International Journal of Basic & Clinical Pharmacology
Pottirayil A et al. Int J Basic Clin Pharmacol. 2021 Apr;10(4):373-380
http://www.ijbcp.com
pISSN 2319-2003 | eISSN 2279-0780

DOI: https://dx.doi.org/10.18203/2319-2003.ijbcp20211018

Original Research Article

A prospective, open label clinical study to evaluate the safety, efficacy and tolerability of azadvir herbal steam inhaler in asymptomatic, mildly symptomatic COVID-19 patients and health care workers posted to covid wards

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Received: 24 January 2021
Revised: 07 March 2021
Accepted: 08 March 2021

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ABSTRACT

Background: COVID-19 patients experience cytokine storm which cause pulmonary and extra-pulmonary complications even with currently available of standard of care. Additional antiviral and immune boosters are the need of hour to treat COVID-19 and to prevent post covid complications.
Methods: In this study we enrolled 40 asymptomatic to mild COVID-19 patients to receive azadvir herbal steam inhaler along with standard of care. We evaluated the benefits of azadvir herbal steam inhaler by assessing RT-PCR conversion, clinical outcomes and improvement in immune markers (LDH, CRP, D-DIMER).
Results: At the end of the study the immune markers improved significantly in study patients. In mild symptomatic cases IL-6 was 23.2 pg/ml on day 0 and 21.8 pg/ml on day 14. Reduction in IL-6 in mild symptomatic patients was statistically highly significant (p=0.0056). Mean IL-6 in asymptomatic patients was 22.3 pg/ml on day 0 and 21.1 pg/ml on day 14. Reduction in IL-6 in asymptomatic patients was statistically highly significant (p=0.0035). Mean D-dimer was showing decreasing trend from day 0 to day 14 in mild symptomatic patients. In asymptomatic patients D dimer was 0.8 µg/ml on day 0 and 0.6 µg/ml on day 14. D-dimer decreased significantly from day 0 to day 14 (p value =0.0013). Mean LDH values on day 0 in mild symptomatic patients was 319.4 U/l and 219.3 on day 14. The reduction in LDH values in mild symptomatic patients is statistically significant (p value <0.0122). In asymptomatic patients mean LDH values on day 0 was 237 U/l and 194 U/l on day 14. The reduction in LDH values in asymptomatic group was statistically significant. Mean CRP values in mild symptomatic patients on day 0 was 12.2 mg/l and 3.8 mg/l on day 14. There was significant reduction in CRP values in mild symptomatic group which was statistically significant (p value =0.0546). Mean CRP values in asymptomatic patients on day 0 was 4.9 mg/l and 2.8 mg/l on day 14. There was significant reduction in mean CRP in asymptomatic patients which was statistically significant (p value =0.0446). In the present study all 40 patients (100%) cleared the virus and became negative for RT PCR test within 6 days. None of the patients progressed to severe COVID-19 and none of the patients succumbed to the disease.
Conclusions: Azadvir accelerated recovery of COVID-19 patients by RT-PCR conversion, early improvement in clinical symptoms and immune markers in this study. This study results clearly indicates that azadvir has antiviral, immune booster activity and has definitive role in the management of asymptomatic to mild COVID-19 patients along with standard of care (CTRI no. CTRI/2020/06/026181).

Keywords: Azadvir, COVID-19, Pulmonary and extra pulmonary complications

INTRODUCTION

SARS-CoV-2 virus is very contagious and has quickly spread globally. COVID 19 caused by this new virus has resulted 87,589,206 confirmed cases of COVID-19, including 1,906,606 deaths, reported to WHO.[1] In India there have been 10,413,417 confirmed cases of COVID-19 with 150,570 deaths.[2] DIC appeared in most of the deaths. Patients presenting with a virus infection may develop into sepsis associated with organ dysfunction. Sepsis is well established as one of the most common causes of DIC; development of DIC results when monocytes and endothelial cells are activated to the point of cytokine release following injury, with expression of tissue factor and secretion of von Willebrand factor. Circulation of free thrombin, uncontrolled by natural anticoagulants, can activate platelets and stimulate fibrinolysis. At the late stages, levels of fibrin-related markers (D-dimer and FDP) moderately or markedly elevated in all deaths, which suggested a common coagulation activation and secondary hyperfibrinolysis condition in these patients. The other most common complications are respiratory failure, acute respiratory distress syndrome (ARDS), cardiac injury and acute kidney injury. The plausible mechanisms of respiratory failure are hyperinflammation due to "cytokine storm" causing ARDS. Significantly abnormal coagulation parameters were noted in people who succumbed to COVID-19, with higher levels of D-dimer and fibrin degradation products (FDP), and lower levels of the fibrinogen and AT levels.[3] The treatment of COVID is challenging and requires effective drugs. There are some drugs approved for COVID-19 management which includes antivirals and anti-inflammatory drugs and doxycycline etc. However, these drugs are not effective in most of the cases Thus though antiviral and anti-inflammatory drugs are available for treating symptoms, but the benefits of these therapies are not satisfactory and hence search for new drugs continues. Herbal medicines have various biological activities such as anti-viral, immunomodulatory and can be useful in the management of covid. The role of azadvir steam inhaler a poly herbal preparation containing multiple herbal extracts is presented here in an evidence-based approach that can be followed to establish their potential use in the management of corona virus pandemics.[4]

Azadvir steam inhaler

Azadvir steam inhaler is an herbal preparation containing multiple herbal extracts known to have antiviral activity and boost immunity. These herbals are used for various infectious ailments from many centuries and with abundant literature evidences. Azadvir contains multiple herbal ingredients including 1) *Ocimum sanctum*- 20% 2) *Cedrus deodara*- 7.5% 3) *Boswellia serrate*- 7.5% 4) *Azadirachta indica*- 20% 5) *Mentha piperita*- 15% 6) *Thymus vulgaris*- 5% 7) *Cinamomum camphora* 10% 8) *Cymbopogon citrates* oil- 10% 9) *Eucalyptus globulus* oil-5% 10) base oil: coconut oil (*Narikela tailam*), gingely oil (*Tila tailam*).

The active principles in these herb extracts have antiviral activity and enhance the functioning of the immune system by stimulating certain cell types, such as macrophages, lymphocytes, natural killer (NK) cells, dendritic cells, and eosinophils, by mechanisms including modulation of cytokine secretion, immunoglobulin production, phagocytosis, and macrophage activation. These herbs containing various active principles having multiple mechanism of action. These herbs are used from many years for various infections including viral, bacterial and fungal infections in traditional medicine.

In vitro studies of azadvir

Azadvir is also tested in vitro for cytotoxicity and antiviral activity. Cytotoxicity assay and SARS CoV2 pseudovirion assay for Azadvir was conducted at Rajiv Gandhi Centre for Biotechnology, Thiruvananthapuram, Kerala. The dilution used was 1:100 to 1:1000. The samples were further diluted in DMEM containing 10% fetal bovine serum to determine the cytotoxicity in DLD 1 cells. Based on the cytotoxicity, the sample below 1:100 dilution showed moderate cytotoxicity and at 1:1000, no cytotoxic effect on cells (Figure 1).

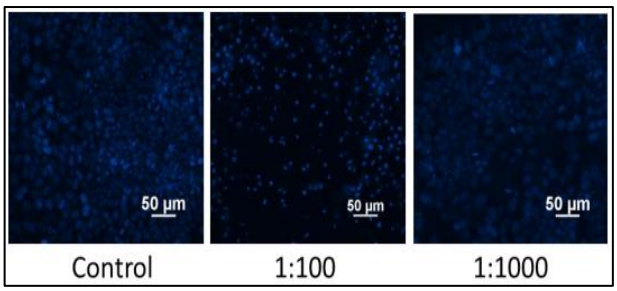

Figure 1: Cytotoxicity in DLD 1 cells.

Pseudovirion assay is based on the lentiviral backbone expressing Td tomato as a traceable marker. We have utilized stable colon cancer cell DLD 1 expressing human ACE2 as the SARS permissive cells. As per the results, AZADVIR inhibited SARS CoV2 pseudoviron to 5% of cells in 1:100 and 8% of cells in 1: 1000 dilution of test samples compared to 19% of cells in untreated control cells (Figure 2, Table 1).

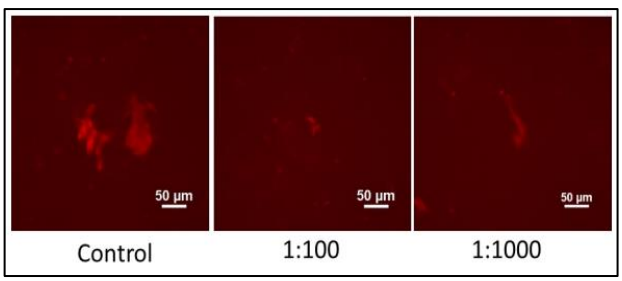

Figure 2: Pseudovirion assay.

Table 1: Pseudovirion assay with different dilutions.

Sample	Average % of Td tomato positive cells (SARS pseudovirion positivity	Inference
Control no test sample	Pseudovirion fluorescence in 19% cells	S protein pseudotyping generally provide 18-22% efficacy with Td tomato platform
Sample 1:100	Pseudovirion fluorescence in only 5% cells	Significant inhibition of pseudovirions in DLD cell
Sample 1:1000	Pseudovirion fluorescence in only 8% cells	Significant inhibition of pseudovirions in DLD cell

Based on the existing information we hypothesized that azadvir supplemented for 14 days would provide a remarkable improvement of Immunity in COVID-19 patients. The purpose of this study was to evaluate the efficacy and tolerability of azadvir in patients with COVID-19. Azadvir contains various potential herbs that have been evaluated for their safety and efficacy against flu viruses and hence can prove to be useful to combat the novel COVID-19 pandemic.

METHODS

Trial design, treatment, and oversight

This prospective, open label study conducted at department of Medicine, Shetty's hospital, Kaveri Nagar, Bommanahalli, Bengaluru, Karnataka 560068. The study was conducted between the months June and July of 2020. The study was approved by the institutional ethics committee at each center. The trial, which was sponsored by Haoma wellness center, Bangalore was conducted in accordance with principles of the ICH-GCP guidelines. The trial has been registered in the clinical trial registry, India (CTRI registration number: CTRI/2020/06/026181).

All the patients had positive results on testing for SARS-CoV-2 either asymptomatic or mildly symptomatic. The investigators reviewed the symptoms, risk factors, and other inclusion and exclusion criteria before enrolment. All the patients provided written informed consent. A total of 48 patients were screened and 40 subjects were enrolled. All subjects completed the study and included in safety and efficacy analysis (n=40).

All the subjects received azadvir (herbal steam inhaler) from Day 0 to Day 7 along with Standard of care. Dr. Shaji's azadvir two drops in boiling water added and inhale in the warm steam through mouth and each nostril three four times and repeated twice daily. Standard of care included paracetamol, antihistamines, glucocorticoids, antibiotics, vitamin C and zinc supplements along with medication for comorbid conditions like diabetes, hypertension, cardiac, thyroid ailments and etc.

Patients

Inclusion criteria

Inclusion criteria for this study included 1) Male or non-pregnant female adult with or without comorbidities between the age group of 18-85 years of age at time of enrolment 2) Had laboratory-confirmed positive COVID-19 infection as determined by RT-PCR or other commercial or public health assay in any specimen, an RT-PCR (nasopharynx, throat, and blood) test was repeated to assess eligibility. 3) Subject (or legally authorized representative) provide written informed consent prior to initiation of any study procedures 4) Health care workers who visited to covid patients.

Exclusion criteria

Exclusion criteria included 1) Testing positive for HIV, HbsAg, HCV infection, VDRL. 2) Females who were currently pregnant or breastfeeding. 3) Allergy or other contraindication to one of the investigational products. 4) Had received eflornithine within the last 10 days. 5) Had received anti-viral, anti-malarial or anti-bacterial within the last 14 days. 6) Alanine aminotransferase (ALT) or aspartate aminotransferase (AST) >5 × upper limit of normal (ULN). 7) QTc interval <500 ms. 8) Recent myocardial infarction (within last 6 months). 9) Known case of (K/C/O) Congestive heart failure. 10) K/C/O chronic kidney disease. 11) K/C/O active tuberculosis. 12) History of drug or alcohol dependence in the past 6 months. 13) In the opinion of the clinical team, progression to death is imminent and inevitable within the next 24 hours, irrespective of the provision of treatments. 14) Anticipated transfer to another hospital which is not a study site within 72 hours. 15) K/C/O of epilepsy or CNS disorders. Patients with other conditions, which in the opinion of the investigators makes the patient unsuitable for enrolment or could interfere in adherence to of the study protocol were also excluded.

Study procedures

All the patients provided written informed consent and entered a 2 day screening period, during which the trial inclusion and exclusion criteria were checked and baseline information gathered including safety and efficacy parameters (LFT, RFT, LDH, CRP, D-DIMER and TLC). Patients were evaluated at day 0 day 5 and 10 after enrolment with a focus on assessment of clinical symptoms and adverse events. The principal investigator was provided with the investigational products.

Outcomes

Efficacy endpoints were improvement in the total leucocyte count (TLC), lactic dehydrogenase (LDH), C-

reactive protein (CRP) and D-dimer and RT-PCR. Safety endpoints were adverse events (AEs), frequency and severity, number of subjects who discontinue study due to adverse events and changes in vital parameters and safety laboratory parameters. Total leucocyte count (TLC), lactic dehydrogenase (LDH), C-reactive protein (CRP) and D-dimer and RT-PCR were monitored for improvement on day 0 and day 14. Renal function test (RFT) and liver functions test (LFT) were monitored on day 0 and day 14 for safety assessment. Along with the laboratory parameters patients were also monitored for vitals, physical examination and adverse events for safety in each visit.

Statistical analysis

'T-test' was used for within group safety and efficacy analysis. 'p' value <0.05 was considered as statistical significance for the study and p' value <0.001 was considered as highly significant. Baseline characteristics were summarized as means and standard deviations, medians and interquartile ranges, or percentages.

Unless otherwise stated, all hypotheses was tested at a significance level of 0.05 and 95% confidence interval.

RESULTS

Among 40 subjects 25 male (62.5%) and 15 female (37.5%) participated in the study. Mean age of participants was 37.5 years.

IL-6

In mild symptomatic cases IL-6 was 23.2 pg/ml on day 0 and 21.8 pg/ml on day 14. Reduction in IL-6 in mild symptomatic patients was statistically highly significant (p=0.0056). Mean IL-6 in asymptomatic patients was 22.3 pg/ml on day 0 and 21.1 pg/ml on day 14. Reduction in IL-6 in asymptomatic patients was statistically highly significant (p=0.0035) (Figure 3).

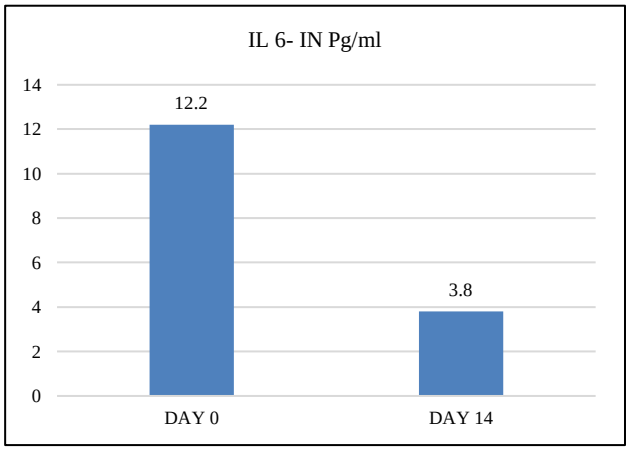

Figure 3: IL-6 in pg/ml from day 0 to day 14.

D-dimer

Mean D-dimer was showing decreasing trend from day 0 to day 14 in mild symptomatic patients. In asymptomatic patients' D dimer was 0.8 µg/ml on day 0 and 0.6 µg/ml on day 14. D-Dimer decreased significantly from day 0 to day 14 (p value =0.0013) (Figure 4).

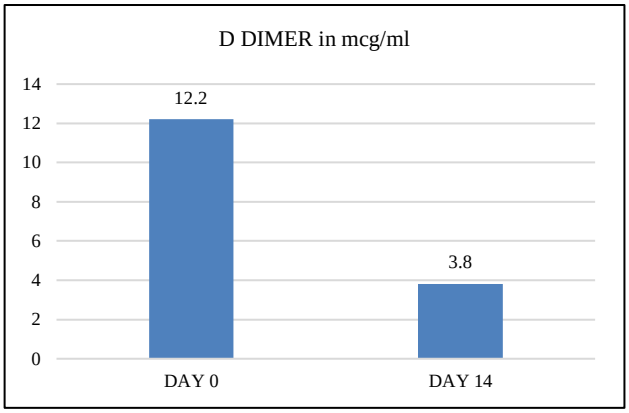

Figure 4: D-dimer in µg/ml from day 0 to day 14.

Lactic dehydrogenase (LDH)

Mean LDH values on day 0 in mild symptomatic patients was 319.4 U/l and 219.3 on day 14. The reduction in LDH values in mild symptomatic patients was statistically significant (p value <0.0122). In asymptomatic patients mean LDH values on day 0 was 237 U/l and 194 U/l on day 14. The reduction in LDH values in asymptomatic group was statistically significant (Figure 5).

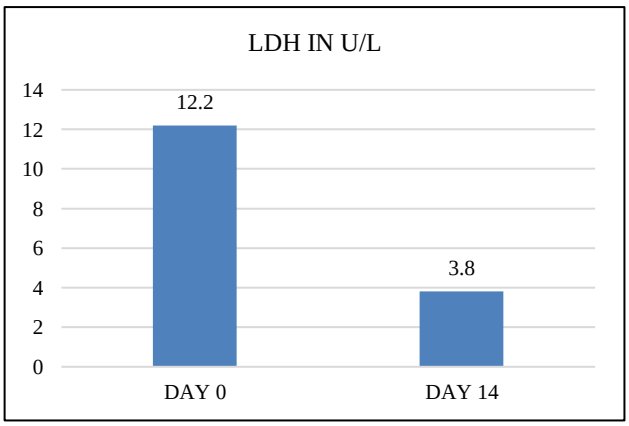

Figure 5: LDH in U/l from day 0 to day 14.

C-reactive protein (CRP)

Mean CRP values in mild symptomatic patients on day 0 was 12.2 mg/l and 3.8 mg/l on day 14. There was significant reduction in CRP values in mild symptomatic group which was statistically significant (p value =0.0546). Mean CRP values in asymptomatic patients on day 0 was 4.9 mg/l and 2.8 mg/l on day 14. There was significant

reduction in mean CRP in asymptomatic patients which was statistically significant (p value =0.0446) (Figure 6).

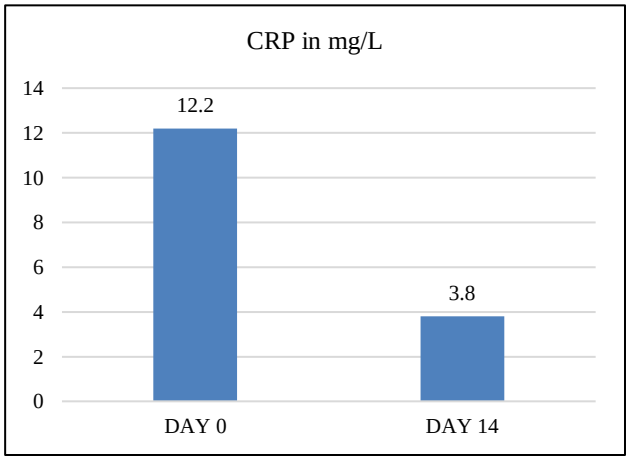

Figure 6: CRP in mg/l from day 0 to day 14.

RT PCR viral conversion

RT-PCR negativity of the throat/nasal swab is an important indicator of elimination of virus particles from the body and active immune status against Corona virus in COVID-19. In many studies COVID-19 patients showed that the average contagious period of SARS-CoV-2 infected patients was 20 days.[15] Hence early conversion will reduce the chances of viral spread among the primary and secondary contacts. In the present study 40 patients (100%) cleared the virus and became negative for RT PCR test within 6 days. None of the patients progressed to severe COVID 19 and none of the patients succumbed to the disease.

Clinical outcomes

Azadvir demonstrated significant improvement in clinical symptoms including fever, cough, sore throat and mild breathlessness as early as day 4 and most of the patients were clinically free of symptoms by day 7-10. In the present study more than 75 % of the patients in test group receiving AZADVIR recovered from the symptoms within 7 days. This early resolution of clinical symptoms correlates with early viral clearance or RT-PCR conversion.

Safety results

Vitals including temperature, systolic and diastolic blood pressure, pulse rate, heart rate and respiratory rate measured and recorded at all the visits. No significant changes in vital parameters were observed. The safety laboratory parameters RFT and LFT were within normal limits at screening and at the end of study. None of the subjects discontinued study due to adverse events. No serious adverse events (SAEs) were observed in the study participants, inferring the investigational product is safe for administration.

DISCUSSION

In this study we examined safety and efficacy of azadvir in asymptomatic and Mild COVID-19 patients. Safety assessment was done throughout the study period. None of the patient discontinued the study due to adverse events. Liver function has been identified as an important predictor for COVID-19 patient mortality. A recent study suggested that SARS-CoV-2 may directly bind to ACE2-positive cholangiocytes, and therefore, liver abnormalities in COVID-19 patients may be due to cholangiocyte dysfunction and other causes, such as drug induced and systemic inflammatory response-induced liver injuries.[16] Regarding the specific and dynamic pattern of liver injury parameters, Lei et al, in a wide retrospective multicenter study involving a COVID-19 cohort-derived data set of 5771 patients, reported that AST is strongly associated with mortality risk compared to other parameters, reflecting liver injury.[17] In present study liver function parameters were within normal limits at screening and on day EOT. And renal functions were also at the end of study period.

Severe infections may cause cytokine-mediated tissue damage and LDH release. Since LDH is present in lung tissue (isozyme 3), patients with severe COVID-19 infections can be expected to release greater amounts of LDH in the circulation, as a severe form of interstitial pneumonia, often evolving into acute respiratory distress syndrome, is the hallmark of the disease. It was also one of the biomarkers most strongly associated with ARDS mortality.[18,19] Hence LDH is an important laboratory parameter in assessing the severity of tissue injury. In the present study mean LDH levels reduced significanctly at the end of study in both asymptomatic and symptomatic subjects and it was statistically significant.

The CRP is an important prognostic marker and found to be significantly increased in the initial phases of the infection for severe COVID-19 patients, also prior to indications of critical findings with CT. Importantly, CRP has been associated with disease development and is an early predictor for severe COVID-19.[20] The increased CRP levels were likely due to COVID-19 related acute inflammatory pathogenesis during which multiple cytokines were released and their amount was associated with disease severity.[21] Hence CRP is an important lab parameter in assessing the severity of inflammation. In the present study Mean CRP levels reduced significanctly in from day 0 to EOT in both asymptomatic and symptomatic subjects and it was statistically significant.

Lymphopenia (lymphocyte count $<1{\cdot}0 \times 10^9$/l) and inflammatory cytokine storm are typical laboratory abnormalities observed during highly pathogenic coronavirus infections, such as the severe acute respiratory syndrome coronavirus (SARS-CoV) and the Middle East respiratory syndrome coronavirus (MERS-CoV) infections, and are believed to be associated with disease severities.[3,22] Recent studies have also reported decreases

in the counts of lymphocytes (e.g., CD4+ T cell, CD8+ T cell) in the peripheral blood and increases in serum inflammatory cytokine levels (e.g., IL-6) in COVID-19 patients.[23-25] Total leucocyte count is a marker to assess the immune response in the viral infections. In the present study none of the patients had low TLC throughout the study period.

D-dimer is a marker of disseminated intravascular coagulation (DIC) and associated with worst prognosis. Recent literature data show that D-dimer values are frequently enhanced in patients with COVID-19, being variably observed in 36 to 43% of positive cases. D-dimer values are even higher in patients with severe COVID-19 than in those with milder forms and therefore, D-dimer measurement may be associated with evolution toward worse clinical picture in COVID-19 patients.[26-30] Notably, Tang et al also recently highlighted that the vast majority of COVID-19 patients who died during hospital stay fulfilled the criteria for diagnosing disseminated intravascular coagulation (71.6 versus 0.6% in survivors). In the present study mean D-dimer values reduced significanctly in all subjects at the end of therapy (EOT) and it was statistically significant.

Post-covid complications and finacial burden to patients

COVID-19 patients experience high levels of proinflammatory cytokines and often progress to acute respiratory distress syndrome (ARDS) and require mechanical ventilation.[31,32] ARDS may cause permanent scarring of the lung tissue, resulting in respiratory problems that persist long after recovery. Between 33 and 75% of patients with COVID-19 require mechanical ventilation, often for weeks at a time. Those on ventilators are more prone to respiratory infections, which, in turn, predispose patients to further harm and risk of permanent lung damage. COVID-19 infection is also associated with high rates of extra-pulmonary complications that may continue to incur morbidity, disability, and delayed mortality in survivors. These include cardiac injury, acute ischemic or hemorrhagic stroke, neurological deficits, acute kidney injury, including the need for dialysis, and liver injury. The thromboembolic complications of COVID-19, such as pulmonary embolism, stroke, and other microinfarctions, can cause a wide range of permanent organ damage. Independent of ARDS, severe pneumonia has been associated with increased risk of incident heart disease both in the immediate aftermath of the infection and in later years.[33] In hospitalised COVID patients it is observed that with increasing hospitalization time requiring ICU/ventilator support and managing post covid complications increased the overall cost of covid management and financial burden to the patient. Effective COVID-19 treatment strategies may lower costs and increase the effectiveness of resource allocation.[34]

None of the patients in present study progressed to severe COVID-19 at the end of study. Azadvir has significantly reduced pro inflammatory markers including CRP, LDH and D-Dimer which are known to cause cytokine storm and thromboembolic events leading to post covid complications. Azadvir demonstrated significant improvement in clinical symptoms as early as day 4 and 75% of the patients were clinically free of symptoms by day 7-10. This early resolution of clinical symptoms correlates with early viral clearance or RT-PCR conversion. Thus in this COVID 19 study azadvir improved COVID 19 clinical features and immune markers significantly.

CONCLUSION

The aim of the present study was to evaluate safety and efficacy of AZADVIR steam inhaler in asymptomatic and mildly symptomatic COVID-19 patients. Azadvir has demonstrated an excellent safety and efficacy profile in COVID-19 patients along with standard of care. Azadvir steam inhaler administered patients demonstrated significant improvement in clinical symptoms and early recovery in more than 75% of the patients. Azadvir when administered in mildly symptomatic COVID-19 patients' demonstrated significant antiviral activity and improvement in immune markers including CRP, LDH and D-dimer. This clearly indicates that azadvir when administered along with standard of care has definitive role in the management of asymptomatic and mildly symptomatic COVID-19 patients.

ACKNOWLEDGEMENTS

Authors are thankful to all the patients and staff of Shetty's Hospital, Bommanahalli, Kodichikkanahalli, Bangalore, Karnataka.

Funding: No funding sources
Conflict of interest: None declared
Ethical approval: All the study related documents were reviewed by Ethics committee- Shetty's hospital, Bengaluru prior to study initiation. The study was approved on 20th Jun 2020 and the study was conducted in compliance with Part 56 of Title 21 of the Code of Federal Regulations (CFR) and International Conference on Harmonization (ICH) guidelines. The aforementioned Ethics Committee was registered under CDSCO with registration number ECR/918/Inst/KA/2017 (Srikakulam and Shetty's hospital, Bengaluru)

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Cite this article as: Pottirayil A, Shankar AS, Kannoth S, Prasad P, Jaikar SKB, Reddy LM. A prospective, open label clinical study to evaluate the safety, efficacy and tolerability of azadvir herbal steam inhaler in asymptomatic, mildly symptomatic COVID-19 patients and health care workers posted to covid wards. Int J Basic Clin Pharmacol 2021;10:373-80.