A prospective, open label, randomized-controlled study to evaluate the efficacy and safety of Herbovir syrup in mildly symptomatic COVID-19 patients

A. Gopal Rao1, Shankar Achar Somashekar2*, Poorna Prasad3, Manjunath Reddy Lekkala4, Sreenivasa Hanumanthaiah4, Muralidhar1

ABSTRACT

Background: COVID-19 patients experience cytokine storm which cause pulmonary and extra-pulmonary complications. Effective antiviral and immune boosters are need of hour to treat COVID-19 as well as post COVID complications.

Methods: In this study involving mild COVID-19 we randomized 40 patients to receive a Herbovir syrup along with standard of care (SOC) or SOC alone in 1:1 ratio. We evaluated the benefits of Herbovir syrup by assessing clinical outcomes and improvement in immune markers (LDH, CRP, D-dimer).

Results: At the end of the study the immune markers in Herbovir group improved significant compared to control group. In patients who received Herbovir, LDH decreased from 334 U/l at baseline to 254 U/l at the end of treatment (p value <0.009), CRP decreased from 7.4 mg/l to 3.1 mg/l (p value=0.0171) and D-dimer decreased from 0.610 mg/l at baseline to 318 mg/l at the end of study (p value=0.001). TLC values did not go below normal range in Herbovir group whereas 8 patients in control group had low TLC at the end of study. Early recovery from COVID 19 symptoms was observed in >75% patients in Herbovir treated group.

Conclusions: Herbovir accelerated recovery of COVID-19 patients by early improvement in clinical symptoms and immune markers in this study and results clearly indicates that Herbovir syrup has antiviral, immune booster activity and has definitive role in the management of mild COVID-19 patients along with standard of care. (Funded by Venkat pharma. CTRI no. CTRI/2020/08/027041).

Keywords: COVID-19, Post COVID complications, Herbovir

INTRODUCTION

The novel coronavirus disease (COVID-19), which began in Wuhan, China, in December 2019, has been declared to be a pandemic by the world health organization (WHO). Caused by the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), COVID-19 has resulted in 53,164,803 confirmed cases of COVID-19 globally, including 1,300,576 deaths, reported to WHO, as of 14 November 2020.1 In India, from Jan 3 to 14 November 2020, there have been 8,773,479 confirmed cases of COVID-19 with 129,188 deaths.2
The most common findings associated with severe disease are older age, higher d-dimer levels, higher SOFA score, elevated IL-6, increased lactate dehydrogenase, hyperferritinemia and lymphopenia on admission. The most common complications are sepsis, respiratory failure, acute respiratory distress syndrome (ARDS), cardiac injury and acute kidney injury. Although not completely understood, multiple pathophysiological mechanisms have been hypothesized for the cause of mortality in COVID-19. The plausible mechanisms of respiratory failure are hyperinflammation due to “cytokine storm” causing ARDS. Another plausible mechanism of respiratory failure is occlusion and micro-thrombosis in small pulmonary vessels. Secondary hemophagocytic lymph histiocytosis (sHLH) is a hyperinflammatory condition characterized by hypercytokinemia with multi-organ failure. sHLH is usually triggered by viral infections and sepsis. Infections account for 6-28% of cases triggering sHLH. Severe COVID resembles sHLH characterized by cardinal features like fever, cytopenia, hyperferritinemia and increased interleukins. 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. Increased levels of D-dimer are commonly reported in one third of patients with severe illness. Occlusion and micro-thrombosis formation in pulmonary small vessels in such patients have also been reported. The endothelial cell dysfunction, induced by infection, results in excess thrombin generation and fibrinolysis shutdown in patients with infection. In addition, hypoxia stimulates thrombosis through not only increasing blood viscosity, but also a hypoxia-inducible transcription factor-dependent signaling pathway.3,4

Current treatment options

The emergence of novel coronavirus has posed a situation that warrants urgent global attention. As of now, there are no effective therapies available for coronavirus infection. There are some drugs approved for COVID-19 management including remdesivir, fabipiravir, hydroxychloroquine, ivermectin and doxycycline etc. There is no specific treatment, although different experimental treatments with antiviral drugs (lopinavir/ritonavir) and interferon are being used. Thus, though antiviral drugs are available in mainstream medicine for treating symptoms, but the benefits of these therapies are mere and hence quest for new and novel drugs continues. In view of this, complementary and alternative medicine (CAM) offers a plethora of interesting possibilities in patients. Herbs exhibit a diverse array of biological activities and can be effectively harnessed for managing pandemic flu. Potentially active herbs can serve as effective antiviral agents. The role of CAM for managing novel COVID-19 and the mode of action of these botanicals is presented here in an evidence-based approach that can be followed to establish their potential use in the management of corona virus pandemics.

### Table 1: Mechanism of action-herbovir ingredients literature review.

| Herbal ingredient         | MOA-Herbovir ingredients literature review                                      |
|---------------------------|----------------------------------------------------------------------------------|
| Ocimum basilicum          | The extract inhibits the virus at the step of attachment and entry into the host cell.5 |
| Andrographolide           | The antiviral activity of andrographolide was evaluated in cell lines which showed that andrographolide has significant anti-viral activity.6 A. paniculata also exhibits a neutralizing activity and effectively inhibit the expression of viral lytic proteins and has the most antiviral inhibitory effects.7 |
| Nigella sativa (NS)       | Antiviral effect accorded with raising the serum level of interferon-gamma and increased numbers of CD4+ helper T cells, suppressor function and numbers of macrophages. By nonspecific cells including natural killer cell (NK cells), and specific cells including CD4 and CD8 T cells, immunity produced to viral infection is controlled. N. sativa suppress viral load. This is due to the increase in number and function of CD4+ve T cells and increased production of interferon-gamma.8 |
| Phyllanthus niruri        | Antiviral testing was carried out using different members of the Phyllanthus family and various species members have reported to demonstrate inhibitory effect against broad spectrum of viruses. Dose dependent antiviral activity and cytotoxicity was observed with Phyllanthus niruri in invitro studies.9 |
| O. majorana               | Has antiviral activity and in invitro studies it showed plaque reduction for various viruses.10 |
| Garlic                   | Virucidal activity and cytotoxicity depended upon the viral envelope and cell membrane, respectively. Activity against non-enveloped virus may be due to inhibition of viral adsorption or penetration.11 |
| Ginger                   | Fresh ginger of high concentration can stimulate mucosal cells to secrete IFN-β that helps to counteract viral infection.12 |
| Anethum suwa fruit       | Important source of the antioxidant, antimicrobial and cytotoxic agent.          |
| Tagetes (marigold)        | Its antiviral activity reflects in reduction of the viral cytopathic effect and viral plaques.13 |
| Tinospora cardifolia      | Expresses antiviral activity by significantly increasing the IFN-γ, IL-2, IL-4, and IL-1 levels in the peripheral blood mononuclear cells (PBMCs) and boosting immune system.14 |

International Journal of Basic & Clinical Pharmacology | January 2021 | Vol 10 | Issue 1 | Page 107
**Herbovir**

Earlier clinical studies using nutraceutical ingredients of the herbal origin have demonstrated significant antiviral and immunomodulatory activity. Herbovir is an herbal preparation containing multiple herbal extracts known to have antiviral activity and boost immunity. These herbs are used for various infectious ailments from many centuries and with abundant literature evidences. Herbovir contains various ingredients from Ocimum basilium whole plant Andrographis paniculata whole plant Nigella sativa seeds, Phyllanthus niruri root, Origum majorana flower, Allium sativum bulb, Zingiber officinale rhizome, Anethum suwa fruit, Taget tenuifolia flower and Tinospora cardifolia stem. 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 the 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 different types of the infections which including viral, bacterial and fungal infections in the traditional medicine.

**Table 2: Herbovir- in vitro cytotoxicity.**

| Name of the test substance | Test conc. (μg/ml) | % cytotoxicity | CTC50 (μg/ml) |
|----------------------------|-------------------|----------------|---------------|
| Test substance             |                   |                |               |
| 1000                       | 65.67±1.77        | 688.08±8.91    |
| 500                        | 40.55±1.08        |                |
| 250                        | 32.65±0.62        |                |
| 125                        | 28.23±0.46        |                |
| 62.5                       | 6.88±2.04         |                |

**Table 3: Herbovir- virucidal assay.**

| Virus | Name of the test substance | Test conc. (μg/ml) | TCID50 | Log reduction |
|-------|----------------------------|-------------------|--------|---------------|
| HSV-1 | Test substance             | 300               | 1.9    | 1.8           |
|       | 150                        | 2.7               |        |               |
|       | Acyclovir (STD)            | 10                | 1.1    | 2.6           |
|       | Pathogen control           | --                | 3.7    | --            |
| HSV-2 | Test substance             | 300               | 2.1    | 1.4           |
|       | 150                        | 2.9               |        | 0.6           |
|       | Acyclovir (STD)            | 10                | 1.3    | 2.2           |
|       | Pathogen control           | --                | 3.5    | --            |

It is also tested in vitro for cytotoxicity and antiviral activity. Herbovir showed dose dependent toxicity against vero cells. In virucidal assay Herbovir showed antiviral activity on HSV-1 and HSV-2 which is comparable to acyclovir as control (Table 2 and 3) (Data on file).

Based on the existing information we hypothesized that the Herbovir supplemented for fourteen days would provide a remarkable improvement of immunity in COVID-19 positive patients. The purpose of this study was to evaluate the efficacy and tolerability of the Herbovir in patients with COVID-19. Herbovir contains various potential herbs that have been evaluated for their safety and efficacy against the 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, randomized-controlled study conducted at government medical college and government general hospital, dept. of general medicine, Balaga, Srikakulam, Andhra Pradesh and Shettys hospital, Bommanahalli Kodichikkanhalli Bangalore, Karnataka. The study was approved by the institutional ethics committee at each center. The trial, which was sponsored by Venkat pharma, 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/2020/08/027041).

All the patients had positive results on testing for SARS-CoV-2 and presented with one or more mild symptoms. The investigators reviewed the symptoms, risk factors, and other inclusion and exclusion criteria before enrollment. All the patients provided written informed consent. From August 2020 through September 2020, a total of 48 patients were screened and 40 subjects were enrolled. These patients were randomized in 1:1 ratio into test group and control group of 20 each. All subjects completed the study and included in safety and efficacy analysis. (n=20 in the test group and n=20 in the control group) Both the groups were managed with the standard of care (SOC). In addition, the test group received Herbovir syrup formulation 10 ml 3 times daily for 14 days. 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. The control group received standard of care treatment only. All subjects were followed up for 14 days or end of treatment whichever is earlier. There was a telephonic visit on day 21 to monitor adverse events if any. Study conducted in August and September months of 2020.

**Patients**

Inclusion criteria for this study included the age limit of 18-65 years and of either sex, who are willing to give consent to the study with COVID-19 positive clinical symptoms and (subsequently) confirmed by the current
recommended confirmatory test, having mild clinical disease, who can take oral medicines and willing to abide by and comply with the study protocol. Exclusion criteria included the age of less than 18 years and more than 65 years, pregnancy and lactation, severe or complicated course of COVID-19 disease, presence of acute hypoxic respiratory failure/need for intensive care unit (ICU) stay/patients who need mechanical ventilation, subjects taking steroid treatment and or any kind of immunosuppressive therapy, any uncontrolled systemic disease/infection and those with serious cardiovascular, cerebrovascular, respiratory, liver or renal disease or any other disorder. 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, lactic dehydrogenase (LDH), C-reactive protein (CRP), D-dimer and total leucocyte count (TLC)). After this screening, patients were randomly assigned to receive either SOC or SOC and Herbovir syrup in 1:1 ratio. Patients were evaluated at day 1, 7 and 14 after randomization, with a focus on assessment of clinical symptoms and adverse events. Repeat assessment of safety and efficacy parameters (LFT, RFT, LDH, CRP, D-dimer and TLC) was done on day 14. Additional visit (telephonic) was scheduled at day 21 for adverse event monitoring. Simple randomization is followed in this study. The principal investigator was provided with the investigational products with the subject’s code number.

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. TLC, LDH, CRP and D-dimer and RT-PCR are monitored for improvement on day 0 and day 14. Renal function test (RFT) and liver functions test (LFT) are 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 separately for within control group (baseline vs. visit-4) and within test group (baseline vs. visit-4) for 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. We included data from all the patients who had undergone randomization in the analyses of the efficacy and safety outcomes, according to the intention-to-treat principle. Baseline characteristics were summarized as means and standard deviations, medians and interquartile ranges, or percentages. Unless otherwise stated, all hypotheses will be tested at a significance level of 0.05 and 95% confidence interval. As per Investigator discretion discontinuation of study on end of treatment (EOT) visit is considered as visit 4 instead of day 14 to keep the safety and well being of patient.

RESULTS

All 40 subjects were distributed equally between two groups. Total 25 male (62.5%) and 15 females (37.5%) participated in study. Mean age of participants 37.5 years.

LDH: In control group mean LDH was 350 U/l on day 0 and 356 on end of therapy (EOT). In test group mean LDH was 334 U/l on day 0 and 254 U/l on EOT. Mean LDH levels reduced significantly in test group compared to control group and it was statistically significant (p<0.009) (Table 4, Figure 1).

![Figure 1: LDH data.](image)

CRP: In control group mean CRP was 6.9 mg/L on day 0 and 5.2 mg/L on EOT. In test group mean CRP was 7.4 mg/L on day 0 and 3.1 mg/L on day 14. Mean CRP levels reduced significantly in test group compared to control group from day 0 to EOT and it was statistically significant (p=0.0171) (Table 3, Figure 2).

TLC: There was no decrease in TLC in test group whereas 8 patients in control group had low TLC count. There was no increase in mean TLC is both groups during period of 14 days (Table 4, Figure 3).
**D-dimer:** Mean D-dimer was 0.610 on day 0 and 0.318 on day EOT. In control group mean D-dimer is 0.730 on day 0 and 0.896 on day EOT. Mean D-dimer values reduced significantly in test group compared to control group at the end of therapy (EOT) and it is statistically highly significant (p value=0.001) (Table 4, Figure 4).

![Figure 2: CRP data.](image1)

![Figure 3: TLC data.](image2)

![Figure 4: D-dimer data.](image3)

**Clinical features:** Herbovir 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. Breathlessness was resolved completely in all patients in test group at day 10 whereas in control group 7 patients still had breathlessness at day 14. Early recovery from signs and symptoms was observed in more than 75% of the patients in test group when compared to control group. 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. Hence early conversion will reduce the chances of viral spread among the primary and secondary contacts. In the present study more than 75% of the patients in test group receiving Herbovir recovered from the symptoms within 7 days which is higher and significant compared to control group. This early resolution of clinical symptoms correlates with early viral clearance or RT-PCR conversion (Table 5).

**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. Hence early conversion will reduce the chances of viral spread among the primary and secondary contacts. In the present study RT-PCR was done at baseline. However, repeat RT-PCR was not done at the end of treatment/discharge as per the revised discharge policy from government of India, which states that there is no need for the RT-PCR for the patient discharge and discharge of the patient should be based on resolution of symptoms. (Revised discharge policy dated 23rd Jun 2020 attached in Annexure) In the present study more than 75% of the patients in test group receiving Herbovir recovered from the symptoms within 7 days which is higher and significant compared to control group. This early resolution of clinical symptoms correlates with early viral clearance or RT-PCR conversion.
Table 4: Descriptive statistics of results.

| Parameter       | Visit     | Test     | Control    |
|-----------------|-----------|----------|------------|
| LDH in U/l      | N         | Day 0    | 19         | 18         |
|                 | Mean (SD) | Day 0    | 334.7 (105.67) | 350.3 (118.47) |
|                 | N         | EOT      | 19         | 18         |
|                 | Mean (SD) | EOT      | 254.1 (68.39) | 356.2 (78.44) |
| CRP in mg/l     | N         | Day 0    | 7.4 (5.95) | 6.9 (5.04) |
|                 | Mean (SD) | EOT      | 3.1 (2.65) | 5.2 (3.98) |
| TLC/microliter  | N         | TLC (Day 0) | 19         | 18         |
|                 | Mean (SD) | TLC (Day 0) | 8425.8 (1894.80) | 7895.6 (1927.38) |
|                 | N         | EOT      | 8554.2 (1510.00) | 7256.7 (2716.48) |
| D-DIMER in mg/l | N         | Day 0    | 0.610 (0.2393) | 0.730 (0.3325) |
|                 | Mean (SD) | EOT      | 0.318 (0.1592) | 0.896 (0.3559) |

Table 5: Clinical features.

| Symptoms               | Assessment | Test group (Herbovir and SOC) | Control group (SOC) |
|------------------------|------------|--------------------------------|---------------------|
|                        |            | Day 0  | Day 4  | Day 7  | Day 10 | Day 14 | Day 0  | Day 4  | Day 7  | Day 10 | Day 14 |
| Fever                  | Febrile    | 20     | 10     | 5      | 0      | 0      | 20     | 11     | 9      | 3      | 0      |
|                        | Afebrile   | 0      | 10     | 15     | 20     | 20     | 0      | 9      | 11     | 17     | 20     |
| Cough                  | +/present  | 20     | 12     | 6      | 1      | 0      | 20     | 14     | 10     | 5      | 2      |
|                        | -/absent   | 0      | 8      | 14     | 19     | 20     | 0      | 6      | 10     | 15     | 18     |
| Sore throat            | +/present  | 20     | 10     | 5      | 0      | 0      | 20     | 12     | 8      | 3      | 1      |
|                        | -/absent   | 0      | 10     | 15     | 20     | 20     | 0      | 8      | 12     | 17     | 19     |
| Mild breathlessness    | +/present  | 18     | 5      | 2      | 0      | 0      | 17     | 12     | 10     | 7      | 7      |
|                        | -/absent   | 2      | 15     | 18     | 20     | 20     | 3      | 8      | 10     | 13     | 13     |

Safety results

Vitals including temperature, systolic and diastolic blood pressure, pulse rate, heart rate and respiratory rate measured and recorded at all the visits. The safety laboratory parameters RFT and LFT were within normal limits at screening and on day 14. There was no clinically significant abnormality observed in test and control group subjects inferring the active product is safe for administration. There were 4 adverse events (2 nausea, 1 head ache, 1 stomach upset) observed for four different subjects in test group which were categorized as mild to moderate in severity with none of the events were judged to be related to study product in investigator’s opinion. In control group there were 5 adverse events of mild severity (3 gastritis and 2 nausea) observed. None of patients discontinued study due to adverse events. All adverse events were managed clinically by routine measures.

DISCUSSION

In this study we examined safety and efficacy of Herbovir in mild COVID-19 patients. Safety assessment was done throughout the study period. Few patients in both groups experienced adverse effects of mild to moderate in severity with none of the events were judged to be related to study product in the Investigator’s opinion. 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.\textsuperscript{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.\textsuperscript{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.\textsuperscript{18,19} Hence LDH is an important laboratory parameter in assessing the severity of tissue injury. In the present study mean LDH levels reduced significantly in test group compared to control group and it was statistically significant (p<0.009) (Table 6).

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.\textsuperscript{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.\textsuperscript{21} Hence CRP is an important lab parameter in assessing the severity of inflammation. In the present study Mean CRP levels reduced significantly in test group compared to control group from day 0 to EOT and it was statistically significant (p=0.0171) (Table 6).

Lymphopenia (lymphocyte count<1.0x10\(^9\)/l)\textsuperscript{3} 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.\textsuperscript{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.\textsuperscript{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 in test group had low TLC whereas 8 patients in control group had low TLC count. There was no increase in TLC at day EOT in both the groups (Table 6).

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.\textsuperscript{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 vs. 0.6% in survivors). In the present study mean D-dimer values reduced significantly in test group compared to control group at the end of therapy (EOT) and it is statistically highly significant (p=0.001) (Table 6).

\textbf{Post-covid complications and financial 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.\textsuperscript{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.\textsuperscript{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

\begin{table}[h]
\centering
\begin{tabular}{|c|c|c|c|}
\hline
\textbf{Visit} & \textbf{Statistic} & \textbf{Z Statistics} & \textbf{P value} \\
\hline
LDH difference (EOT-day 0) & 428.5000 & 2.6136 & 0.0090 \\
\hline
CRP difference (EOT-day 0) & 452.5000 & 2.3841 & 0.0171 \\
\hline
TLC difference (EOT-Day 0) & 313.5000 & -0.8510 & 0.3948 \\
\hline
D-DIMER difference (EOT-day 0) & 175.0000 & 3.1537 & 0.0016 \\
\hline
\end{tabular}
\caption{Summary of statistics.}
\end{table}
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. Herboriv 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. Herboriv 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 which is significant compared to control group. This early resolution of clinical symptoms correlates with early viral clearance or RT-PCR conversion. Thus, in this COVID-19 study Herboriv improved COVID-19 clinical features and immune markers significantly compared to placebo.

CONCLUSION

The aim of the present study was to evaluate safety and efficacy of Herboriv syrup in mildly symptomatic COVID-19 patients. Herboriv has demonstrated an excellent safety and efficacy profile in mildly symptomatic COVID-19 patients along with standard of care. Herboriv Syrup administered patients demonstrated significant improvement in clinical symptoms and early recovery in more than 75% of the patients in test group when compared to control group. Herboriv when administered orally for a period of 14 days 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 Herboriv syrup when administered orally along with standard of care has definitive role in the management of mildly symptomatic COVID-19 patients.

ACKNOWLEDGEMENTS

Authors would like to thank to all the patients and staff of government medical college and general government general hospital, dept. of general medicine, Balaga, Srikakulam, Andhra Pradesh and Shetty’s hospital, Bommanahalli, Kodichikkanahalli, Bangalore, Karnataka.

Funding: funding by Venkat Pharma, Ramanagara, Bangalore

Conflict of interest: None declared

Ethical approval: The study was approved by the Institutional Ethics Committee of Government Medical College-General Hospital ECR/492/Inst/ AP/2013/RR-20 and Srikakulam and Shetty’s hospital, Bengaluru, ECR/918/Inst/KA/2017.

REFERENCES

1. WHO. WHO Coronavirus Disease (COVID-19) Dashboard Data. Global (Updated: 15th Nov 2020; cited on 15th Nov 2020.

2. WHO. WHO Coronavirus Disease (COVID-19) Dashboard Data. India (Updated: 15th Nov 2020; cited on 15th Nov 2020.

3. Tang N, Li D, Wang X, Sun Z. Abnormal coagulation parameters are associated with poor prognosis in patients with novel coronavirus pneumonia. J Thromb Haemost. 2020;18(4):844–7.

4. Levi M, Poll T. Coagulation and sepsis. Thromb Res. 2017;149:38–44.

5. Singh P, Chakraborty P, He D, Mergia A. Extract Prepared from the Leaves of Ocimum Basilicum Inhibits the Entry of Zika Virus. Acta Virol. 2019;63(3):316-21.

6. Panaroka P, Ramphan S, Khongwichit S, Smith D. Activity of andrographolide against dengue virus. Antiviral Res. 2017;139:69-78.

7. Jayakumar T, Hsieh C, Lee J, Sheu J. Experimental and Clinical Pharmacology of Andrographis paniculata and Its Major Bioactive Phytoconstituent Andrographolide. Evid Based Complement Alternat Med. 2013;2013:846740.

8. Yimer E, Tuem K, Karim A, Ur-Rehman N, Anwar F. Nigella sativa L. (Black Cumin): A Promising Natural Remedy for Wide Range of Illnesses. Evid Based Complement Alternat Med. 2019;2019:1528635.

9. Tan W, Jagannath I, Manikam R, Sekaran S. Evaluation of Antiviral Activities of Four Local Malaysian Phyllanthus Species against Herpes Simplex Viruses and Possible Antiviral Target. Int J Med Sci. 2013;10(13):1817-29.

10. Guerra-Boone L, Alvarez-Román R, Salazar-Aranda R, Torres-Cirio A, Rivas-Galindo V et al. Antimicrobial and antioxidant activities and chemical characterization of essential oils of Thymus vulgaris, Rosmarinus officinalis, and Origanum majorana from northeastern México. Pak J Pharm Sci. 2015;28(1):363-9.

11. Weber ND, Andersen DO, North JA, Murray BK, Lawson LD, Hughes BG. In vitro virucidal effects of Allium sativum (garlic) extract and compounds. Planta Med. 1992;58(5):417-23.

12. Chang JS, Wang KC, Yeh CF, Shiieh DE, Chiang LC. Fresh ginger (Zingiber officinale) has anti-viral activity against human respiratory syncytial virus in human respiratory tract cell lines. J Ethnopharmacol. 2013;145(1):146-51.

13. Jaime MFV, Redko F, Muschietti LV, Campos RH, Martino VS, Cavallaro LV. In vitro antiviral activity of plant extracts from Asteraceae medicinal plants. Virol J. 2013;10: 245.

14. Sachan S, Dhamo K, Latheef SK, Samad HA, Mariappan AK, Munuswamy P et al. Immunomodulatory Potential of Tinospora cordifolia and CpG ODN (TLR21 Agonist) against the Very Virulent, Infectious Bursal Disease Virus in SPF Chicks. Vaccines (Basel). 2019;7(3):106.

15. Xiao AT, Tong YX, Gao C, Zhu L, Zhang YJ, Zhang S. Dynamic profile of RT-PCR findings from 301 COVID-19 patients in Wuhan, China: A descriptive study. J Clin Virol. 2020;127:104346.
16. Chai X, Hu L, Zhang Y, Han W, Lu Z, Ke A et al. Specific ACE2 expression in cholangiocytes may cause liver damage after 2019-nCoV infection. BioRxiv. 2020;1-13.

17. Pan L, Mu M, Yang P, Sun Y, Wang R, Yan J et al. Clinical Characteristics of COVID-19 Patients with Digestive Symptoms in Hubei, China: A Descriptive, Cross-Sectional, Multicenter Study. Am J Gastroenterol. 2020;115(5):766-73.

18. Henry BM, Santos de Oliveira MH, Benoit S, Plebani M, Lippi G. Hematologic, biochemical and immune biomarker abnormalities associated with severe illness and mortality in coronavirus disease 2019 (COVID-19): a meta-analysis. Clin Chem Lab Med. 2020;58(7).

19. Shi J, Li Y, Zhou X, Zhang Q, Ye X, Wu Z et al. Lactate dehydrogenase and susceptibility to deterioration of mild COVID-19 patients: a multicenter nested case-control study. BMC Med. 2020;18:168.

20. Tan W, Zhao X, Ma X, Wang W, Niu P, Xu W et al. A Novel Coronavirus Genome Identified in a Cluster of Pneumonia Cases Wuhan, China 2019-2020. China CDC Weekly. 2020;2(4):61-2.

21. Huang C, Wang Y, Li X, Ren L, Zhao J, Hu Y et al. Clinical features of patients infected with 2019 novel coronavirus in Wuhan, China. Lancet. 2020;395(10223):497-506.

22. Chen N, Zhou M, Dong X, Qu J, Gong F, Han Y et al. Epidemiological and clinical characteristics of 99 cases of 2019 novel coronavirus pneumonia in Wuhan, China: a descriptive study. Lancet. 2020;395(10223):507-13.

23. Qin C, Zhou L, Hu Z, Zhang S, Yang S, Tao Y et al. Dysregulation of Immune Response in Patients with Coronavirus 2019 (COVID-19) in Wuhan, China. Clin Infect Dis. 2020;71(15):762-8.

24. Khan S, Ali A, Shie H, Siddique R, Shabana, Nabif G et al. COVID-19: Clinical aspects and therapeutics responses. Saudi Pharmaceutical J. 2020;28(8):1004-8.

25. Ge H, Wang X, Yuan X, Xiao G, Wang C, Deng T et al. The epidemiology and clinical information about COVID-19. Eur J Clin Microbiol Infect Dis. 2020;1-9.

26. Lippi G, Mattiucci C, Bovo C, Plebani M. Current laboratory diagnostics of coronavirus disease 2019 (COVID-19). Acta Biomed. 2020;91(2):137-45.

27. Mishra Y, Pathak BK, Mohakuda SS, Sen S, Singh R, Singh AR. Relation of D-dimer levels of COVID-19 patients with diabetes mellitus. Diabetes Metab Syndr. 2020;14(6):1927-30.

28. Rostami M, Mansouriforghabeh H. D-dimer level in COVID-19 infection: a systematic review. Expert Rev Hematol. 2020;1-11.

29. Vidal S, Morosetti D, Cossu E, Luisi MLE, Pancani S, Semeraro Y et al. D-dimer as an indicator of prognosis in SARS-CoV-2 infection: a systematic review. ERJ Open Res. 2020;6(2):00260-2020.

30. Yu H, QinC, Chen M, Wang W, Tian D. D-dimer level is associated with the severity of COVID-19. Thromb Res. 2020;195:219-25.

31. Heneka MT, Golenbock D, Latz E, Morgan D, Brown R. Immediate and long-term consequences of COVID-19 infections for the development of neurological disease. Alzheimers Res Ther. 2020;12(1):69.

32. Dasgupta A, Kalhan A, Kalra S. Long term complications and rehabilitation of COVID-19 patients. J Pak Med Assoc. 2020;70(3-5):S131-5.

33. Jiang DH, McCoy RG. Planning for the Post-COVID Syndrome: How Payers Can Mitigate Long-Term Complications of the Pandemic. J Gen Intern Med. 2020;35(10):3036-9.

34. Lee JK, Kwak BO, Choi JH, Choi EH, Kim JH, Kim DH. Financial Burden of Hospitalization of Children with Coronavirus Disease 2019 under the National Health Insurance Service in Korea. J Korean Med Sci. 2020;35(24):e224.