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Montelukast and Coronavirus Disease 2019: A Scoping Review

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ABSTRACT

Coronavirus disease 2019 (COVID-19) is an emerging worldwide issue, that has affected a large number of people around the world. So far, many studies have aimed to develop a therapeutic approach against COVID-19. Montelukast (MK) is a safe asthma controller drug, which is considered as a potential antiviral drug for severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2). This review has a systematic approach to investigate the reports on the use of MK as a part of treatment or a prophylactic agent in COVID-19. The search was conducted in PubMed, Web of Science, and Scopus databases and yielded 35 studies containing the influence of MK on SARS-CoV-2. Ultimately, MK appears to be worth being used as an adjuvant therapeutic and prophylactic drug against SARS-CoV-2. Nevertheless, more clinical trials are required to accurately investigate its effectiveness.

Keywords: COVID-19; Leukotriene antagonists; Leukotriene D4 receptor; Montelukast; SARS-CoV-2

INTRODUCTION

Coronavirus disease 2019 (COVID-19) is an emerging worldwide concern that has affected over 175 million people so far. Common symptoms of COVID-19 include respiratory symptoms, fever, cough, shortness of breath, and dyspnea. In more severe conditions, the infection can cause pneumonia, severe acute respiratory syndrome, and even death.[1] The poor outcome in severe cases results from an uncontrolled "cytokine storm" with local and systemic production of inflammatory cytokines through activating nuclear factor κB (NF-κB) pathway.[2] A worse outcome of COVID-19 in obese patients could also be attributed to the existence of the inflammatory state in obesity.[3,4] Moreover, it is reported that angiotensin-converting enzyme 2 (ACE2) is an entry gate for severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) and would be a potential therapeutic option in COVID-19.[5]

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Currently, the only Food and Drug Administration (FDA)-approved drug for the treatment of COVID-19 is Remdesivir.[6] Given the fact that developing new drugs is expensive and time-consuming, a practical approach could be to repurpose existing drugs. Some off-label drugs have been used in the treatment regimen of SARS-CoV-2 patients, such as montelukast (MK), hydroxychloroquine (HCQ), and lopinavir/ritonavir.[7] MK is a selective cysteinyl leukotrienes (cysLTs) receptor antagonist which blocks leukotriene-D4 (LTD4)-induced bronchoconstriction that is primarily used as an FDA-approved asthma-controller drug, exercise-induced bronchoconstriction prophylaxis, and treatment of allergic rhinitis.[6] Of note, not only does it have an inhibitory effect on bradykinin-induced airway hypersensitivity that is the downstream molecule of ACE2, but it also modulates the inflammatory cytokines through the inhibition of NF-κB activation.[9,10]

Moreover, the beneficial anti-viral activity of MK against middle-east respiratory syndrome coronavirus (MERS-CoV) has been recently reported.[11] So, considering the common ancestral origin of SARS-CoV-2 and MERS-CoV,[12] the same effect of MK can be expected in SARS-CoV-2. Additionally, Barré J, et al, summarized a list of potential properties of MK reported in previous studies including improving fiber re-organization and long-term functional recovery after brain ischemia, alleviating the ischemia/reperfusion, anti-atheromatous, antioxidant, and anti-fibrosis ones. They connected these properties with reported SARS-COV-2 involvements and concluded a therapeutic possibility for MK in COVID-19.[13]

Here, we aimed to review all the related articles implying MK as a potential treatment and prophylaxis option in COVID-19.

MATERIALS AND METHODS

On April 21st 2021 a comprehensive search was conducted in PubMed, Web of Science, and Scopus databases with no time restrictions, applying the following keywords: “montelukast”, “montelukast sodium”, “Leukotriene Antagonists”, “singulair”, “MK-0476”, “MK 0476”, “leukotriene D4 receptor”, in combination with subsequent terminology: “covid 19”, “COVID-19”, “SARS-CoV-2” “COVID-19 drug treatment”, “2019-nCov”, “COVID”, “novel coronavirus”, “new coronavirus”, “coronavirus”. The search yielded 93 articles and 3 additional records identified through other sources. All the abstracts were charted and reviewed by two researchers. We included the studies that reported the use of MK as a part of treatment or the beneficial effect of MK as a prophylactic agent. This work was approved by the local ethical committee of Alborz University of Medical Sciences (reference No IR.ABZUMS.REC.1400.017).

RESULTS

Thirty-five studies that reported the influences of MK on SARS-CoV-2 were identified (Figure 1). We categorized the included studies based on whether they were conducted on humans, in silico, or expressed potential mechanisms of MK against SARS-CoV-2.

Our search included 11 (30.5%) in silico studies. A total of 8 out of 11 (72.7%) considered MK as a potential main protease (Mpro) inhibitor of SARS-CoV-2[21,23,36-41] and two (18.2%) expressed MK’s ability to dock the RNA dependent RNA polymerase (RdRp) site of SARS-CoV-2.[21,42] Spike glycoprotein site (S1 subunit)[23] and papain-like protease (PLpro)[22] were the other connection sites, each reported in one study.
One of the articles introduced MK as an effective drug on mutated SARS-CoV-2, mostly against A191V site mutation within the SARS-CoV-2 Mpro.[41]

Six articles (16.7%) proposed MK as a potential treatment in SARS-CoV-2 positive patients through altering NF-kB signaling pathway, targeting the increased vascular permeability, suppressing recruitment of the innate immune response as well as bronchoconstriction resulted from cytokine release and also lung injury.[14,15,29-31,43] MK was evaluated as the only applied medicine in four out of six surveys.[29-31,43] However, the combination of MK with zileuton controlled-release (CR) in one study and MK with levocetirizine in another survey was suggested to be beneficial in COVID-19 patients.[14,15] Table 1 provides more information.

Eighteen studies (50%) involved confirmed SARS-CoV-2 positive patients (Table 2) comprising two studies that detected high levels of leukotrienes (LTs) in the sera from COVID-19 patients,[44,45] indicating a therapeutic role for MK as an effective leukotriene inhibitor. Two other articles showed positive effects of MK as the main treatment in COVID-19 patients.[35,46]

One survey reported a decreased prevalence of SARS-CoV-2 infection in elderly asthmatic patients,[47] and two studies indicated the effect of MK along with other anti-asthmatic drugs in reducing the severity of the disease.[32,48] The other studies described a mixed therapeutic approach consisting of MK as an adjuvant drug.

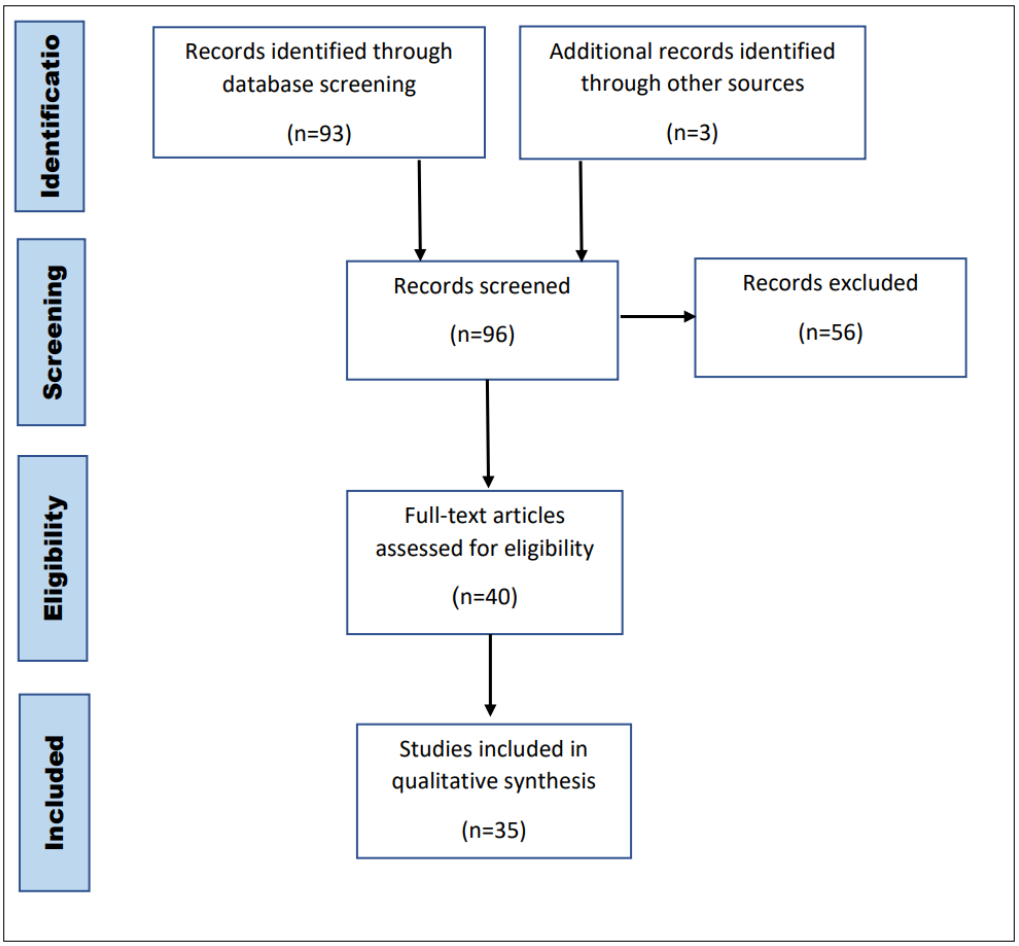

Figure 1. Modified study flow chart

Table 1. In silico studies and hypothesis of montelukast effect on SARS-CoV-2

NO	Author	Outcome	Ref.
1	Wu C. et al.	In silico; MK is a potential 3C-like Mpro inhibitor site of SARS-CoV-2	36
2	Copertino DC. Jr. et al.	In silico; MK is likely to dock to both the Mpro and the RdRp site of SARS-CoV-2	21
3	Salman M. et al.	In silico; MK is a potential inhibitor for the Mpro site of SARS-CoV-2	37
4	Li Z. et al.	In silico; Identified MK as a potent SARS-CoV- Mpro inhibitor via accelerated free energy perturbation-based virtual screening of existing drugs.	38
5	Ma C. and J. Wang	In silico; MK was not SARS-CoV-2 Mpro inhibitor according to FRET-based enzymatic assay	19
6	Farag A. et al.	In silico; MK demonstrated a very high affinity for the terminal site of Mpro SARS-CoV-2.	39
7	Abu-Saleh A. A. A. et al.	In silico; MK had good inhibitory efficacy on Mpro SARS-CoV-2. MK had also good stability inside the binding site of the Mpro.	40
8	Sharma T. et al.	In silico; MK has a high affinity to bind SARS-CoV-2 Mpro and is most active against A191V site mutation within the SARS-CoV-2 Mpro.	41
9	Maffucci I. and A. Contini	In silico; MK is likely to dock to the both Mpro and spike glycoprotein site (S1 subunit) of SARS-CoV-2 using the Nwat-MMGBSA approach.	23
10	Kumar S. et al.	In silico; MK is likely to dock to PLpro unit of SARS-CoV-2.	22
11	Baby K. et al.	In silico; MK is likely to bind to SARS-CoV-2 RdRp.	42
12	Funk C. D. and A. Ardakani	MK might decrease the risk of ARDS, vascular leakage, and activation of the transcription factor NF-kB in SARS-CoV-2 Suggested: Zileuton CR and MK be administered orally for approximately 1–3 weeks in positive SARS-CoV-2 individuals presenting with minor symptoms until symptoms resolve completely.	15
13	Fidan C. and A. Aydoğdu	MK might inhibit bradykinin-induced tracheal smooth muscle contraction and suppress T-helper type-2 cytokines in SARS-CoV-2	29
14	Sanghai N. and G K Tranmer	MK might inhibit NF-kB signaling and cytokine storm associated with SARS-CoV-2 and its severity correlated with gender, age, and obesity. Suggested: using high-dose MK in patients with severe COVID-19, with or without other drugs and -low-dose MK in patients with confirmed mild/moderate COVID-19 -low-dose MK, prophylactically and post-infection in a high-risk population	31
15	Citron F. et al.	MK might prevent lung injury by inhibiting inflammation, controlling increased vascular permeability, suppressing recruitment of the innate immune response, and bronchoconstriction.	43
16	Bhattacharyya D.	MK and levocetirizine both could be repurposed either alone or in combination as an antiviral against SARS-CoV-2 due to their anti-cytokine effect.	14
17	Almerie M. Q. and D. D. Kerrigan	MK might reduce the severity of immune-mediated multi-organ damage resulting from COVID-19, particularly in patients with central obesity and metabolic syndrome.	30

MK; Montelukast, Mpro; Main protease, RdRp; RNA dependent RNA polymerase, Nwat-MMGBSA; Number of water molecules (Nwat)- molecular mechanics generalized born surface area, PLpro; Papain-like protease, ARDS; Acute respiratory distress syndrome, NF-κB; Nuclear factor-kappa B, zileuton CR; zileuton controlled release, FRET; Fluorescence resonance energy transfer

Table 2. Human-based studies of montelukast effect on SARS-CoV-2.

NO.	Author	Case	Treatment	Outcome	Ref.
1	Yalcin Kehribar D. et al.	25 asymptomatic patients 35 patients with lung involvement 22 HS	-	Serum LTs levels were significantly higher in the group of SARS-CoV-2 infection without lung involvement compared to HS (*p<0.001*). COVID-19 patients with lung involvement had significantly higher serum LTs levels compared with those without lung involvement and HS (*p<0.001*).	44
2	Doğan HO. et al.	41 patients 44 HS	-	Prominent up-regulation in LTD4 in patients *(p=0.02)*. LTD4 may have a role in the regulation of lung inflammation in COVID-19.	45
3	Norouzi A.	20 patients with mild to moderate symptoms	Oral MK 20 mg first day; then 10 mg from days 2 to 10	All clinical signs of COVID-19 patients were gradually disappeared after treatment.	35
4	Khan AR. et al.	92 hospitalized patients: 30 received montelukast 62 (control) patient	Oral MK 10 mg days 1-3	Patients receiving MK experienced significantly fewer events of clinical deterioration (*p= 0.022*).	46
5	Bozek A. and J. Winterstein	445 elderly patients with severe asthma under treatment with high doses of ICS and LABA; 327 case 118 control patients	MK for 2 months	Elderly asthmatic patients receiving MK had fewer episodes of confirmed COVID-19 infection (*p<0.01*).	47
6	Lima-Morales R. et al.	768 patients; 481 cases received the TNR4 therapy 287 received another treatment	TNR4 multidrug therapy: orally Ivermectin, 12 mg single dose Azithromycin 500 mg for 4 days MK, 60 mg on the first day and then 10 mg between days 2 to 21 Acetylsalicylic acid, 100 mg for 30 days	The likelihood of recovery within 14 days was 3.4 times greater among the TNR4 group than in the comparison group. Patients treated with TNR4 had a 75% and 81% lower risk of being hospitalized or death, respectively.	32
7	Downing S. et al.	Case report	CAM therapy: 650 mg of aspirin every 4 h tapered in 2 weeks, colchicine 0.6 mg every 12 h for 1 month, and MK 10 mg daily for 1 month, acetaminophen 1000 mg at 8 h intervals if needed	Returned to daily activities after 72 h of treatment.	48
8	Tatu A. L et al.	Two patients with dermatologic involvements	The first patient received MK 1 month before the infection. The other patient received MK, Azithromycin, NSAIDs, and Corticosteroids after diagnosis.	The first patient had only mild symptoms, The second patient experienced remission	49
9	Raëth J. et al.	A lung transplant recipient	She was on MK, everolimus (1.25 mg twice a day), tacrolimus ER 1 mg daily, and prednisone 5 mg per day to prevent chronic lung allograft dysfunction that was continued during the infection along with lopinavir/ritonavir.	Discharged in good health.	50

10	Nazir N. et al.	Case report	HCQ (400 mg BD on the first day followed by 200 mg BD for the next 6 days), tab oseltamivir 150 mg BD for 7 days, tab Montair LC™ (a combination of MK and levocetirizine) daily (for 10 days), tab ranitidine 150 mg daily (for 10 days)	Discharged in good health.	51
11	Kimambo H. et al.	Case report	Intravenous amoxicillin/clavulanic acid, MK, salbutamol inhaler, and pantoprazole, azithromycin 500 mg daily for days 9-15, and enoxaparin	Full recovery.	52
12	Li W. et al.	3 asymptomatic children	MK sodium tablets, immunoglobulin therapy, one patient received Interferon	Good health.	53
13	Hoq MI. et al.	Case report	Azithromycin, ciprofloxacin, MK sodium INN, paracetamol Different citrus fruits, tea with ginger	Recovery.	54
14	Hirayama T. et al.	Patient with asthma	Continued budesonide, formoterol fumarate Hydrate, and MK. IV immunoglobulin therapy for developing GBS.	Symptoms improved.	55
15	He TP. et al.	Case report	intravenous infusion of 40 mg methylprednisolone sodium succinate once a day for 4 d, oral ceftazidime for 7 d, moxifloxacin for 5 d, oral doxofylline tablets, MK Sodium Chewable Tablets, and inhaled budesonide formoterol powder three times a day for 3 d	Symptoms improved.	56
16	Garcia-Pachon E. et al.	Asthmatic patient under treatment with LABA, ICs, MK, Omalizumab	-	Asymptomatic infection.	57
17	Haroun-Díaz E. et al.	3 severe asthma patients under treatment with SABA, ICs, MK, Tiotropium bromide (2 patients), Mepolizumab (1 case)	HCQ, Azithromycin	No patients developed cytokine storm and did not develop an aggressive form of COVID-19 infection (ARDS) and did not require intensive care.	58
18	Al-Makki A. and T. Taber	A kidney transplant patient	HCQ, Azithromycin, ICS, SABA, MK, Tacrolimus	Symptoms resolved.	59

MK; Montelukast, HS; healthy subject, TNR4 multidrug therapy; a therapeutic regimen including Ivermectin, Azithromycin, Montelukast, and Acetylsalicylic acid, ER; Extended-release, HCQ; Hydroxychloroquine, d; day, GBS; Guillain-Barre syndrome, SABA; Short-Acting Beta Agonists, LABA; Long-Acting Beta-Agonists, ICS; Inhaled Corticosteroids

DISCUSSION

MK is a safe FDA-approved drug with no serious adverse reaction or special contraindication.[6] However, it is worth mentioning that FDA has recently added a safety warning box about the minimal but important neuropsychiatric adverse effects of this medicine such as altering the mood and increasing the risk of suicide in patients taking it. Mood changes and suicidal tendencies should be enquired in patients whose therapeutic regimen MK has recently been added.[16-18] In this article, we reviewed the studies related to MK used for prophylaxis and treatment of SARS-CoV-2 infection. There are some possible mechanisms of MK in COVID-19. In silico studies announced a high affinity of MK to dock to the Mpro site of SARS-CoV-2 and probably disrupt its viral replication. On the other hand, Ma C. and J. Wang declared no inhibitory effect for MK using fluorescence resonance energy transfer (FRET)-based enzymatic assay.[19] However, Li Z. et al, replied that determining the activity of MK by using the assay with their tagged Mpro might not reflect the actual activity with native Mpro.[20] Interestingly, Copertino D.C Jr et al, reported that MK is likely to dock to the both Mpro and RNA-dependent RNA polymerase (RdRp) site of SARS-CoV-2.[21] Spike glycoprotein (S1 subunit) and PLpro were also the other connection sites of MK introduced by Maffucci I. and A. Contini and Kumar S. et al.[22,23]

LTs have already been shown to be involved in acute respiratory distress syndrome (ARDS) and increasing vascular permeability.[24,25] Considering the significantly higher levels of LTs in the COVID-19 patients' sera, an inhibitory role for MK against COVID-19 could be assumed. Furthermore, MK can inhibit the NF-kB signaling pathway and decrease the release of the pro-inflammatory cytokines,[26,27] which is in agreement with Barré J. et al, expressing the role of MK in inhibiting COVID-19 serious outcomes.[13]

Bradykinin is a potent vasoactive mediator that is normally degraded by the angiotensin-converting enzyme (ACE). The dysregulated Bradykinin signaling is hypothesized to take part in COVID-19 respiratory complications.[28] Given the previous evidence of LTs interaction with bradykinin, MK was assumed to inhibit bradykinin-induced tracheal smooth muscle contraction in SARS-CoV-2.[29] The related known comorbidities of SARS-CoV-2 encompassing obesity and age were also considered to be manageable with montelukast in the context of COVID-19.[30,31]

Of note, in almost all surveys, MK has been used as an adjuvant along with other anti-viral drugs rather than the only applied medicine in the treatment of confirmed SARS-CoV-2 positive patients, which makes the judgment of MK's impact on SARS-CoV-2 harder. Lima-Morales R. et al, reported a greater likelihood of recovery, lower risk of hospitalization and death with a therapeutic regimen consisted of Ivermectin, Azithromycin, MK, and Acetylsalicylic acid in SARS-CoV-2 positive patients.[32] However, regarding the recent data about the ineffectiveness of Ivermectin and Azithromycin, the role of MK in the COVID-19 therapeutic approach, particularly as an adjuvant drug, seems to be more prominent than expected.[33,34]

MK has also been used as the only therapeutic drug by Norouzi A in mild to moderate COVID-19 patients and provided symptom alleviation.[35] Additionally, the positive result of MK in decreasing the risk of infection and disease severity in asthmatic patients under treatment with MK has been detected in a few articles. The best dosage and course of action of MK during the prophylaxis and treatment of COVID-19 are also important factors that need to be determined in future trials.

In the light of the reviewed data, MK appears to be worth being used as a therapeutic and prophylactic drug against SARS-CoV-2. It has had promising effects in both in silico and clinical studies, used solely or in combination with other antiviral drugs. However, more clinical trials are required to investigate this matter. Currently, clinical trials are conducting on a large group of SARS-CoV-2 patients assessing the role of MK (COSMO, ID: NCT04389411).

CONFLICT OF INTEREST

The authors declare that they have no competing interests.

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