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ORIGINAL ARTICLE

The Effect of Montelukast Treatment on Elderly Patients Diagnosed with COVID-19

COVID-19 Tanısı Konan Yaşlı Hastalarda Montelukast Tedavisinin Etkisi

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ABSTRACT

Objective: The clinical course in COVID-19 patients can vary from asymptomatic cases to acute respiratory distress syndrome (ARDS), multi-organ dysfunction and respiratory failure. Clinical progression is thought to be mainly due to the release of proinflammatory cytokines. The most common symptoms are shortness of breath, fever, malaise, and cough. Montelukast, which is used in the treatment of seasonal allergic rhinitis and asthma, started to be used in Covid-19 infection due to its anti-inflammatory and cytokine release-reducing effect. There are studies in the literature showing that montelukast treatment is beneficial in the treatment of COVID-19. However, there are not enough studies evaluating the efficacy of montelukast treatment in elderly patients.
The aim of our study is to evaluate the clinical and laboratory efficacy of montelukast treatment in patients aged 60 and over in COVID-19 disease, and to indicate the differences from the studies in the literature.
Method: Our research was planned as a retrospective, single-center, observational study. The medical records of 75 COVID-19 patients aged 60 and over who were hospitalized in the internal medicine clinic of Ankara Bilkent City Hospital between September 2021 and December 2022 were included.
Results: Clinical findings and results were compared between the patients who received montelukast and the control group. There was no statistically significant difference between two groups in terms of cough, dyspnea, gastroenteritis and oxygen theraphy requirement. There wa no significant difference between the groups in terms of the need for intensive care unit admission and mortality. The length of hospital stay was compared in both groups, it was 10.88±7.24 days in the control group and 10.51±5.44 days in the montelukast group, and there was no statistically significant difference between the groups. The laboratory parameters of the patients in both groups were compared. The neutrophil count and leukocyte count measured before hospitalization were found significantly lower in the patient group receiving montelukast ($p<0.05$). No significant difference was found in other laboratory parameters.
Conclusion: Although montelukast treatment has positive effects on prognosis in COVID 19 disease in the literature, a similar effect was not observed in the population aged 60 and over in our study. We did not find a beneficial effect of short-term montelukast use on prognosis in COVID-19 patients aged 60 and over. We thought that this was due to the low efficacy of montelukast in the elderly population. Our study is a rare study in that it examines montelukast treatment in the geriatric population with COVID-19.

Keywords: Montelukast, COVID-19, Elderly, Geriatrics, SARS-CoV-2

ÖZ

Amaç: COVİD-19 hastalarında klinik seyir asemptomatik vakalardan akut solunum sıkıntısı sendromuna (ARDS), solunum yetmezliğine ve çoklu organ fonksiyon bozukluğuna kadar değişebilmektedir. Klinik ilerlemenin temel olarak proinflamatuar sitokinlerin salınımına bağlı olduğu düşünülmektedir. En sık görülen semptomlar ateş, öksürük, halsizlik ve nefes darlığıdır. Mevsimsel alerjik rinit ve astım tedavisinde kullanılan montelukast, antiinflamatuar ve sitokin salgısını azaltıcı etkisi nedeniyle COVİD-19 enfeksiyonunda da kullanımını gündeme getirmiştir. Literatürde montelukast tedavisinin COVİD-19'un prognozu ve mortalitesi üzerine olumlu etkisi olduğunu gösteren pek çok çalışma bulunmaktadır. Ancak yaşlı hastalarda montelukast tedavisinin etkinliğini değerlendiren yeterli çalışma bulunmamaktadır.
Çalışmamızın amacı, COVİD-19 hastalığında 60 yaş ve üzeri hastalarda montelukast tedavisinin klinik ve laboratuvar etkinliğini değerlendirmek ve literatürdeki çalışmalardan farklılıklarını ortaya koymaktır.
Metod: Araştırmamız retrospektif, tek merkezli, gözlemsel bir çalışma olarak planlandı. Eylül 2021 ile Aralık 2022 tarihleri arasında Ankara Bilkent Şehir Hastanesi dahiliye kliniğinde yatarak tedavi gören 60 yaş ve üzeri 75 COVİD-19 hastasının tıbbi kayıtları dahil edildi.
Bulgular: Montelukast alan hastalar ile kontrol grubu arasında klinik bulgular ve sonuçlar karşılaştırıldı. Öksürük, dispne, gastroenterit ve oksijen tedavisi gereksinimi açısından gruplar arasında istatistiksel olarak anlamlı fark saptanmadı. Yoğun bakıma yatış ihtiyacı ve mortalite değerlendirildiğinde gruplar arasında anlamlı fark yoktu. Hastanede kalış süreleri her iki grupta karşılaştırıldığında kontrol grubunda 10,88±7,24 gün, montelukast grubunda 10,51±5,44 gün olup gruplar arasında istatistiksel olarak anlamlı fark saptanmadı. Her iki gruptaki hastaların laboratuvar parametreleri karşılaştırıldı. Montelukast alan hasta grubunda hastaneye yatmadan önce ölçülen nötrofil sayısı ve lökosit sayısı anlamlı olarak düşük bulundu ($p<0,05$). Diğer laboratuvar parametrelerinde anlamlı bir fark bulunamadı.
Sonuç: Literatürde montelukast tedavisinin COVİD-19 hastalığında prognoza olumlu etkileri olmasına rağmen çalışmamızda 60 yaş ve üzeri popülasyonda benzer bir etki gözlenmedi. Kısa süreli montelukast tedavisinin COVİD-19 nedeniyle hastaneye yatırılan 60 yaş ve üzeri hastaların prognozlarına olumlu etkisini bulamadık. Bunun yaşlı popülasyonda montelukastın etkinliğinin düşük olmasından kaynaklandığını düşündük. Çalışmamız, COVID-19'lu geriatrik popülasyonda montelukast tedavisini inceleyen ilk çalışmalardan biridir.

Anahtar Kelimeler: COVID-19, Montelukast, Yaşlı, Geriatri, SARS-CoV-2

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Introduction

Coronavirus disease 2019 (COVID-19) is a pandemic caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), which broke out in 2019. At the onset of the disease, the use of various treatment regimens such as remdesivir and hydroxychloroquine was recommended, but there were conflicting reports in the literature about the effects of these agents. Therefore, studies on the use of effective agents for the treatment have continued (1, 2).

The clinical course in patients can vary from asymptomatic cases to acute respiratory distress syndrome (ARDS). The most common symptoms are cough, fever, malaise, shortness of breath and phlegm. Clinical progression is thought to be mainly due to the release of proinflammatory cytokines (3-5).

Interleukins (IL-6, IL-2, IL-10), procalcitonin (PRC), tumor necrosis factor alpha (TNF- a) and C-Reactive Protein (CRP) levels were detected high in COVID-19 patients (6). In addition, in severe COVID-19; cytokine release syndrome and ARDS, characterized by the uncontrolled release of proinflammatory cytokines, may develop (7). ARDS is the clinical definition of acute injury due to inflammation of the lungs, which is frequently observed in severe COVID-19 infection but not clearly understood due to its complex pathogenesis. The production of interleukins (IL-1/6/8) and TNF released in the early phase and the production of other proinflammatory cytokines in the late phase stimulate leukocyte migration to the infected tissue. Reactive oxygen radicals and proteases released from accumulated and activated leukocytes damage capillary endothelial tissue and alveolar epithelium (8, 9). Due to the increased release of inflammatory cytokines in COVID-19, the use of various anti-inflammatory agents in the treatment has come to the fore.

In the suppression of the proinflammatory process resulting from the damage of in-vitro astrocytes, decreased IL-6 levels were observed in the culture treated with curcumin and piperine compared to the control group (10). Additionally, it has been experimentally shown that the use of montelukast in an in vitro eosinophilic upper respiratory tract inflammation model has a significant inhibitory effect on the production of granulocyte macrophage colony stimulating factor (GM-CSF) and interleukins (IL-6/8) (11).

Coronovirus disrupts the gas exchange balance in alveolar cells with its cytotoxic effect (12). COVID-19 causes pneumonia by reaching alveolar angiotensin converting enzyme-2 (ACE-2) receptors (8, 9). Increased bradykinin level as a result of ACE inhibition may cause increased airway sensitivity and bronchoconstriction. Montelukast, as a selective Leukotriene D4 (LTD4) antagonist, reduces these effects of bradykinin accumulation with an unknown mechanism (13, 14). Montelukast, which is used in the treatment of seasonal allergic rhinitis and asthma, has brought its use in COVID-19 infection due to its previously mentioned eosinophilic anti-inflammatory and cytokine secretion-reducing effect (15, 16).

There are studies suggesting that montelukast can be used in the treatment of COVID-19 (1, 17-19). However, the number of studies evaluating the efficacy of montelukast treatment on elderly patients in COVID-19 is insufficient. The efficacy of montelukast treatment in elderly asthma patients differs from adult asthma patients (20). The aim of our study is to evaluate the clinical and laboratory efficacy of montelukast therapy in patients aged 60 and over in COVID-19 disease.

Material and Method

Our research was planned as a retrospective, single-center, observational study. In this study, the medical records of 75 COVID-19 patients aged 60 and over who were hospitalized in the internal medicine clinic of Ankara Bilkent City Hospital between September 2021 and December 2022 were included. Diagnosis of COVID-19 was confirmed with a reverse transcription polymerase chain reaction (RT-PCR) test from nasopharyngeal swab. Thirty-five patients who were treated with montelukast before hospitalization for COVID-19 were defined as the montelukast treatment group. 40 patients who had never received montelukast treatment were determined as the control group.

The definition of montelukast use was defined as patients using a therapeutic dose of 10 mg once daily in addition to standard treatment during their hospitalization. Patients aged 60 years and older hospitalized for COVID-19 were randomized from the system in both groups.

The patients were not followed up after discharge. Age, gender, prognosis, patient clinic, laboratory parameters, mortality, length of hospital stay and the need for intensive care were examined. Clinical findings and symptoms were evaluated during the hospitalization period. Laboratory findings were evaluated as the hospitalization day of the patients and the parameters checked at discharge. In our hospital, the need for ICU is determined as patients with a MODS (multiple organ dysfunction score) of 1 and above. Mortality was evaluated during the hospitalization period.

Statistical analysis

Statistical analyzes were performed using the SPSS 25.0 program. The conformity of the variables to the normal distribution was evaluated with histogram graphs and Kolmogorov-Smirnov test. While descriptive analysis are presented; mean, standard deviation, median min-max values were used. Categorical variables were compared with the Chi-Square Test. The Mann Whitney U Test was used when evaluating non-normally distributed (non-parametric) variables between two groups. While the change in measured values was evaluated between groups, Repeated Measures Analysis was used. P-values below 0.05 were considered as statistically significant results.

Results

Clinical findings and outcomes were compared between the montelukast group and the control group. There was no statistically significant difference between the groups in terms of cough, dyspnea, gastroenteritis and oxygen demand. There was no significant difference between two groups in terms of intensive care admission and mortality. The data are summarized in Table 1.

Table 1. Clinical findings and outcomes

	Montelukast				
	No		Yes		p
	n	%	n	%	
Female	19	(47.50)	16	(45.71)	0.877
Male	21	(52.50)	19	(54.29)	
O2 demant	22	(55.00)	19	(54.29)	0.951
Dyspnea	22	(55.00)	19	(54.29)	0.951
Cough	28	(70.00)	21	(60.00)	0.364
Gastroenteritis	28	(70.00)	21	(60.00)	0.364
Mortality	4	(10.00)	3	(8.57)	0.832
ICU admission	3	(7.50)	5	(14.29)	0.342

Chi-Square Test
p: Statistical difference between the groups

The length of hospital stay was compared in both groups, with an average of 10.88±7.24 days in the control group, and 10.51±5.44 days in the group receiving montelukast, and no statistically significant difference was found between the groups. When the groups were compared, no significant difference was found in terms of age. The data are summarized in Table 2.

The laboratory parameters of the patients in both groups were compared. The neutrophil count and white blood cell count measured before treatment were significantly lower in the montelukast treatment group. (p=0.022, p=0.016). No significant difference was found in other laboratory parameters. When the p^2 values were compared, there was no difference between the groups. The data are summarized in Table 3.

Table 3. Comparison of laboratory parameters between two groups

	Montelukast			
	No	Yes	p^1	p^2
	Mean±s.s.	Mean±s.s.		
Neutrophil 1 (x10^9/L)	6.38±3.28	4.66±3.05	0.022	0.525
Neutrophil 2 (x10^9/L)	7.06±3.99	6±3.34	0.220	
Lymphocyt 1 (x10^9/L)	1.01±0.53	1.16±0.57	0.252	0.496
Lymphocyt 2 (x10^9/L)	1.62±1.17	1.96±1.34	0.244	
Procalcitonin 1 (mg/dl)	0.16±0.18	0.21±0.41	0.485	0.342
Procalcitonin 2 (mg/dl)	0.39±1.89	0.13±0.27	0.433	
Fibrinogen 1 (mg/dl)	4.23±1.54	4.38±1.63	0.681	0.280
Fibrinogen 2 (mg/dl)	3.44±1.26	4.04±1.38	0.052	
NLR1	6.86±6.62	6.87±6.7	0.577	0.496
NLR2	7.27±9.44	5.77±5.86	0.953	
Eosinophil 1 (x10^9/L)	0.05±0.06	0.05±0.06	0.800	0.589
Eosinophil 2 (x10^9/L)	0.09±0.13	0.08±0.09	0.957	
WBC 1 (x10^9/L)	8.07±3.26	6.29±3.69	0.016	0.757
WBC 2 (x10^9/L)	9.43±4.09	7.98±4.5	0.104	
CRP 1 1 (mg/dl)	34.83±58.74	30.7±65.32	0.823	0.773
CRP 2 (mg/dl)	8.85±21.43	0.71±2.12	0.709	
Ferritin 1 (mg/dl)	316.91±336.99	280.57±297.41	0.592	0.862
Ferritin 2 (mg/dl)	356.74±655.06	307.34±400.24	0.603	
D-Dimer 1 (mg/dl)	2.62±6.63	0.9±0.61	0.811	0.738
D-Dimer 2 (mg/dl)	2.94±7.44	0.74±0.63	0.224	

[1]Independent T-Test
[2]Repeat Measurements Analysis
p^1: Statistical difference between the groups in terms of laboratory values
p^2: Statistical value showing the relationship between pre- and post-treatment laboratory parameters in the groups
1: Parameter before Covid-19 standard treatment
2: Parameter after Covid-19 standard treatment

Table 2. Comparison of age and length of hospital stay between groups

	Montelukast				p
	No		Yes		
	Mean±s.s.	Median (Min-Max)	Ort±s.s.	Median (Min-Max)	
Lenght of Hospital Stay (day)	10.88±7.24	9 (2-32)	10.51±5.44	9 (3-28)	0.810
Age (year)	65.35±4.31	64 (60-75)	66.14±5.04	64 (60-75)	0.465

İndependent t test
p: Statistical difference between the groups

Discussion

There are studies suggesting that leukotriene antagonists can be used in the treatment of COVID-19 disease (1, 17-19, 21-22). There is no study in the literature evaluating the efficacy of montelukast treatment in elderly COVID-19 patients. There are studies in the literature showing that the effectiveness of montelukast treatment in asthma patients differs between adults and the elderly (20,23). In our study, we examined whether this difference exists in the treatment of elderly COVID-19 patients.

In our study, there was no significant difference in prognosis, mortality and laboratory parameters after montelukast treatment in patients over the age of 60 who were diagnosed with COVID-19 compared to the control group. Many studies in the literature stated that treatment had positive effects on prognosis, laboratory and mortality (1,17-19, 21-22). In the study of Schihilone et al., it was emphasized that further studies should be conducted on the long-term use of montelukast in elderly asthma patients. They noted that available data on the role of montelukast in the treatment of elderly asthmatics in the study do not indicate a specific role for this drug in this age group. (24). We thought that the lack of a similar effect of montelukast treatment in our study may be due to the low efficiency of the treatment in elderly patients.

It has been shown in the literature that these drugs have protective effects after cerebral ischemia and reperfusion (25). We suggest examining the effects of these drugs on elderly patients in Covid 19-induced cerebral ischemia.

Gastroenteritis has been reported as a side effect of montelukast treatment in the literature (26). However, in our study, inconsistent with the literature, we could not detect a significant difference between the treatment group and the control group. In the study of Scichilone et al., elderly patients had the highest incidence of headache, abdominal pain, nausea and diarrhea (24). We recommend studying the effect of montelukast treatment in geriatric patients with diarrhea in large patient groups. Because elderly patients are more sensitive to electrolyte disturbances due to Covid 19-related nausea, vomiting and diarrhea.

Kerget et al. reported that patients receiving montelukast treatment had significantly lower levels of lactate dehydrogenase, D-dimer(18). However, no significant difference was found in our study. In addition, we did not detect any significant change in these values before treatment and before discharge.

Limitations

There were some limitations in our study. Our study includes symptoms at the time of hospitalization. We could not examine the effect of montelukast treatment on these symptoms. In addition, the small number of patients was our limitation. The patients in our study had no lung disease diagnosed. However, we thought that there may be patients with previously undiagnosed lung disease. In addition, the fact that the mean age of our patient groups matched the early geriatric population was a limitation of our study. We recommend that different studies should be conducted on elderly geriatric patients.

Conclusion

In conclusion, many side effects of montelukast treatment are similar to the symptoms detected in COVID-19. We recommend conducting large-scale studies investigating the effects of montelukast treatment on these symptoms in elderly patients. Although montelukast treatment has positive effects on clinical and prognosis on many COVID-19 cases in the literature, we did not detect this efficacy in the population over 60 years of age in our study. In the study of Sánchez et al. montelukast treatment was found effective in long-term use in elderly patients, unlike younger patients (27). Therefore, we recommend using montelukast therapy for a longer period of time in patients with COVID-19 and further comprehensive studies should be conducted in this regard.

Our study is one of the first to examine montelukast therapy in the geriatric population with COVID-19. Unlike studies involving all age groups, we did not find a positive effect on the prognosis and clinic in patients over 60 years of age.

Ethical Approval

Ethical approval for the study was granted by the Ethics Committee of Ankara City Hospital (Date: 12/04/2023, Number: E2-23-3911).

Authorship Contributions

All of the authors declare that they have all participated in the design, execution, and analysis of the paper and that they have approved the final version.

Conflict of Interests

The authors have no conflicts of interest to declare.

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