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Impact of montelukast as add on treatment to the novel coronavirus pneumonia (COVID-19): protocol for an investigator-initiated open labeled randomized controlled pragmatic trial

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Abstract

Background: Montelukast, a safe drug widely use in asthmatic patients, may be an adjuvant in the treatment of Covid-19, either by improving lung injury and inflammation, or by acting as an anti-viral drug. We aim to assess the efficacy and safety of montelukast as add-on treatment in patients with Covid-19.

Methods: We propose a randomized, controlled, parallel, open-label trial involving 160 hospitalized adult patients with confirmed Covid-19. Patients will be randomly assigned in a 1:1 ratio to receive either montelukast 10 mg, once a day for 14 days, in addition to standard of care (SoC), or SoC alone. SoC will follow the best practice for treating these patients, according to updated recommendations. The primary outcome is time to recovery. Participants will be assessed using diary cards to capture data on treatment-related improvements in an 8-point ordinal scale. Secondary endpoints will include changes in respiratory and inflammatory parameters, and adverse events. This phase IV clinical trial will take place at the University Hospital of São João, Porto. EudraCT number: 2020-001747-21.

Results: This study intends to generate scientific evidence on efficacy and safety of montelukast as add-on treatment in Covid-19. The results will be essential to improve clinical outcomes which remains to be determined.

Conclusion: Montelukast has been suggested as a potential drug with 2 main actions on Covid-19. The validation of montelukast as an adjuvant treatment may improve lung injury, inflammation, and symptoms leading to a better prognosis. The use of this drug may fulfil the existing gap on therapeutic options.

Keywords: coronavirus, Covid-19, montelukast, randomized controlled trial, SARS-CoV-2, treatment

Introduction

Considering the urgent clinical demand, clinical trials on testing adjuvant treatments for the novel coronavirus-19 disease (COVID-19) have risen. There is no specific drug treatment approved against the infection by SARS-CoV-2. Hence, identification of readily available drugs for repurpose in COVID-19 therapy are a rapid option to be studied to improve clinical management and prognosis.

The SARS-CoV-2 is a beta-coronovirus genus, which is an enveloped and positive-stranded RNA virus.[1] In humans, angiotensin-converting enzyme 2 (ACE2) has a spike protein receptor for SARS-CoV and SARS-CoV-2 that is expressed in many organs, including the lung, heart, kidney, and intestine.[2,3] Spike protein is responsible for interact with the host cells by binding to receptors that mediate virus entry in the host and then it is cleaved by the host cells proteases, such as TMPRSS2, to become functional. The off-label use of camostat mesylate was proposed to have anti-viral activity against SARS-CoV-2 by blocking TMPRSS2 protease activity, consequently limiting its entry in the host cells via ACE2 receptor.[2] In experimental models of SARS-CoV infection, spike protein engagement decreases

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ACE2 expression, which is a negative regulator of the renin-angiotensin system (RAS), increasing the production of angiotensin II.[4] Lately, angiotensin II levels were found elevated in SARS-CoV-2 infected patients highlighting that RAS was likely to be deregulated in these patients.[5] Increased levels of angiotensin II mediate vasoconstrictive, pro-inflammatory and oxidative effects promoting lung injury.[6,7] In SARS-CoV and MERS-CoV, similar conditions to SARS-CoV-2 (79% and 51.8% of genetic homology),[8] it was reported an immune dysfunction response and increased levels pro-inflammatory mediators, such as tumour necrosis factor alpha (TNF-α) and cytokines (IL-1β, IL-2, IL-6, and IL-8), leading to apoptosis of epithelial and endothelial cells, vascular leakage, and abnormal T cell and macrophages responses.[9] Thus, targeting immune pathways may improve respiratory symptoms, lung function and the overall prognosis of SARS-CoV-2 infected patients.

Montelukast, a leukotriene receptor antagonist (LTRA) with a good safety profile widely use in asthmatic patients, may interfere in immune modulation by inhibiting pro-inflammatory mediators of the 5-lipooxygenase pathway that play an important role in bronchoconstriction and endothelial cell permeability, improving lung function and respiratory symptoms.[10,11] Moreover, a study reported that montelukast prevents lung collagen deposition and fibrotic response in animal models, concluding that LTRAs might be useful in pulmonary fibrosis.[12] A different experimental study analysed the effect of LTRA administration in a murine model with a viral double-stranded RNA.[13] Montelukast significantly attenuated the viral-induced infection and decreased the number of eosinophils, the levels of inflammatory mediators such as IL-13, IL-9, and CCL3 in BALF (bronchoalveolar lavage fluid) and airway hyperresponsiveness.

In addition to immune modulation and improvement of lung injury, montelukast may have a potential anti-viral activity. The 3-chymotrypsin-like protease (3CLpro), also called main protease (Mpro), is one of the replicase polyproteins involved in the viral replication and infection of SARS-CoV-2.[14] 3CLpro catalyses their own release from the polyprotein and activates the maturation of other non-structural proteins to initiate virus-mediated RNA replication.[15] Wu et al[16] reported that 3CLpro enzymes are highly conserved between coronavirus, especially in the functional region. Montelukast also exhibited low binding energy to 3CLpro and fitted well in the active pocket of SARS-CoV-2 3CLpro, in which several hydrophobic amino acids create a relatively hydrophobic environment to contain the compound and stabilize its conformation, being a potential 3CLpro inhibitor to be used as an anti-viral therapy in Covid-19 patients.[16,17] Furthermore, based on a database of more than 3000 FDA approved drugs, montelukast was also reported as being useful for the therapy of COVID-19, namely by the inhibition of 3CLpro activity.[18]

LTRA might have a role in viral infections, either by improving lung injury and inflammation, or by acting on 3CL proteinase of SARS-CoV-2. Thus, we hypothesize that montelukast may be an adjuvant drug in COVID-19 treatment. This study aims to evaluate the efficacy and safety of montelukast in the adjuvant treatment of COVID-19 pneumonia.

Methods

Design

This single center, phase IV, randomized, parallel, controlled clinical trial will take place in Centro Hospitalar Universitário de São João EPE, Porto, Portugal. It is estimated to last about 3 months. The study will be conducted prospectively with the aim of collecting data safely, and to minimize the loss of information.

Participants

Participants will include adult patients admitted to the hospital with a diagnosis of moderate or severe COVID-19 pneumonia. To be a part of this study, participants will have to accomplish the following criteria: (1) To be admitted to the hospital ward less than 72 hours, with a diagnosis of moderate or severe COVID-19 pneumonia, defined as: moderate cases, when showing fever and respiratory symptoms with radiological findings of pneumonia; or severe cases, when meeting any of the following criteria: (i) respiratory distress ($\geq$30 breaths/min); (ii) oxygen saturation $\leq$93% at rest without oxygen inhalation; (iii) PaO2/FiO2 (fraction of inspired oxygen) $\leq$ 300 mmHg; (iv) with chest imaging that showed obvious lesion progression within 24 to 48 hours >50%; (2) To provide written informed consent prior to the initiation of any study procedures, and to understand and agree to comply with the planned study procedures; (3) To allow the collection of oropharyngeal swabs; (4) Male or non-pregnant female adult, 18 years of age or older at the time of enrolment; (5) To have laboratory-confirmed acute SARS-CoV-2 infection as determined by polymerase chain reaction (PCR) or other commercial or public health assay in any specimen prior to randomization; (6) Women of childbearing potential must agree to either abstinence or use at least one primary form of contraception not including hormonal contraception from the time of screening through day 29 of the study.

Individuals are not eligible if they present at least one of the following criteria: (i) Admitted to the hospital with a diagnosis of critical COVID-19 pneumonia defined as any of the follow: (i) requiring mechanical ventilation, extracorporeal life support (ECMO, ECCO2R, RRT); shock, or multiple organ dysfunction syndrome; (ii) participating in another drug clinical trial; (iii) requiring dialysis; (iv) pregnant or breast feeding women; (v) allergy to any study medication; (vi) severe basic diseases that affect survival, including uncontrolled malignant tumors that have metastasized and cannot be removed, blood diseases, cachexia, active bleeding, severe malnutrition, and HIV; (vii) pulmonary tumors caused by obstructive pneumonia, severe interstitial fibrosis, alveolar proteinosis, allergic alveolitis; (viii) continued use of immunosuppressive agents or organ transplants in the last 6 months; (ix) expected deaths within 48 hours; (x) clinicians judge inappropriate.

Recruitment and randomization

Subjects with COVID-19 admitted to the Hospital will be invited to participate in a screening visit in order to evaluate eligibility criteria and to provide informed consent after explanation of the study rationale and protocol by one of the research members. The informed consent form will be administered and signed by each participant before any study-specific procedure.

A number will be attributed to each participant at the screening evaluation. The investigator will contact the Pharmacy Department after confirming that the subject fulfils all the eligibility criteria and participants will be randomly assigned to one of the 2 treatment arms in a 1:1 ratio. Each participant will be randomly allocated, using a computer-generated random number, to a predetermined intervention order without the knowledge of the researchers involved in the intervention procedure. Participants may withdraw voluntarily from the study at any time.

Intervention

Participants in the intervention arm (Arm A) will receive montelukast 10 mg once daily orally in addition to standard of care (SoC) for 14 days. The control group will receive SoC alone (Arm B). SoC is essentially symptomatic and supportive and will follow the best practice for treating COVID-19 patients, according to updated national and international recommendations.

Participation will be completed after the last follow-up visit, unless the patient is lost to follow-up, informed consent has been withdrawn or if serious adverse event is reported.

Assessments and schedule

Screening visit will be made within the first 72 hours of hospital admission. Subjects will be assessed daily while hospitalized. If the subjects are discharged from the hospital, they will have study visit conducted by phone. If discharged from the hospital prior day 14, a presential visit at the research centre will be scheduled to return the blister pack. Clinical data will be recorded using the WHO-ISARIC (World Health Organization-International Severe Acute Respiratory and Emerging Infections Consortium) case record form.[19] Clinical data will be recorded on case record forms, double-entered into an electronic database, and then validated by trial staff.

Serial oropharyngeal and nasal swab samples obtained on day 1, 5, 10, 14, 21, and 28 until discharge, or as medical care supersedes, or death had occurred will be tested at Pathology Lab within the research centre, using quantitative real-time RT-PCR.

Primary outcome

The primary outcome is time to recovery by Day 29. Participants will be assessed daily using diary cards to capture data on treatment-related improvements of COVID-19 disease status in an 8-point ordinal scale. The ordinal scale is as follows: (1) Death; (2) Hospitalized, on invasive mechanical ventilation or extracorporeal membrane oxygenation (ECMO); (3) Hospitalized, on non-invasive ventilation or high flow oxygen devices; (4) Hospitalized, requiring supplemental oxygen; (5) Hospitalized, not requiring supplemental oxygen—requiring ongoing medical care (COVID-19 related or otherwise); (6) Hospitalized, not requiring supplemental oxygen—no longer requires ongoing medical care; (7) Not hospitalized, limitation on activities and/or requiring home oxygen; (8) Not hospitalized, no limitations on activities.

Secondary outcomes

Secondary outcomes are change from baseline in alanine transaminase (ALT), aspartate transaminase (AST), creatinine, glucose, hemoglobin, platelets, prothrombin time (PT), total bilirubin, and white blood cell count with differential; and change in National Early Warning Score (NEWS) from baseline. The NEW score has demonstrated an ability to discriminate patients at risk of poor outcomes. This score is based on 7 clinical parameters (respiration rate, oxygen saturation, any supplemental oxygen, temperature, systolic blood pressure, heart rate, level of consciousness), and is being used as an efficacy measure.[20,21] Other secondary endpoints include duration of hospitalization, of new non-invasive ventilation or high flow oxygen use, duration of new oxygen use, duration of new ventilator or ECMO use, incidence of new non-invasive ventilation or high flow oxygen use, incidence of new oxygen use, incidence of new ventilator or ECMO use, number of non-invasive ventilation/high flow oxygen free days, number of oxygenation free days, and subject 28-day mortality.

Safety outcomes

Safety outcomes will be adverse events (AEs) occurred during treatment, serious adverse events (SAEs), and premature discontinuation of treatment. Safety endpoints will include the cumulative incidence of Grade 3 and 4 AEs; and cumulative incidence of SAEs. Grade 3 AEs are defined as events that interrupt usual activities of daily living, or significantly affects clinical status, or may require intensive therapeutic intervention. Grade 4 AEs are defined as events that are potentially life threatening. A SAE is defined as an AE or suspected adverse reaction that is considered serious if results in death, life-threatening AE, prolongation of existing hospitalization, persistent or significant incapacity or substantial disruption of the ability to conduct normal life functions, or a congenital anomaly/birth defect. Adverse events will be registered on the subject's medical chart by the medical staff

Sample size

The original total sample size was set at 160 (80 participants in each group), since it would provide the trial with 80% power to detect a difference, at a 2-sided significance level of $\alpha = 0.05$, of 8 days in the median time to clinical improvement between the 2 groups, assuming that the median time in the standard-care group was 20 days and that 75% of the patients would reach clinical improvement.[22]

Statistical analysis

This is a superiority study that aims to determine if montelukast is more effective than the SoC alone, in terms of patient-reported outcomes and biological markers of disease. All randomized patients will be included in an intention-to-treat analysis, provided that all necessary information has been collected for the determination of the outcomes related to the primary and secondary endpoints, for each participant.

Data will be entered into a database, and statistical analyses will be performed using the Statistical Package for the Social Sciences® (version 23.0, SPSS® 50). To assess the validity of the normal distribution, Kolmogorov-Smirnov test, histogram and QQ plot distribution will be used. Continuous variables will be represented by median and inter-quartile range or by mean and standard deviation, as appropriate. Discrete variables will be represented as proportions or counts. According to the normality of the distributions, Student's t test and Mann-Whitney U test for continuous variables and Chi-square test or Ficher's exact test for categorical variables will be used to compare differences between groups. All statistical procedures will be presented as adjusted means (least-square means) with standard errors, odds ratios with 95% confidence intervals and prevalence rates. Statistical significance is established when P value $<.05$ and difference between means is non-zero. For skewed distributions, whenever possible to obtain a normal distribution through logarithmic transformation, comparisons will be made assuming that normality.

Primary efficacy analysis will be on an intention-to-treat. The time to clinical improvement will be assessed after all patients had reached day 28, with failure to reach clinical improvement or death before day 28 considered as right-censored at day 28. Time to clinical improvement is defined as the time from randomization to an improvement of 2 points (from the status at randomization) on an 8-category ordinal scale or live discharge from the hospital, whichever came first. The time to clinical improvement will be portrayed by Kaplan–Meier plot and compared with a log-rank test. Hazard ratios with 95% confidence intervals will be calculated by means of the Cox proportional-hazards model.

Ethical considerations and registration

Informed, written consent will be obtained following screening for eligibility criteria. The study will be conducted in accordance with the ethical principles of the Declaration of Helsinki and the International Council for Harmonization-Good Clinical Practice guidelines. The protocol was registered at EudraCT 2020-001747-21 and approved by the National Ethical Committee for Clinical Research (CEIC 20200436) and by the National Authority of Medicines and Health Products, I.P.

Discussion

The identification of a new therapeutic indication for montelukast—meaning that a very well-known molecule in common use in asthma and allergic inflammation—with a strong safety profile, but showing potential efficacy for COVID-19, will be investigated under this purpose. This is particularly relevant as compared with the traditional de novo drug discovery pipeline, which is more time consuming and expensive. Thus, repurposing montelukast, for which preclinical and safety studies in humans for the original indication have already been performed, enable a faster, cheaper, and more efficient translation from bench to bedside. However, there are no clinical studies evaluating the potential use of montelukast as an add-on therapy in COVID-19. Hence, we proposed this phase IV randomized pragmatic clinical trial to evaluate efficacy and safety of montelukast as an add-on therapy in the COVID-19 patients.

The results of this randomized trial will be essential to improve clinical outcomes related to SARS-CoV-2 infection, which remains to be determined. A significant improvement in primary and secondary outcomes will reflect the importance to add montelukast to SoC to reduce the risk of adverse clinical outcomes.

Conclusion

To the best of our knowledge, this is the first study aiming to evaluate efficacy and safety of montelukast as an adjuvant therapy of COVID-19. Montelukast has been suggested as a potential drug with 2 main actions on this infection, either by improving lung inflammation and injury, or by acting on the virus, limiting its replication in the host cells. Thus, the use of this drug may fulfil the existing gap on therapeutic options. The main beneficiaries will be, primarily, the hospitalized infected patients. The validation of montelukast as an adjuvant treatment may improve lung injury, inflammation, and symptoms leading to a better prognosis and, potentially, reduce the duration of hospitalisations. Consequently, reducing hospitalisation time for infected patients may diminish the burden and costs for hospitals and, ultimately, for the health systems worldwide.

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Author contributions

All authors participated in developing the design of the study and contributed to and critically appraised the manuscript. The authors have given final approval of the version to be published.

Conflicts of interest

The authors declare no conflicts of interest.

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