miss your medication last weekend?						
Yes	9	33.3	18	66.7	21.897	0.000
No	110	78.0	31	22.0		

Pearson Chi-Square, Fisher's Exact test, Percentage of rows used; MPR: Medication Possession Rate.

tirement, additional medication use, and medication skip times were found to have a statistically significant effect on treatment compliance ($p<0.05$) (Table 7).

In the multivariate analysis performed by collecting the variables that were significant in the single analysis in a single model, it was found that the variables of drug withdrawal in the past 4 days and in the past 3 months in the 2nd step had a statistically significant effect on MPR compliance ($p<0.05$) (Table 8).

In <10% of patients, the cause of missed drug included avoiding adverse effect, thoughts about toxicity, having many drugs to be taken and problems ingesting drugs at specified time points.

Discussion

There is no gold standard method; however, multiple strategies have been developed to measure treatment adherence in the patients in the literature.[7] Treatment adherence is a dynamic process. Patients with chronic hepatitis B are generally asymptomatic and may not perceive benefits of drug use.

Methods solely relying on self-report may not be reliable since patients tend to overestimate their adherence due to fear of being not approved by clinician.[7] Several studies showed that adherence as rated by self-report is higher than those rated by other methods such as electronic follow-up or pill count. However, methods such as electronic

Table 5. Average distribution of patients age, age at diagnosis and treatment initiation, time difference between diagnosis and initiation of treatment, treatment duration, biopsy results and current AST, ALT and AFP values according to MPR treatment compliance

	Treatment compatible		Treatment is incompatible		Z	p
	Mean±SD	Median (Min.-Max.)	Mean±SD	Median (Min.-Max.)		
Age	44.8±10.35	45 (21-85)	40.65±9.84	39.5 (26-69)	-2.763	0.006
Age at diagnosis	34.43±10.77	35 (11-61)	29.42±10.89	27 (17-63)	-3.097	0.002
Age of start of treatment	37.4±10.27	37 (15-61)	33.5±11.31	32 (18-67)	-2.442	0.015
HAI	7±2.46	7 (2-13)	7.54±2.55	7 (2-14)	-1.145	0.252
Fibrosis	2.33±0.7	2 (1-5)	2.28±0.75	2 (1-5)	-0.602	0.547
C-AST	24.75±8.1	23 (12-57)	23.96±8.89	22.5 (12-58)	-0.967	0.333
C-ALT	27.1±15.55	23 (8-93)	29.73±18.56	25 (8-91)	-0.697	0.485
C-AFP	2.50±1.25	2.1 (1-9.9)	2.73±1.15	2.5 (1-7.9)	-2.135	0.033

Mann Whitney U analysis; C: current; HAI: Histologıcal activity index; AST: Alanine transaminase; ALT: Aspartat transaminase; AFP: Alfa feto protein.

Table 6. The distribution of initial and current HBV DNA positivity rates according to MPR treatment compliance of the cases

	MPR				X^2	p
	Treatment compatible		Treatment incompatible			
	n	%	n	%		
B-HBV DNA copy/mL						
HBV DNA <50	1	100.0	0	0.0	0.414	1.000
HBV DNA >50	118	70.7	49	29.3		
C-HBV DNA copy/mL						
HBV DNA <50	110	75.3	36	24.7	10.972	0.001
HBV DNA >50	9	40.9	13	59.1		

Pearson Chi-Square, Fisher's Exact test (B: Beginning, C: Current); MPR: Medication Possession Rate.

follow-up are not feasible in clinical practice due to cost and practical difficulties.[8] Review of medical and pharmacy records can be used to measure adherence. Adherence measurement by pharmacy registry may provide more objective results.

In our study, adherence was measured by self-reported survey as well as MPR calculated using pharmacy registry. In the previous studies assessing treatment adherence using different methods, Chotiyaputta et al. reported adherence to antiviral treatment as 87.8%, while Allard et al. reported as 80%. In our study, adherence rate as measured by MPR was 0.8% and lower than previous studies.[4,5]

Majority of the previous studies on treatment adherence showed that the age is associated with adherence. In one study, it was found that treatment adherence was lower in younger individuals, while another study reported that there was no significant difference in adherence among age groups.[4,9] In our study, it was observed that adherence to antiviral treatment was higher on middle-age and that mean age, mean age at diagnosis, and mean age at treatment onset were higher in adherent group when compared to non-adherent group. This may be explained by greater concern about health, awareness of risk for complications related to HBV infection in advanced ages. In addition, lower level of concern regarding chronic disorders and insufficient recognition of importance of regular drug use and treatment adherence may also affect treatment adherence in younger patients. In some studies, gender was reported as a factor that affects treatment adherence; however, no significant difference was detected in treatment adherence between male and female gender.[9,10]

It has been thought that literacy and low educational status may have important effect on treatment adherence. In a study, it was found that literacy and educational level had no significant effect on treatment adherence in general, while another study reported that high education level improved treatment adherence. In our study, treatment adherence (as proportion) was decreased by increasing edu-

Table 7. Univariate logistic regression analysis for variables thought to be effective in MPR compliance

	B	p	Exp(B)	95% C.I.	
Age	0.046	0.011	1.047	1.01	1.09
Age at diagnosis	0.047	0.007	1.048	1.01	1.08
Age of onset of treatment	0.038	0.025	1.039	1.00	1.07
Gender	-0.063	0.859	0.939	0.47	1.89
Education Status					
İlliterate		0.608			
Primary Education	-0.386	0.574	0.680	0.18	2.61
High School	-0.736	0.318	0.479	0.11	2.03
University	-0.811	0.291	0.444	0.10	2.00
Working Status	0.063	0.859	1.065	0.53	2.14
Not Working					
Student		0.036			
Retired	3.045	0.033	21.000	1.27	346.93
Housewife	1.173	0.358	3.231	0.27	39.28
Marital Status					
The married		0.674			
Single	-0.367	0.446	0.693	0.27	1.78
Divorced	0.460	0.685	1.584	0.17	14.61
Additional disease	0.680	0.092	1.975	0.89	4.36
A-Hypertension	1.432	0.062	4.188	0.93	18.79
B-Diabetes	-0.794	0.227	0.452	0.12	1.64
C-Heart disease	-1.241	0.248	0.289	0.04	2.38
D-Other	0.129	0.806	1.138	0.41	3.19
Additional medication use	0.954	0.027	2.595	1.11	6.06
How many years has he been receiving treatment	0.013	0.704	1.013	0.95	1.08
Drug skip					
In the last 4 days	-1.643	0.000	0.193	0.09	0.43
Within the last 1 week	-1.171	0.001	0.310	0.15	0.64
In the last month	-1.239	0.001	0.290	0.14	0.58
In the last 3 months	-1.580	0.000	0.206	0.09	0.45

Table 8. Multivariate analysis by collecting the variables found to be significant in a single analysis in a single model

	B	p	Exp(B)	95% C.I.	
In the last 4 days	-1.076	0.016	0.341	0.14	0.82
In the last 3 months	-1.168	0.008	0.311	0.13	0.74
Constant	1.887	0.000	6.600		

cation level on illiterate group, but the difference did not reach statistical significant.[7,11]

Comorbid disorders and concurrent drug use appear to be an important determinant of treatment adherence. In long-term treatment, patients with chronic disorders may experience reduction in treatment adherence and loss of motivation, complaining continuous drug use.[7] In a previous study, it was found that antiviral use with no concurrent drug improved adherence while another study concluded that the use of additional drugs had no effect on treatment adherence.[12,11] On contrary to previous studies, we assessed comorbid disease subgroups and found that treatment adherence was higher in patients with hypertension and in the group requiring additional drugs in general.

Adverse effects of drug used seem as an important cause for drug incompliance. NAs widely used at long-term have substantially lower adverse effects when compared to retroviral agents.[9] In a previous study, it was found that treatment with oral antiviral agents other than LAM improved adherence, while no significant difference regarding antiviral agent used between adherent and non-adherent groups.[10]

In treatment, primary goal is to maintain HBV DNA below detectable levels by continuous suppression and prevent progressive liver injury.[13] In a study by Sogni et al., no significant difference was detected in HBV DNA level at baseline between adherent and non-adherent groups as similar to our study.[14]

In some studies, no genotypic resistance was detected in patients with virological failure using TDF and ETV that have high threshold for resistance, suggesting that virological failure may be explained by poor treatment adherence.[15,16]

Inadequate awareness regarding severity of disease, insufficient counseling at treatment onset in newly diagnosed patients, or switching NAs treatment due to several reasons in patients with the previous experience of treatment may affect treatment adherence. In the study of compliance with warfarin, which is an important agent related to treatment compliance, insufficient information about the drug and the disease, and lack of counseling at the beginning affect the treatment compliance of the patients negatively.[17] In some studies, being NAs-naïve patients and recent treatment onset were found as criteria for better treatment adherence, while others found higher adherence in patients on long-term treatment.[10,11,18] In our study, no significant difference was detected in treatment adherence according to treatment duration.

When treatment adherence and associated factors were evaluated, forgetfulness was reported as reason for missed drug by 90% in the study of Jain et al. and by 56.3% in the study of Giang et al.[7,19] In our study, forgetfulness appeared as most common cause for missed drug in the MPR non-adherent group. Forgetfulness may be affected by many cognitive factors such as awareness regarding disease-related risk for health and insufficient knowledge. Thus, patients should have to be actively counseled regarding importance of compliance to antiviral treatment and potential consequences of missed NAs doses.

In some studies, it was concluded that drug costs may affect treatment adherence. However, drugs are reimbursed in patients with treatment indication by insurance organization; thus, we did not evaluate relationship between drug cost and adherence.[19]

In many studies, alteration in daily routine and inoccupation is among common causes of poor drug compliance as similar to our study.[19,7]

As it is the case in many chronic diseases, some patients with chronic hepatitis B infection are exposed to discrimination during daily life and in working environment by individuals who are unaware of transmission routes of the disease. In most instances, HBV results are demanded before employment, causing psychological distress in patients. In a study by Xu et al., some patient reported that they missed their doses since they do not want to be seen during drug intake.[11] We also observed same reason in our patients. Declaration of HBV status can have negative influence on treatment adherence.

Conclusion

In our study, treatment adherence calculated using MPR was found as 70.8%. This adherence rate was lower in the studies on chronic hepatitis B infection, while it was higher than those on chronic disorders other than chronic hepatitis B.

MPR treatment adherence showed as positive correlation with middle age, retirement, and drug use with diagnosis of comorbid disease and hypertension. Age at diagnosis and age at treatment onset were found to be significantly higher in adherent group when compared to non-adherent group.

No significant relationship was detected between treatment adherence and educational status, marital status, smoking or alcohol consumption habits, type of NAs used, time and mode of drug intake, and treatment duration.

It was found that forgetfulness, being outside of home, alteration in daily routine, and inoccupation were reported as most common causes of missed drug.

It is important to establish a trustful relationship with patient and to inform patient about disease and treatment process. This may reduce missed drug due to altered daily routine or inoccupation by improving awareness of patient.

Treatment adherence should be monitored and encouraged in patients on long-term drug therapy by clinicians.

Limitations

Our study has any limitations. The study was conducted in a single center, and the number of patients is not sufficient to generalize to the society.

Disclosures

Ethics Committee Approval: Approval of the ethics committee was obtained on January 9, 2018, with the decision number of 1858.

Peer-review: Externally peer-reviewed.

Conflict of Interest: None declared.

Authorship Contributions: Concept – D.O., D.Y.S., C.A.T.; Design – D.O., D.Y.S., C.A.T., I.D.; Supervision – D.Y.S., A.G., A.O.; Data collection &/or processing – D.O., D.Y.S., C.A.T., A.O.; Analysis and/or interpretation – D.O., D.Y.S., A.O., A.G.; Literature search – D.O., C.A.T., I.D.; Writing – D.O., D.Y.S., A.G., A.O; Critical review – A.G., A.O., I.D.

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