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Montelukast in hospitalized patients diagnosed with COVID-19

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ABSTRACT

Objective: Several therapeutic agents have been assessed for the treatment of COVID-19, but few approaches have been proven efficacious. Because leukotriene receptor antagonists, such as montelukast have been shown to reduce both cytokine release and lung inflammation in preclinical models of viral influenza and acute respiratory distress syndrome, we hypothesized that therapy with montelukast could be used to treat COVID-19. The objective of this study was to determine if montelukast treatment would reduce the rate of clinical deterioration as measured by the COVID-19 Ordinal Scale.

Methods: We performed a retrospective analysis of COVID-19 confirmed hospitalized patients treated with or without montelukast. We used "clinical deterioration" as the primary endpoint, a binary outcome defined as any increase in the Ordinal Scale value from Day 1 to Day 3 of the hospital stay, as these data were uniformly available for all admitted patients before hospital discharge. Rates of clinical deterioration between the montelukast and non-montelukast groups were compared using the Fisher's exact test. Univariate logistic regression was also used to assess the association between montelukast use and clinical deterioration. A total of 92 patients were analyzed, 30 who received montelukast at the discretion of the treating physician and 62 patients who did not receive montelukast.

Results: Patients receiving montelukast experienced significantly fewer events of clinical deterioration compared with patients not receiving montelukast (10% vs 32%, $p=0.022$). Our findings suggest that montelukast associates with a reduction in clinical deterioration for COVID-19 confirmed patients as measured on the COVID-19 Ordinal Scale.

Conclusions: Hospitalized COVID-19 patients treated with montelukast had fewer events of clinical deterioration, indicating that this treatment may have clinical activity. While this retrospective study highlights a potential pathway for COVID-19 treatment, this hypothesis requires further study by prospective studies.

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Background

Coronavirus disease 2019 (COVID-19), caused by the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), has been the focal point of the global community since its outbreak in December 2019 due to its impact on international health and mortality, and the global economy. The lockdown in response to the pandemic has greatly affected the worldwide economy with the threat of depression. Following the release of conflicting reports of the efficacy of hydroxychloroquine and the expedited clinical trial evaluation of remdesivir, the biomedical community has struggled to find sufficient, effective therapeutic regimens to manage patients with COVID-19 infection (1). The clinical spectrum of COVID-19 ranges from mild, self-limiting respiratory tract illness to severe progressive pneumonia, acute respiratory distress syndrome

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(ARDS), multi-organ failure, and death (2). In a series outlining the clinical characteristics of hospitalized COVID-19 confirmed patients, common symptoms included fever (88.7%), cough (67.8%), fatigue (38.1%), sputum production (33.7%), and shortness of breath (18.7%) (2). To date, there are no accepted guidelines for the supportive care of COVID-19 patients and the effective management of symptoms, and stop gap therapies represent an unmet need.

Increasing evidence suggests that the severity of COVID-19 infection is modulated by excessive inflammation, as there are increased levels of interleukin-6 (IL-6), C-Reactive Protein (CRP), procalcitonin, interleukin-2 (IL-2), interleukin-10 (IL-10), and tumor necrosis factor alpha (TNF-α) observed in patients who undergo hospitalization (3). Moreover, patients with severe COVID-19 infection develop the potentially lethal inflammatory complications of cytokine release syndrome and ARDS (4). In addition, SARS-CoV-2 directly infects alveolar cells, further limiting gas exchange within the lung (5).

In a murine model of influenza infection, alveolar injury, and compromised respiratory function, leading to ARDS was mediated by leukotriene receptor signaling in Type-1 Alveolar Epithelial Cells (T1AECs) (6). In this preclinical study by Braciale et al., leukotriene receptor antagonists (LTRAs) prevented the development of fatal influenza pneumonia in mice with influenza infection (6). LTRAs prevented the uptake of influenza virus by the terminal airway alveolar cells and infection of these cells, involved in oxygen exchange (6). This infection in the lungs manifested as diffuse alveolar damage leading to ARDS (6). Therefore, it appears that virally mediated lung injury from SARS-CoV-2 and influenza may precipitate similar molecular mechanisms in the lung parenchyma resulting in ARDS.

LTRAs, including montelukast, are used to treat seasonal allergic rhinitis and asthma, and evidence suggests that its administration can be used in other upper airway inflammatory diseases (7). Mullol et al. explored montelukast's anti-inflammatory properties in an *in vitro* model of upper eosinophil inflammation and found that montelukast had a significant inhibitory effect on the production granulocyte-macrophage colony-stimulating factor (GM-CSF), interleukin-6 (IL-6), and interleukin-8 (IL-8) (8). These anti-inflammatory effects on epithelial cell cytokine secretion and on eosinophil survival suggest that montelukast may contribute to the reduction of eosinophilic inflammation in upper-airway inflammatory diseases. Also, in an additional mouse model of ARDS, montelukast decreased the release of pro-inflammatory cytokines implicated in severe COVID-19 (IL-6 and TNF-α) (9). In sum, this indirect evidence suggests that LTRAs such as montelukast may prevent progression to severe lung disease associated with COVID-19. Accordingly, clinicians reported that montelukast helps hospitalized patients with COVID-19 recover sooner and/or reverse respiratory decline (10). Montelukast therapy reduces the number of pro-inflammatory cytokines and, thus, may serve as a potential treatment for COVID-19 (1).

We examined the impact of montelukast administration in confirmed COVID-19 positive patients who were hospitalized based on the understanding that montelukast can reduce inflammatory markers contributing to improved pulmonary function. The objective of this retrospective review was to evaluate the change in clinical deterioration following montelukast administration. We hypothesized that montelukast administration in hospitalized patients with confirmed COVID-19 infection would reduce clinical deterioration as measured by the COVID-19 Ordinal Scale (11).

Materials and methods

We conducted a retrospective, IRB-approved, study at Robert Wood Johnson University Hospital, Rutgers University (Pro2020001307) in New Brunswick, NJ. From late March to early April 2020, upon admission, at the discretion of the treating provider, patients received montelukast. We identified a group of 30 patients who received montelukast and 62 non-montelukast (control) patients. All patients identified were hospitalized for at least three days. The patients who received montelukast were started on Day 1 of hospital admission with the standard dose of 10 mg oral once a day (QD). All patients in this group were not previously been treated with montelukast. The control group of patients was selected consecutively from a hospital database listing confirmed COVID-19 patients who survived to at least the fourth day of admission. Patients in both the control and montelukast group were included from the hospital database listing of confirmed COVID-19 patients. Two hundred and fifty-six patients were screened for the following factors: hospitalization length of stay and montelukast. All patients in this study were not taking montelukast prior to admission and were not using it as a means of asthmatic control. Montelukast was prescribed at health care provider's discretion as supplemental care for COVID-19 infection. Physician discretion was not mandated by any guidelines within the hospital protocol and was prescribed by a variety of practitioners.

Table 1. COVID-19 Ordinal Scale for clinical improvement (11).

Patient state	Descriptor	Score
Uninfected	No clinical or virologic evidence of infection	0
Ambulatory	No limitation of activities	1
	Limitation of activities	2
Hospitalized, mild disease	Hospitalized, no oxygen therapy	3
	Oxygen by mask or nasal prongs	4
Hospitalized, severe disease	Non-invasive ventilation or high-flow oxygen	5
	Intubation and mechanical ventilation	6
	Ventilation + additional organ support – vasopressors, RRT, ECMO	7
	Death	8

From March 19–March 27, 2020, the standard treatment for patients hospitalized at Robert Wood Johnson University Hospital with confirmed COVID-19 consisted of hydroxychloroquine 400 mg BID for 5 days and azithromycin. After this time, this institutional guideline changed to remove hydroxychloroquine from the treatment regimen. All patients but one included in this study received hydroxychloroquine. Data collected included patient demographics, medical history, vital signs including pulse oximetry, laboratory test results, medication administration, supplemental oxygen usage, physician assessments, and radiology reports. Based on the objectivity of assessing supplemental oxygen use, these data were the focus of this study. Specifically, we employed the COVID-19 Ordinal Scale, which allowed for categorization of oxygen escalation through a widely accepted, standardized scale (Table 1) (11). For the purposes of this study, patients were included only if found to have an Ordinal Scale score of 3 or higher indicating the need for hospitalization at the time of their assessment. When analyzing Ordinal Scale scores, laboratory results, and vital signs in both the montelukast and non-montelukast groups, a delta calculation was used between Day 1 and Day 3. Day 1 and Day 3 were chosen to be analyzed as it was the most consistent time point, given the variations in lengths of stay.

Statistical analysis

We first assessed differences in baseline patient and treatment characteristics (Table 2) between the montelukast and non-montelukast groups. Association of categorical variables was assessed with the Fisher's exact test, as appropriate. Means of continuous variables were compared with an independent two-sample's *t*-test or Wilcoxon's rank-sum test, depending on normality of their distributions.

Additionally, we assessed the differences in Day 1 key laboratory values (white blood cell count [WBC], creatinine, lactic acid dehydrogenase (LDH), CRP, ferritin, and D-dimer) between groups, as well as differences in the change in laboratory values from Day 1 to Day 3, using the Wilcoxon's rank-sum test and Wilcoxon's signed-rank test, respectively.

Table 2. Baseline demographics and clinical characteristics in montelukast ($n = 30$) and non-montelukast patients ($n = 62$).

	Montelukast ($N = 30$)	**Non-montelukast ($N = 62$)**	*p* value
Median age (range)	67 (37–93)	59 (46–75)	0.011*
Male, *n* (%)	15 (50)	38 (61.3)	0.30
Race, *n* (%)			0.51
Asian	3 (10)	8 (12.9)	
Black	4 (13.3)	8 (12.9)	
Hispanic	7 (23.3)	24 (38.7)	
White	3 (10)	5 (8.1)	
Other	13 (43.3)	17 (27.4)	
Symptoms on Admission, *n* (%)[a]			
Fever	23 (76.7)	52 (83.9)	0.40
Cough	27 (86.7)	47 (75.8)	0.11
Shortness of breath	22 (73.3)	48 (77.4)	0.67
Baseline comorbidity, *n* (%)			
Cardiac disorder	13 (43.3)	15 (24.2)	0.06
Diabetes	13 (43.3)	23 (37.1)	0.57
Hypertension	21 (70)	34 (54.8)	0.16
Hyperlipidemia	9 (30)	17 (27.4)	0.80
Cancer	2 (6.7)	3 (10)	0.66
Asthma	11 (36.7)	4 (6.5)	0.0005*
Steroid use between Day1 and Day 3 – number only, *n* (%)	5 (16.7)	14 (22.6)	0.51
Baseline immunosuppression, *n* (%)	3 (10)	8 (12.9)	0.67
Medications during hospital stay, *n* (%)			
Anticoagulants	27 (90)	58 (93.5)	0.55
Statin or ARB	12 (40)	20 (46.8)	0.54
Glucocorticoids	10 (33.3)	25 (40.3)	0.52
Azithromycin	4 (13.3)	25 (40.3)	0.01*
Median length of hospitalization in days (IQR)	7 (4–10.5)	8(6–12)	0.26

*Statistically significant *p* values.
[a]Patient reported symptoms.

We chose "clinical deterioration" as the primary end point, a binary outcome defined as any increase in the COVID-19 Ordinal Scale value from Day 1 to Day 3 of hospital stay, as these data were uniformly available for all admitted patients before discharge. Rates of clinical deterioration between the montelukast and non-montelukast groups were compared using the Fisher exact test. Univariate logistic regression was also used to assess the association between montelukast use and clinical deterioration. Multivariable logistic regression was also used to control for age, given the difference in age between groups. Because of the limited number of events, we included a total of two variables in multivariable models (receipt of MTK and age). Odds ratio (OR) along with 95% confidence interval were estimated. To assess the potential confounding effect of other covariates on the primary outcome, we conducted three separate sensitivity analyses excluding patients with asthma, patients who received azithromycin, and patients who received steroids (dexamethasone and prednisolone).

All statistical tests were two-sided, and we considered $p < 0.05$ as statistically significant and $p < 0.10$ as a trend toward significance. We performed analyses using SAS version 9.4 (Cary, NC).

Results

Baseline characteristics

Table 2 demonstrates baseline patient and treatment characteristics in the montelukast and non-montelukast groups. Patients who received montelukast were older (median age, 67 years vs. 59 years, $p = 0.01$), had a greater proportion with asthma (36.7% vs. 6.5%, $p = 0.0005$), and received azithromycin at a lower rate (13% vs. 40%, $p = 0.009$). All patients were started on montelukast at the time of admission and did not have montelukast cited as an outpatient medication. There were no significant differences in other characteristics between groups, including Day 1 COVID-19 Ordinal Scale distribution ($p = 0.61$) or receipt of steroids between days 1 and 3 of hospital stay (16.7% for montelukast group vs. 22.6% for non-montelukast group, $p = 0.51$).

Laboratory values

Baseline laboratory values (Table 3), as well as changes in laboratory values from Day 1 to Day 3, between groups were assessed (Table 4). Baseline LDH was lower in the montelukast group (median 344.5 vs. 439, $p = 0.04$). No other differences in baseline laboratory values were noted. There were no differences in the change in laboratory values (from Day 1 to Day 3) between groups.

Table 3. Median laboratory values at baseline.

Laboratory values – median (range)	Montelukast	Non-montelukast	*p*-value
WBC	7.2 (2.9 – 21.5)	7.55 (2.1 – 20.9)	0.68
D-Dimer	898.5 (359 – 11984)	888 (8.3 – 103565)	0.75
Ferritin	598.5 (80 – 5983)	937.5 (63 – 15708)	0.23
LDH	344.5 (153 – 625)	439 (156 – 1716)	0.04
CRP	10.72 (2.47 – 29.19)	12.8 (0.57 – 39.8)	0.14
Creatinine	0.9 (0.2 – 6.5)	0.9 (0.3 – 15.5)	0.85
Pulse Ox	93% (61%–99%)	91% (57%–100%)	0.67

Table 4. Laboratory values of Delta Day 1 to Day 3.

Laboratory value – Delta Day 1 to Day 3	Montelukast	Non-montelukast	*p*-value
WBC	–0.4	–1	0.52
D-Dimer	–84.5	–54	0.62
Ferritin	55.5	41	0.78
LDH	3	–19	0.9
CRP	1.36	0.32	0.31
Creatinine	–0.1	–0.2	0.66
Pulse Ox	–1%	–1%	0.81

Table 5. Delta Ordinal Scale and overall clinical deterioration from Day 1 to Day 3.

Delta COVID-19 Ordinal Scale – Number (%)	**Montelukast (*N* = 30)**	**Non-montelukast (*N* = 62)**	Total
–1	1 (0)	3 (6.3)	4
0	26 (84)	39 (66.7)	65
1	3 (12)	17 (20.8)	20
2	0 (0)	3 (6.3)	3
Total	**30**	**62**	**92**
Clinical deterioration (any escalation in Ordinal Scale Value Day 1 to Day 3)	**3 (10)**	**20 (32.2)**	**23**

Clinical deterioration

Table 5 shows the specific changes in the Ordinal Scale value from Day 1 to Day 3 for the montelukast and no montelukast groups. Clinical deterioration (any escalation in Ordinal Scale value from Day 1 to Day 3) occurred in significantly fewer patients in the montelukast group (10% vs. 32.2%, $p = 0.022$). In univariate logistic regression, the montelukast group had a lower risk of clinical deterioration (odds ratio 0.23, $p = 0.029$, CI = 0.063–0.86). On multivariable logistic regression, after accounting for age ≥60 (binary), receipt of montelukast was marginally associated with a lower risk of clinical deterioration (odds ratio 0.28, $p = 0.058$, CI = 0.072–1.04). Sensitivity analysis among those without asthma showed a trend toward fewer clinical deterioration events in the montelukast group than

non-montelukast groups (11% vs. 33%, $p = 0.077$). Sensitivity analysis among those who did not receive azithromycin showed fewer clinical deterioration events in the montelukast group than non-montelukast groups (8% vs. 32%, $p = 0.030$).

Discussion

The objective of this retrospective study was to evaluate the efficacy of montelukast in preventing clinical deterioration among patients hospitalized with COVID-19. Clinical deterioration was measured by changes in the COVID-19 Ordinal Scale. Oxygen escalation occurred in 32% of patients without montelukast versus 10% of patients taking montelukast. This was evident despite the montelukast group being of significantly older age ($p = 0.022$). Furthermore, patients receiving montelukast had higher rates of baseline asthma and tended to have more cardiac comorbidities, potentially suggesting these patients had increased risk for clinical decompensation during COVID-19 infection. These findings suggest that montelukast may have clinical efficacy in reducing complications of COVID-19. With further evaluation, montelukast may be a potential therapy for COVID-19 infection.

We examined the effects of montelukast on laboratory values associated with COVID-19 illness and found no differences in inflammatory laboratory values including CRP, D-dimer, ferritin, and LDH between montelukast versus non-montelukast patients. It is feasible that there were, in fact, no differences in the trends of laboratory values between patients treated with montelukast vs. non-montelukast. However, given the lack of a method to grade these particular laboratory values, the differences in these values could not be accurately compared among patients. We anticipate that the laboratory values of patients could be impacted by montelukast, but we were unable to derive an answer in this dataset. In addition, a limitation to this study was the lack of specific systemic or pulmonary cytokine measurements or serial SARS-CoV-2 viral loads that may better reflect the potential effect of montelukast on virally-mediated pathways in SARS-CoV-2 infection. We found no difference in length of hospitalization between the two groups. However, we considered length of stay a subjective indicator of clinical outcome as there is no standardization between physician practices for decisions surrounding discharge time and planning.

Montelukast is a leukotriene receptor antagonist and binds with high affinity and selectivity to the CysLT1 receptor (cysteinyl leukotriene). Eicasanoids including all cysteinyl leukotrienes (LTC4, LTD4, LTE4) are products of arachidonic acid metabolism and are released from cells including mast cells and eosinophils (12). These eicosanoids bind to cysteinyl leukotriene (CysLT) receptors, which are found in the human airway (including airway smooth muscle cells and airway macrophages) and on other pro-inflammatory cells (12). CysLTs have been correlated with the pathophysiology of asthma and allergic rhinitis (12). In asthma, leukotriene-mediated effects include airway edema, smooth muscle contraction, and altered cellular activity associated with the inflammatory process. Furthermore, clinical findings indicate that montelukast can be used in the effective management of acute and post viral-induced wheezing, and it can quickly improve respiratory function in acute asthmatic patients with an increased FEV1 at 60-min post-montelukast administration and at all time points up to 120 min ($n = 583$) (13,14). Another study documented data that asthmatic children treated with montelukast had higher lung function, decreased airway inflammation, and lower symptom scores compared with the children not receiving montelukast (15). While baseline asthma has not been found to be a risk factor for severe outcomes in COVID-19, other comorbidities such as hypertension and diabetes have been correlated with worse prognosis (16,17). In our study, 15 patients had a baseline diagnosis of asthma, 11 of whom received montelukast during hospitalization.

The progression of COVID-19 infection to severe clinical complications is thought to be due to ARDS and a hyperinflammatory cytokine syndrome, or cytokine storm (18). Secondary hemophagic lymphohistiocytosis (sHLH) is a hyperinflammatory syndrome leading to a fulminant and fatal hypercytokinemia with multiorgan failure in the setting of viral infections, and demonstrates unremitting fever, cytopenias, and hyperferritinemia; pulmonary involvement including ARDS occurs in 50% of patients (18). Cytokine profiles having sHLH resemble COVID-19 disease severity, with increased IL-2, IL-7, GM-CSF, IFN-gamma-inducible protein 10, monocyte chemoattractant protein 1, macrophage inflammatory protein 1-alpha, and tumor necrosis factor alpha (18). Viral hyperinflammation appeared to drive COVID-19 fatalities in Wuhan, China, and predictors of mortality from COVID-19 cases in Wuhan included an elevated ferritin (1297.6 ng/mL in non-survivors vs. 614 ng/mL in survivors, $p < 0.001$), suggesting that fatalities are driven by viral hyperinflammation (18). NF-KB (nuclear factor kappa-light-chain-enhancer of activated B cells) can regulate immune responses, and its inhibition by MTK may attenuate the symptoms of

COVID-19 by downregulating other inflammatory cytokines such as IL-6 and IL-8, mitigating the severity of infection and decreasing symptoms (19).

We noted that treatment with montelukast had interesting results in subpopulations of interest. Sensitivity analysis among those without asthma showed a trend toward fewer events of clinical deterioration in the montelukast group compared with the non montelukast group. While montelukast is commonly used an asthma maintenance therapy, our results suggest a benefit of montelukast independent from that found in its traditional use in asthma. Sensitivity analysis among those who received steroids did not reveal a difference in clinical deterioration events. Thus, co-administration may have blunted the anti-inflammatory effects of montelukast.

The standard dosing of montelukast is 10 mg orally per day for allergic rhinitis, asthma, and prevention of exercise-induced asthma. Montelukast has a favorable side effect profile with limited toxicities, indicating the potential to evaluate higher doses, with possible relative safety (20). The most common side effects of montelukast as per the US prescribing information include upper respiratory infection, fever, headache, sore throat, and cough. Additionally, the US prescribing information includes a boxed warning regarding the risk of neuropsychiatric events with montelukast. Further, Glockler-Lauf et al. published on the association between montelukast use in children and neuropsychiatric events, but there is currently no indication for its use in treating viral symptoms of SARS-CoV-2 infection (21). Given that montelukast is a well-tolerated and a low-cost agent, information about dose responses in COVID-19 infection could be an important aspect to evaluate new dosing regimens, and could have impact on the duration and severity of symptoms of COVID-19 as well as which patients are most likely to benefit. These favorable characteristics of montelukast are especially critical during the COVID-19 pandemic, as preventing clinical deterioration can save the use of depleted resources such as intensive care unit beds and mechanical ventilators.

While the results of this retrospective review are encouraging, they are not without limitations. The small sample size, retrospective nature of the study contributing to selection bias, the administration of montelukast as dictated by physician discretion, and limited data points in evaluation warrant further study with a larger prospective sample size. Additionally, a main limitation to our study is the lack of ability to control for multiple potential confounders.

Our findings suggest that montelukast administration can be used to quell clinical deterioration associated with COVID-19 infection. A recently reported retrospective observational study found a statistically significant reduction in confirmed COVID-19 cases among elderly asthmatic patients treated with montelukast (22). Also, it has been hypothesized that montelukast can limit progression of disease for COVID-19 positive patients, specifically in high risk factor obese patients (1,23). Similar findings for the treatment of COVID-19 infection with montelukast would bolster the support for montelukast as a therapeutic agent for COVID-19. Rather than incorporation into practice without further study, we advocate for confirmatory clinical trials and additional retrospective data to support the incorporation of montelukast for the treatment of COVID-19. One such trial appears to be ongoing, such as NCT04389411, a phase 3 trial evaluating the use of montelukast compared with placebo for COVID-19 infection.

Conclusions

Montelukast treatment among hospitalized COVID-19 patients resulted in fewer events of clinical deterioration, described by the COVID-19 Ordinal Scale. Given the global toll of COVID-19 internationally on the burden of death and disease, new approaches, such as treatment with montelukast, are urgently needed to decrease the impact of the disease on global healthcare systems, economies, and daily life.

Author's contributions

All the authors listed meet authorship requirements. ARK, NYR, SK, and SKJ wrote the manuscript. Data collection was performed by ARK, CM, CM, and SKJ. NYR and SK performed the statistical analysis. Manuscript approval: all authors.

Ethics approval and consent to participate

This study was IRB-approved, at Robert Wood Johnson University Hospital, Rutgers University (Pro2020001307).

Data availability statement

The data that support the findings of this study are available from the corresponding Author, upon reasonable request.

Disclosure statement

No financial/nonfinancial disclosures except: CH is the Chairman and CEO of Certa Dose, Inc. Neither CH nor Certa Dose have any financial interests in the sale of Montelukast or any companies that manufacture Montelukast. JM, Research funding: BMS, Beyond Spring, Celldex, Biohaven; Advisory board: Astra Zeneca. MG is a Director of Scientific Affairs at

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