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Retrospective evaluation of COVID-19 incidence during smoking cessation treatment with varenicline

Sigara Bırakma Tedavisi Olarak Vareniklin Kullanan Hastalarda COVID-19 Insidansının Retrospektif Değerlendirilmesi

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Öz

Giriş ve Amaç: Kolinerjik anti-inflamatuar yol, α7-nikotinik asetilkolin reseptörünün (α7nAChR) aktivasyonu ile inflamatuar süreçlerin endojen kontrolünü sağlamaktadır. Sigarayı bırakma tedavisinde kullanılan vareniklin, bir α7nAChR'lerine agonist etkisi ile anti-inflamatuvar etkiler ortaya çıkarmaktadır. Bu çalışmada sigara bırakma tedavisi olarak vareniklin kullanan hastalarda koronavirüs hastalığı (COVID-19) görülme sıklığı değerlendirilmiştir.

Yöntemler: Bu retrospektif kesitsel çalışmada, COVID-19 pandemisi sırasında XXXXXX Üniversitesi Tıp Fakültesi Sigara Bırakma Polikliniği'ne başvuran 111 hastanın kayıtları değerlendirilmiştir. SARS-COV-2 PCR pozitif olan hastalarda COVID-19 gelişimi ve hastalık belirtileri, vareniklin kullanan ve kullanmayan hastalarda karşılaştırmalı olarak değerlendirilmiştir.

Bulgular: Değerlendirilen 68 hastadan düzenli olarak vareniklin kullanan 38 hastada SARS-CoV-2 PCR pozitifliği saptanmamıştır. Sigara bırakma amacıyla farklı tedavileri alan veya düzensiz vareniklin kullanan 30 hastanın 13'ünde (%43,3) SARS-CoV-2 PCR pozitifliği saptanmıştır ($p<0,001$).

Sonuç: Sigarayı bırakma tedavisi gören hastalarda, vareniklin kullanmayanlara hastalara kıyasla düzenli vareniklin kullanımı süresince COVID-19 gelişmemesi, bu da ilacın COVID-19 gelişiminde koruyucu bir rolü olabileceğini düşündürmektedir.

Anahtar Kelimeler: COVID-19, SARS-CoV-2, Retrospektif Araştırma, Sigara Bırakma Tedavisi, Vareniklin

Abstract

Background: Cholinergic anti-inflammatory pathway endogenously controls inflammatory processes through activation of the α7-nicotinic acetylcholine receptor (α7nAChR). Varenicline, used in smoking cessation therapy, is a full α7nAChR agonist with anti-inflammatory effects. In this study, the frequency of coronavirus disease (COVID-19) was evaluated in patients using varenicline as a smoking cessation treatment.

Methods: In this retrospective cross-sectional study, records of the 111 patients admitted to Smoking Cessation Outpatient Clinic of XXXXX University Faculty of Medicine during the COVID-19 pandemic were evaluated. The development of COVID-19 disease according to the status of the patients being positive for SARS-COV-2 was evaluated comparatively in patients who received varenicline or not. Additionally, the disease symptoms were questioned.
Results: SARS-CoV-2 PCR positivity was not detected in any of 38 patients who regularly used varenicline out of 68 patients evaluated. SARS-CoV-2 PCR positivity was detected in 13 (43.3%) of 30 patients who received other treatments or irregularly used varenicline ($p<0.001$).
Conclusions: Patients under smoking cessation treatment did not develop COVID-19 during the period of varenicline use compared to non-users suggesting that the medication may have a protective role in the development of COVID-19 which might be further investigated by clinical trials.

Keywords: COVID-19, SARS-CoV-2, Retrospective Study, Smoking Cessation Therapy, Varenicline

1.Introductıon

The Novel Coronavirus Disease (COVID-19) is a disease was first identified in late December 2019 which affects many different organs besides pulmonary system in which respiratory symptoms such as cough and shortness of breath dominate. Although the clinical findings of COVID-19 infection are variable, acute respiratory distress syndrome (ARDS) due to infection is the leading cause of mortality and morbidity [1]. Systemic inflammatory response syndrome (SIRS) and cytokine storm are involved in the pathogenesis of COVID-19. Moreover, studies have shown that unrestrained pro-inflammatory cytokine release in COVID-19 may be one of the main factors determining the prognosis of the disease [2–4] and sepsis is the most common complication in COVID-19 patients admitted to intensive care units (ICU) [5–8]. Treatment of COVID-19 infection includes anti-inflammatory and immunomodulatory drugs in addition to antiviral therapies [9]. Regarding the hyperinflammatory state, systemic glucocorticoid use is recommended to control the cytokine storm that develops due to severe COVID-19 infection [10]. Inflammatory status can be controlled by activating the cholinergic system and its receptors. This endogenous pathway is called the cholinergic anti-inflammatory pathway (CAP), and CAP can be modulated by pharmacological interventions [11]. Pharmacological activation of cholinergic receptors or stimulation of the vagal system inhibited pro-inflammatory cytokine release in various *in vivo* models and clinical trials [12]. Studies demonstrated that the cholinergic receptors, especially alpha 7 nicotinic acetylcholine receptors (α7nAChR), play a crucial role in CAP activation. Supporting evidence demonstrated that cholinomimetic drugs and α7nAChR agonists such as nicotine, acetylcholinesterase (AChE) inhibitors, and GTS-21 anti-inflammatory effects in patients with sepsis [13,14].

Varenicline is a drug used in smoking cessation therapy through its partial agonistic effect on α4β2nAChRs in the central nervous system [15]. Varenicline also showed potent and full agonistic activity on α7nAChRs [16]. Varenicline administration decreased cerebral endothelial damage and oxidative stress caused by cigarette smoke, ischemia-induced inflammation, increased alveolar expansion via α7nAChR activation, and decreased the number of inflammatory cells in different experimental models [17–19]. Consistent with previous studies, our previous study showed that varenicline activates CAP via α7nAChR and decreases 14 different pro-inflammatory cytokines in lipopolysaccharide (LPS) induced *in-vitro* model of inflammation in macrophages. In this study, the anti-inflammatory effect of varenicline was compared with that of dexamethasone, a glucocorticoid, and the anti-inflammatory effect did not differ statistically [20]. Real-time cell analysis studies of our study showed that, LPS-induced macrophage cell proliferation and migration decreased with varenicline administration as well.

Along with the previous evidence, the present study was designed to evaluate the COVID-19 incidence in patients used varenicline during smoking cessation treatment in comparison with that of varenicline-naive patients.

2. Materials And Methods

2.1. Characteristics of Study and Patients

This retrospective cross-sectional study was approved by Non-interventional Research Ethics Committee of Dokuz Eylul University Faculty of Medicine (DEUFM) (No:469-SBKAEK) and carried out within the framework of the Declaration of Helsinki, Good Clinical Practices Guide and relevant legislation provisions.
In this study, records of the patients admitted to DEUFM Chest Diseases Smoking Cessation outpatient clinic between 01.01.2020-01.01.2022 were evaluated. Patients included in the study were 18-years of age or above and received pharmacological therapy.
2,1 All patients were interviewed via phone and their oral consent was obtained. Sociodemographic data of all patient groups, such as age, gender, smoking history, chronic diseases, vaccination status and status of being SARS-CoV-2-PCR positive (+) were

recorded. SARS-CoV-2-PCR records of patients who used varenicline regularly during smoking cessation treatment for 3 months, and 1 month after the treatment were questioned. The same parameters were also questioned in patients who did not use varenicline regularly as well as in patients using other treatment options (ie. nicotine patch). The patients who were positive for SARS-CoV-2 were identified with PCR analysis of nasopharyngeal swab samples and were diagnosed with COVID-19, evaluated. For SARS-CoV-2-PCR (+) patients, the symptoms of the disease (fever, cough, dyspnea, headache, sore throat, runny nose, muscle and joint pain, weakness, loss of smell and/or taste, diarrhea) were questioned

2.2Statistical Analyses

Descriptive statistics were presented as numbers (n) and percentages (%) for categorical variables and mean and standard deviations (mean±SD) for continuous variables. Categorical variables were compared with the Pearson chi-square test or Fisher's Exact test, while the Mann-Whitney U test was also used to compare continuous variables. The data were analyzed by using Statistical Package for the Social Sciences (SpSS-24, SPSS INC.Chicago,IL,USA) and double-sided p-values of less than 0.05 were considered significant.

3. Results

Electronic medical records (EMR) of 111 patients who admitted to the smoking cessation outpatient clinic between January 1st, 2020, and December 31st, 2021, was evaluated. Among them contact details of 38 patients could not be obtained from EMR. Also, five patients could not be reached by the available contact information.

The data of 68 (61.3%) patients who could be reached and who gave consent to participate in the study were evaluated. Of these, 32 (47.1%) patients were female, and 36 (52.9%) patients were male. The mean age of the patients was 46.6±11.8.

21 (30.9%) of the patients had chronic diseases, including asthma (n=8), hypertension (n=6), diabetes mellitus (n=4), thyroid disorder (n=4), hypercholesterolemia (n=2), and heart failure (n=1). Among them 5 patients with chronic diseases (thyroid disorder (n=1), asthma and hypertension (n=1), hypertension, thyroid disorder and diabetes mellitus (n=1), heart failure and hypertension (n=1)) developed COVID-19.

Of the patients 49 (72.1%) of were active smokers, 13 (19.1%) had a history of COVID-19, 38 (55.9%) had a history of varenicline use regularly (Table 1). 22 people out of 38 (57,9%) participants who received varenicline treatment and used regularly were healthcare workers. 44.1% of the patients had regular use of varenicline at 1 mg twice a day for 3 months. In the remaining 55.9% of the participants; 2 patient (6,6 %) had nicotine patch use and 28 patient (94,4%) had irregular use of varenicline (less than 1 month) or used varenicline before the official announcement of the COVID-19 outbreak in Turkey, 11 March 2020.

Table 1. Demographic characteristics of the patients (n=68)

	n (%)
Gender	
Female	32 (47.1)
Male	36 (52.9)
Chronic diseases	
None	47 (69.1)
Have	21 (30.9)
Smoking history	
Not using	19 (27.9)
Using	49 (72.1)
History of having COVID-19	
Yes	13 (19.1)
No	55 (80.9)
Use of varenicline	
Yes	38 (55.9)
No	30 (44.1)

The mean age of the patients was 47.4 ± 12.1 in COVID-19-negative group (n=55) and 43.3±10.3 in COVID-19 positive group (n=13, p=0.0228). Evaluation of COVID-19 development between patients who used or did not use varenicline regularly revealed that none of the 38 regular varenicline users were diagnosed with COVID-19 during the smoking cessation treatment period while 30 patients who used nicotine patch or varenicline irregularly were detected COVID-19 positivity was detected by PCR in 13 (43.3%) of the patients ($p<0.001$). There was no statistical difference between COVID-19-positive and COVID-19-negative patients according to gender, smoking history, presence of chronic disease and vaccination status (Table 2).

12 patients (92.3%) of SARS-CoV2 PCR-positive group complained about the most common three symptoms such as myalgia (84.6%), tiredness/fatigue (84.6%), and cough (69.2%) followed by headache, fever, dyspnea, sore throat, sneezing and loss of smell and taste. One patient was asymptomatic and SARS-CoV2 PCR-positive, which detected with PCR test due to the contact tracing management (Table 3).

Table 2. COVID-19 positivity and negativity according to varenicline use, gender, presence of chronic disease, smoking status and vaccination history

	COVID-19 (-) (n=55) n (%)	COVID-19 (+) (n=13) n (%)	*p*
Varenicline use			
Yes	38 (100%)	0 (0.00%)	*p<0.001*
No	17 (56.7%)	13 (43.3%)	
Gender			
Female	25 (78.1%)	7 (21.9%)	*0.813*
Male	30 (83.3%)	6 (16.7%)	
Smoking			
No	17 (89.5%)	2 (10.5%)	*0.325*
Yes	38 (77.6%)	11 (22.4%)	
Chronic disease			
No	39 (83.0%)	8 (17.0%)	*0.520*
Yes	16 (76.2%)	5 (23.8%)	
Vaccination status*			
No	1 (1.9%)	0 (0.00%)	*1.000*
Yes	54 (98.1%)	13 (100.00%)	
Vaccination before covid infection			
No	-	9 (69.3%)	
Yes	-	4 (30.7%)	

***** Two doses of COVID-19 vaccine (Sinovac or BioNTech) are recommended by minister of health in Turkey for immunization and this recommendation is accepted as completed vaccination for this study.

Table 3. COVID-19 symptoms of SARS-CoV2 PCR positive patients

	n (%)
Symptom	12 (92.3%)
Muscle pain	11 (84.6%)
Fatique	11 (84.6%)
Cough	9 (69.2%)
Headache	8 (61.5%)
Fever	7 (53.8%)
Dyspnea	6 (46.2%)
Sore throat	6 (46.2%)
Sneezing	5 (38.5%)
Loss of smell and taste	4 (30.8%)

4. Discussion

This study evaluated the incidence of COVID-19 disease among patients using varenicline as a smoking cessation aid and those receiving treatments other than varenicline. In this retrospective cross-sectional study, COVID-19 disease was not detected in patients using varenicline regularly during smoking cessation treatment compared to those of irregular varenicline users or treated with other options (i.e. nicotine patch).

Coronavirus disease 2019 (COVID-19) is an infectious disease caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2). Although anti-inflammatory and immunomodulatory drugs in addition to antiviral therapies used in the treatment of COVID-19 disease, there is no current prophylactic drugs against COVID-19 development [9]. Systemic inflammation has an important role in the pathogenesis of COVID-19 and recent studies indicate that uncontrolled release of proinflammatory cytokines in COVID-19 disease may be one of the main factors determining the prognosis of the disease.

Cholinergic anti-inflammatory pathway (CAP), which has been shown to suppress inflammation by activating the cholinergic system and its receptors in the body, has an important role in the control of inflammation [11]. Pharmacological activation of cholinergic receptors activates CAP and inhibits proinflammatory cytokine release in various *in vivo* models and clinical trials, including ischemia, pancreatitis, colitis, hemorrhage, and sepsis. Studies demonstrated that among the cholinergic receptors, α7nAChR play a crucial role in CAP activation, and pharmacological agonists of α7nAChRs produce anti-inflammatory effects [22].

Varenicline is a drug that used in smoking cessation therapy. Underlying mechanism of smoking cessation is related its partial agonistic effect on α4β2nAChRs in the central nervous system [15]. Additionally, varenicline has been shown to be a potent and complete agonist of α7nAChRs [16]. Our previous study demonstrated that varenicline decreases pro-inflammatory cytokine levels, including macrophage inflammatory protein (MIP-

1α, the MIP-1β, and MIP-2), IL -1, IL-6, IL-27, TNFα, RANTES (regulated upon activation and normal T-cell expressed or CCL5), interferon gamma-stimulated protein 10 (IP-10), and monocyte chemoattractant protein (MCP) by activating CAP via α7nAChR in lipopolysaccharide (LPS) induced *in vitro* model of inflammation in macrophages. The anti-inflammatory effect of varenicline on cytokine levels increased because LPS application was compared with dexamethasone, a glucocorticoid, and the anti-inflammatory effect did not differ statistically [20].

These findings suggest that varenicline suppresses inflammation by activating CAP by stimulating α7nAChRs. There are also numerous studies reporting the anti-inflammatory effectiveness of varenicline. Varenicline administration decreased cerebral endothelial damage caused by cigarette smoke in rats and showed a protective effect on endothelium [23]. Another study showed that one-week varenicline treatment for prophylaxis increased the use of damaged limbs in mice with cerebral ischemia via decreasing inflammation in the corpus striatum [17]. Varenicline administration also increased alveolar expansion via α7nAChR activation and decreased the number of inflammatory cells (macrophage, neutrophil, and T cells) in the lung tissues of mice with emphysema induced by inhalation of porcine pancreatic elastase [19]. In a randomized controlled study conducted on smokers, 3-month varenicline treatment reduced oxidative stress, atherosclerosis, and endothelial damage by decreasing urinal prostaglandin metabolites [18]. Moreover, positive allosteric modulator of α7nAChR and a well-known antiparasitic drug, ivermectin, have been shown to effectively reduce SARS-CoV-2 replication in vitro [24,25].

This retrospective study showed that none of the patients who used varenicline regularly as a smoking cessation treatment developed COVID-19 disease. On the other hand, 43.3% of those who did not use varenicline regularly or used nicotine patch developed COVID-19 disease. Moreover, there was no significant difference between SARS-CoV-2-PCR positive and negative patients according to gender, smoking history, presence of chronic disease and vaccination status. The mean age was significantly higher in the varenicline-treated group that might be considered as a risk factor for development of COVID-19 for some variants of the virus although type of the SARS-CoV-2 variant was not evaluated in clinical practice so that the information was not included this study.

Regarding the prophylaxis of COVID-19, vaccines have great importance. In our country, the COVID-19 vaccine has been administered to all healthcare personnel, over the age of 65 and risky groups as of January 2021, and to the entire public as of June. In this study the records were evaluated between January 1st, 2020, and December 31st, 2021. During this period varenicline was shortfall from the market since September 2021. Thus, vaccination was not considered as a major confounding factor for this study. In our study, no significant difference between vaccination status and vaccination rates were also very high in the evaluated patients.

Limitations

As with any retrospective study, our study includes recall bias as a concern. Our sample size was relatively insufficient to conduct multiple variable analyses. Also, in the scope of our study design, the information about varenicline use in asymptomatic carriers was not recorded. A significant strength of this study is the high response rate.

Despite low evidence certainty, this retrospective study provides new insights into possible therapeutic uses of varenicline along with the previous findings. The possible protective effects of varenicline in COVID-19 development need to be confirmed unequivocally by further studies.

Conclusion

The findings of this study suggest that varenicline might exert protective properties against COVID-19 development. The underlying modulatory mechanism of varenicline on inflammatory status by activating the CAP awaits for further studies. Moreover, potential prophylactic role of varenicline could be investigated by clinical studies conducted with different patient groups.

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