J Nephropharmacol. 2024; x(x): e11650.

https://jnephropharmacology.com DOI: 10.34172/npj.2023.11650

Journal of Nephropharmacology

Evaluation of the effect of montelukast drug in improving the clinical condition of patients with COVID-19 in referral hospitals in Isfahan; a randomized clinical trial

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ARTICLE INFO

Article Type:
Clinical Trial

Article History:
Received: 7 Aug. 2023
Accepted: 9 Nov. 2023
ePublished: 29 Jan. 2024

Keywords:
COVID-19
Leukotriene
Montelukast
Viral infection

ABSTRACT

Introduction: COVID-19 is associated with a cascade of inflammatory responses potentially lead to devastating outcomes.

Objectives: The current study aims to investigate the efficacy of montelukast, a leukotriene receptor antagonist (LTRA), on laboratory parameters in COVID-19 infection.

Patients and Methods: The current randomized clinical trial (RCT) conducted on 67 patients with moderate-to-severe COVID-19 pneumonia in 2020-2021. All patients received treatments according to the national guidelines, while the case group additionally applied 10 mg montelukast for 14 days. The clinical disease improvement and laboratory data (complete blood cells count and differentiation, C-reactive protein (CRP), erythrocyte sedimentation rate (ESR), D-dimer, blood urea nitrogen (BUN), creatinine (Cr), aspartate aminotransferase (AST), alanine aminotransferase (ALT), lactate dehydrogenase (LDH) were assessed within two weeks after the infection and compared between the groups.

Results: Baseline assessed parameters did not differ between the groups ($P>0.05$). A significant decrease in pulse rate, also in normal ranges, was notified in the montelukast-treated group compared with the baseline ($P=0.001$) and with controls ($P=0.033$); however, other vital signs were not statistically different ($P>0.05$). CRP ($P<0.001$), ESR ($P=0.008$), BUN ($P=0.015$), and AST ($P<0.001$) significantly decreased in the post-intervention assessment of the montelukast-treated group. The comparison of the groups in post-intervention reviews revealed significantly lower CRP ($P=0.042$) and D-dimer ($P=0.008$) in the intervention group versus controls.

Conclusion: Based on the findings of this study, montelukast use with a daily dose of 10 mg for 14 days could remarkably decrease inflammatory indices in patients with COVID-19 pneumonia. Further studies on this issue are strongly recommended.

Trial Registration: The trial protocol was approved by the Iranian Registry of Clinical Trials (identifier: IRCT20181208041886N3, https://www.irct.ir/trial/51633; ethical code #IR.MUI.MED.REC.1399.382).

Implication for health policy/practice/research/medical education:
Montelukast can remarkably decrease inflammatory indices in patients with COVID-19 pneumonia.

Please cite this paper as: Pourahmad M, Aria A, Momenzadeh M, Nikoukar F, Ataei B, Shams M, Shahzamani K, Nasirharandi S. Evaluation of the effect of montelukast drug in improving the clinical condition of patients with COVID-19 in referral hospitals in Isfahan; a randomized clinical trial. J Nephropharmacol. 2024;x(x):e11650. DOI: 10.34172/npj.2023.11650.

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Clinical Trial

Introduction

SARS-CoV2 that was emerged in the late December 2019 in China caused clusters of respiratory infection(1). In February 2020, the World Health Organization (WHO) announced this outbreak as COVID-19 and by March officially represented its pandemic (2). The clinical spectrum of COVID-19 varies from non-symptomatic conditions to mild manifestations of self-limited respiratory illness to the Severe courses progressively affecting the respiratory system, acute respiratory distress syndrome (ARDS), multi-organ damage and mortality (3). Evidence in the literature have presented that the most common clinical characteristics of COVID-19 include fever, cough, fatigue, sputum production, and shortness of breath. Despite the efforts made for the management of this disease, the primary outcomes using hydroxychloroquine revealed inefficacy and further investigations regarding remdesivir showed insufficient and controversial outcomes (4).

Accordingly, further efforts were made to distinguish the potential clinical manifestations and pathophysiological mechanisms by which SARS-CoV-2 affect the body cells and provide medical approaches to control the disease, prevent from the infection, minimize the clinical symptoms and improve the outcomes (5). Increasing level of evidence suggest that COVID-19 infection severity is modulated by the excretion of cytokines such as C-reactive protein (CRP), interleukin (IL)-6, procalcitonin, IL-2, IL-10 and tumor necrosis factor-alpha (TNF-α). This cytokine release is significant to the extent that cytokine storm is responsible for severe COVID-19 infection, ARDS, multi-organ failure and mortality (6).

The murine mode assessing influenza infection revealed that leukotriene receptor in type-1 alveolar cells was associated with ARDS in this infection. Accordingly, a study on mice showed that leukotriene receptor antagonists (LTRAs) could prevent fatal pneumonia caused by influenza. LTRA restricted the virus uptake by the terminal airway alveolar cells, involved in oxygen exchange (7). Therefore, it was culminated to a conclusion that virally mediated lung injury from SARS-CoV-2 and influenza may precipitate similar molecular mechanisms in the lung parenchyma (8).

Montelukast, among other LTRAs, has been successfully applied for the management of allergic rhinitis and asthma. Furthermore, it has been suggested that LTRAs can regulate upper airway inflammatory reactions by substantial inhibition of granulocyte-macrophage colony-stimulating factor (GM-CSF), IL-6, IL-8 and TNF-α leading to the reduction of pro-inflammatory responses responsible for adverse outcomes of COVID-19 (8,9). Accordingly, it is assumed that LTRAs, such as montelukast, might potentially contribute to the decreased risk of COVID-19 Severe manifestations. Despite the efforts made to assess montelukast effect on the clinical presentations of COVID-19, paucity of knowledge is available (4,10,11).

Objectives

The current study aims to investigate the efficacy of montelukast on COVID-19 severity and response to treatment.

Patients and Methods

Study population

The randomized clinical trial (RCT) enrolled 67 patients who had tested positive for COVID-19. The trial was conducted at the COVID-19 clinics affiliated with Isfahan University of Medical Sciences between August 2020 and June 2021.

Over 15 years old patients with clinical manifestations of COVID-19 infection (fever, cough, fatigue, myalgia, productive sputum, shortness of breath) referring to the Infectious and Tropical Diseases Specialist whose infection was confirmed by COVID-19 real-time polymerase chain reaction (RT-PCR) entered to the study if they were applicable for further follow-up.

The presence of concurrent other diseases (bacterial, fungal, cardiopulmonary or rheumatological disorders) justifying the symptoms, the concurrent use of rifampin and phenobarbital, applying other medications than the guidelines used in this study, inability to follow the patients and over 20% defect in the medical records were defined as the exclusion criteria.

The study patients entered the study through block randomization sampling and then, were randomly assigned to one of the intervention or control groups using Excel Random Allocation Software. Each block consisted of two patients. The patients and the person responsible for the assessment of the therapeutic approach outcomes were blinded to the groups of the study.

Intervention

All the patients were treated according to the national guideline provided by the health ministry. The intervention group was treated with daily 10 mg montelukast (Abidi Company, Iran) for 14 days, while the controls received placebo produced by pharmacy faculty, Isfahan university of medical sciences.

Data collection

The patients were primarily categorized as moderate-to-severe pneumonia based on the WHO classifications (12). They were followed for a period of 14 days.

The patients' primary information was obtained at the first visit. The data included demographic characteristics (age and gender), at onset clinical presentations (fever, cough, shortness of breath, and gastrointestinal symptoms), chronic medical comorbidities (hypertension, diabetes mellitus, hyperlipidemia, cardiovascular disease, cancer and chronic pulmonary disease—chronic obstructive pulmonary disease or asthma) and primary medications

(remdesivir and hydroxychloroquine) were recorded.

Besides, the on-admission vital signs (respiratory rate, pulse rate, systolic and diastolic blood pressure and oxygen saturation) and laboratory parameters including complete blood count and differentiation (CBC diff), CRP, erythrocyte sedimentation rate (ESR), D-dimer, blood urea nitrogen (BUN), creatinine (Cr), alanine aminotransferase (ALT), aspartate aminotransferase (AST) and lactate dehydrogenase (LDH) were recruited from the medical records.

Primary outcomes

The patients were followed for 14 days. The primary outcome of this study was to assess the clinical outcomes including vital signs and laboratory parameters at baseline versus within the next 14 days.

Statistical analysis

The obtained data were entered into the Statistical Package for Social Sciences (SPSS; version 16.0, SPSS Inc., Chicago, IL, USA). The descriptive data were presented in mean and standard deviation for the continuous variable, as well as absolute numbers and percentages for categorical variables. The chi-square test and Fisher's exact test were utilized to compare the categorical variables between the groups. The continuous variables were compared using independent t-test and paired t-test. A *P* value of less than 0.05 was considered as a significant level.

Results

The current study has been conducted on 67 patients with the manifestations moderate-to-severe COVID-19 pneumonia among which 28 ones (41.8%) received montelukast, while the remained 39 ones (58.2%) did not (Figure 1). The mean age of the studied population is 51.78 ± 9.81 years old consisting of 40 males (59.70%). Coughing (80.59%), dyspnea (59.70%) and fever (59.70%) were the most common presentations of the studied patients, respectively.

The studied groups were not statistically different regarding age ($P=0.346$), gender distribution ($P=0.886$) and chronic medical diseases ($P=0.153$), the primary symptoms of COVID-19 ($P>0.05$) and the received medications other than montelukast ($P>0.05$). Detailed information is demonstrated in Table 1.

Vital signs and laboratory parameters have been presented in Table 2. Baseline assessed parameters did not differ between the groups. Significant decrease in pulse rate, also in normal ranges, was notified in the montelukast -treated group compared with their baseline ($P=0.001$) and with controls ($P=0.033$); however, other vital signs were not statistically different ($P>0.05$). Our study showed WBC count and hemoglobin level remarkably decreased in both groups at the end of the interventions ($P<0.05$); however, the intervention group and the controls did not differ ($P>0.05$). Moreover, CRP ($P<0.001$), ESR ($P=0.008$), BUN ($P=0.015$) and AST

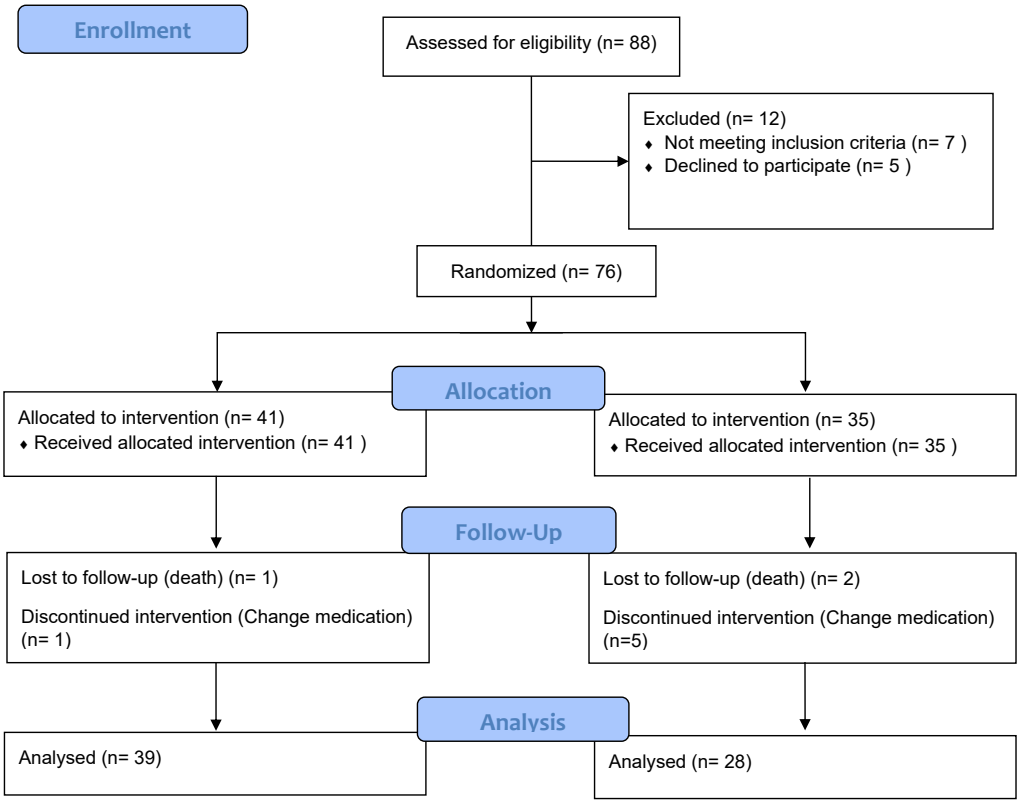

Figure 1. CONSORT flowchart of the study.

Table 1. Demographic, medical, clinical and therapeutic characteristics of the studied population

Variables	Control (n = 39)	Montelukast intervention (n = 28)	*P* value
Demographic characteristics			
Age (years), mean ± standard deviation	50.82±10.62	53.14±8.70	0.346[a]
Gender (male), n (%)	23 (59)	17 (60.7)	0.886[b]
Chronic medical disease, n (%)			
Chronic medical disease (yes)	9 (23.1)	11 (39.3)	0.153[b]
Hypertension	11 (28.2)	10 (35.7)	0.513[b]
Diabetes mellitus	9 (23.1)	7 (25)	0.586[b]
Ischemic heart disease	5 (12.8)	6 (21.4)	0.348[b]
Dyslipidemia	11 (28.2)	7 (25)	0.77[b]
Malignancies	3 (7.7)	2 (7.1)	0.999[c]
Asthma	4 (10.3)	3 (10.7)	0.999[b]
COVID-19 associated symptoms, n (%)			
Cough	31 (79.5)	23 (82.1)	0.786[b]
Fever	22 (56.4)	18 (64.3)	0.517[b]
Dyspnea	23 (59)	17 (60.7)	0.886[b]
Gastrointestinal symptoms	10 (25.6)	13 (46.4)	0.077[b]
COVID-19 medications			
Remdesivir	25 (64.1)	18 (64.3)	0.998[a]
Hydroxychloroquine	4 (10.3)	0 (0)	0.134[c]

[a] Independent t-test; [b] Chi-square; [c] Fisher's exact test.

($P<0.001$) significantly decreased in post-intervention assessment of montelukast-treated group. Besides, the comparison of the groups in post-intervention assessments revealed significantly lower CRP ($P=0.042$) and D-dimer ($P=0.008$) in the intervention group versus controls.

Discussion

The current study tried to evaluate the efficacy of montelukast, a LTRA, to improve COVID-19 infection. The studied populations were similar in terms of demographic, chronic medical disease and at onset medical and clinical characteristics as well as the administered medications; therefore, the differences between the groups could merely attribute to the effects of montelukast. We found dramatic decrease in the levels of inflammatory biomarkers, CRP and ESR, among those treated with montelukast; however, CRP only was significantly lower in the intervened group. WBC count, hemoglobin level, BUN and AST were the other parameters that statistically decreased in both groups.

The findings of our study are in line with the previous investigations in the literature, as most of them emphasized on the usefulness of montelukast in the trend of improvement in parameters in COVID-19 infection, particularly inflammatory indices including CRP and ESR (13,14). In addition, further studies have presented promising outcomes regarding montelukast use in terms of symptoms relief, alleviation of disease severity in critically ill patients and response to treatment (8,15-17). Khan et al assessed the influence of montelukast with 10 mg daily dose on the consequences of severe COVID-19 in critically ill patients and represented that the intervention group experienced less clinical deterioration than the controls; however, similar to our findings reported significant decrease in CRP levels in montelukast -treated patients versus the controls (1). The other study by Parisi and colleagues compared he efficacy of montelukast versus inhaled corticosteroids on wheezing induced by COVID-19 infection and declared comparable outcomes (15). May et al were the other group of researchers who intended to assess montelukast use in COVID-19 and stated the significant reduced mortality among the patients treated with this agent (17).

The mechanisms by which montelukast might potentially affect COVID-19 has been hypothesized. The most principal etiology of death in COVID-19 is respiratory failure with progressive unresponsiveness to the treatment (18, 19). ARDS is the devastating process occurring among the COVID-19 patients with severe lung involvement. This condition is the result of an acute inflammatory lung injury which pathogenesis is not well-elucidated; however, probably occurs in response to an intense inflammation (20). Recent investigations showed, pro-inflammation is a process initiating with the production of IL-6, IL-10, TNF-α and IL-1, while other cytokines release in the following. The consequence of this cytokine overproduction is the migration of leukocytes to the injured region. This leukocyte accumulation activates and induces overproduction and over-secretion of reactive oxygen species and proteases that damages capillary endothelium and alveolar epithelium (21). Montelukast as a LTRA has an inhibitory effect on the production of IL-6, IL01b and TNF-α that potentially restricts lung injury in COVID-19 (10).

Table 2. The comparison of vital signs and laboratory parameters between the groups

Variables		Control (n=39)	Montelukast intervention (n=28)	*P* [a]
Vital signs, mean±standard deviation				
Respiratory rate (min-1)	On-admission	21.54±3.24	21.14±3.86	0.651
	Post-intervention	21.92±5.29	19.96±3.11	0.084
P [b]		0.699	0.243	
Pulse rate (min-1)	On-admission	87.97±17.76	83.21±19.40	0.302
	Post-intervention	90.36±18.32	76.21±14.45	0.001
P [b]		0.536	0.033	
Systolic blood pressure (mm Hg)	On-admission	116.77±13.19	116.86±11.80	0.978
	Post-intervention	114.74±21.78	111.79±16.08	0.545
P [b]		0.622	0.245	
Diastolic blood pressure (mm Hg)	On-admission	73.31±10.89	73.93±8.19	0.800
	Post-intervention	70.82±13.25	71.54±10.20	0.812
P [b]		0.060	0.097	
O2 saturation (%)	On-admission	93.26±6.19	93.39±3.76	0.918
	Post-intervention	90.10±7.80	91.36±5.76	0.473
P [b]		0.060	0.097	
Hematological indices, mean±standard deviation				
White blood cells (mL-1)	On-admission	11389.47±6321.77	11675±4993.97	0.844
	Post-intervention	7679.49±3345.40	8775±4210.18	0.240
P [b]		0.002	0.007	
Neutrophil ratio (%)	On-admission	81±8.07	81.37±10.63	0.870
	Post-intervention	80.87±9.30	83.50±9.54	0.265
P [b]		0.724	0.255	
Lymphocyte ratio (%)	On-admission	12.19±5.75	11.96±7.93	0.89
	Post-intervention	11.24±7.30	9±5.56	0.18
P [b]		0.732	0.095	
Platelet count (ml-1)	On-admission	203236.84±106269.78	192037.04±111729.58	0.683
	Post-intervention	168487.18±55867.26	162296.30±56949.25	0.662
P [b]		0.034	0.100	
Hemoglobin (g/dL)	On-admission	12.41±1.68	12±2.23	0.399
	Post-intervention	11.29±2.07	11.12±2.51	0.757
P [b]		0.011	0.036	
Other laboratory indices				
C-reactive protein	On-admission	57.28±32.24	60.18±40.65	0.746
	Post-intervention	43.89±42.63	24.54±33.07	0.042
P [b]		0.060	<0.001	
Erythrocyte sedimentation rate	On-admission	46.33±26.28	52.37±25.58	0.357
	Post-intervention	42.15±37.17	45.16±29.39	0.763
P [b]		0.785	0.008	
D-dimer	On-admission	1812.86±1505.11	1292.90±1294.36	0.135
	Post-intervention	3770.58±2879.24	1670.12±1643.10	0.008
P [b]		0.634	0.052	
Blood urea nitrogen	On-admission	25.51±19.31	32.71±18.18	0.128
	Post-intervention	18.36±9.86	22.82±12.76	0.111
P [b]		0.006	0.015	

Table 2. Continued

Variables		Control (n=39)	Montelukast intervention (n=28)	*P* [a]
Creatinine	On-admission	1.08±0.78	1.15±0.47	0.660
	Post-intervention	1.05±0.25	1.28±0.66	0.051
P [b]		0.818	0.378	
Alanine aminotransferase	On-admission	44.90±55.39	47.25±33.04	0.835
	Post-intervention	46.11±60.21	88.32±150.80	0.130
P [b]		0.993	0.190	
Aspartate aminotransferase	On-admission	39.64±25.82	51.52±30.54	0.098
	Post-intervention	31.86±21.18	30.16±13.87	0.726
P [b]		0.010	<0.001	
Lactate dehydrogenase	On-admission	928.14±836.24	781.76±350.06	0.413
	Post-intervention	1235.31±1345.45	891.91±329.57	0.412
P [b]		0.597	0.452	

[a] Independent t-test; [b] Paired t-test.

The other pathway by which montelukast can have positive effect on the patients with lung involvement due to COVID-19 refers to its inhibitory effect against bradykinin production that in turn limits smooth muscles contraction (22). The investigations on the patients with asthma, influenza and allergic rhinitis revealed promising data in term of montelukast use to control wheezing due to airway hyper-responsiveness to the environmental allergens and smooth muscles contractions (23, 24).

The other mechanism by which montelukast might protect the lungs is its potent antagonizing effect on cysteinyl leukotriene receptor which significantly suppresses oxidative stress. Csteinyl leukotrienes can physiologically affect the production of the cytokines; therefore, the high doses of montelukast might suppress T-helper-2 cytokines which causes anti-inflammatory effect following reduced protein expression occurring following reduced levels of IL-4, IL-5 and IL-13 (25).

As mentioned above, montelukast can limit viral invasion to the lungs and prevent adverse consequences through diverse mechanisms; however, the findings in the current study were not consistent with literature.

Conclusion

Based on the findings of this study, montelukast use with daily dose of 10 mg for 14 days could remarkably decrease inflammatory indices in the patients with COVID-19 pneumonia. Further studies in this issue are strongly recommended.

Limitations of the study

The small sample population of the study and indefinite definition of response to the treatment are the most significant limitations of this study.

Authors' contribution

Conceptualization: MP
Methodology: MP
Validation: M.P, FK, BA, MSH, KSH
Formal Analysis: MM
Investigation: MM, SN,AA
Resources: MM
Data Curation: MM
Writing—Original Draft Preparation: MM,AA
Writing—Review and Editing: MM
Visualization: MM
Supervision: MP
Project Administration: MP

Ethical issues

The study was conducted in accordance with the principles of the Declaration of Helsinki. The Ethics Committee of Isfahan University of Medical Sciences approved the research (Ethical code#IR.MUI.MED.REC.1399.382). All participants provided written informed consent before any intervention. The trial protocol was registered in the Iranian Registry of Clinical Trials (identifier: IRCT20181208041886N3, https://www.irct.ir/trial/51633). The authors have taken care to address ethical issues, including plagiarism, data fabrication, and double publication.

Conflicts of interest

The authors declare that they have no competing interests.

Funding/Support

Dr. Abidi Pharmaceuticals Company provided some support for this study and the current study was financially supported by the Vice-Chancellery of Research of Isfahan University of Medical Sciences.

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