Original Article

Thalidomide for the Treatment of COVID-19 Pneumonia: A Randomized Controlled Clinical Trial

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Abstract

Background: Coronavirus disease 2019 has become a public health concern with a high number of fatalities. Thalidomide can target inflammatory mediators and decrease inflammation in SARS-CoV-2.

Materials and Methods: An open-label, randomized controlled trial was conducted on patients with compatible lung high-resolution computed tomography scan for COVID-19 pneumonia and moderate involvement. Childbearing-age women were excluded. A total of 20 patients in the control group receiving usual treatment were compared with 26 patients in the case group who in addition to the same regimen also received thalidomide. The primary outcome was time for clinical recovery (TTCR) and intensive-care unit (ICU) admission.

Results: From April 25 to August 8, 2020, based on the inclusion criteria, 47 patients were assigned to the study. Patients receiving thalidomide had a mean TTCR of days 5.5 (95% confidence interval [CI], 0.7–10.3), as compared with days 5.3 (95% CI, 1.7–8.9) with control (odds ratio 0.01; 95% CI, −1.58–1.59, $P = 0.807$). The incidence of ICU admission was 27% in the thalidomide group compared with 20% in the control group (odds ratio 3.89; 95% CI, 0.55–27.4, $P = 0.425$). The mean length of stay in hospital in both groups was 10 days. Progressive improvement in respiratory rate, fever, and O_2 saturation during the study was seen in both groups without a significant difference between the thalidomide and control group ($P > 0.05$).

Conclusion: This study investigated the effects of thalidomide to treat moderate COVID-19 clinical outcomes. The results established that this drug regimen did not add more effect to usual treatment for moderate COVID-19 pneumonia.

Keywords: COVID-19, intensive-care unit (ICU), length of stay, pneumonia, thalidomide

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Introduction

In December 2019, a new coronavirus disease 2019 (COVID-19) was recognized in Wuhan city, China, which rapidly spread all over the world, and it is one of the worst global pandemics.[1]

In 2003 and 2012, coronavirus caused the epidemics of the severe acute respiratory syndrome (SARS) and Middle East respiratory syndrome (MERS), respectively. In 2019, COVID-19, another coronavirus (SARS-CoV-2) caused SARS.[2]

The contagious disease spread around 200 other countries within a few months.[3] Accordingly, the World Health Organization (WHO) declared the COVID-19 outbreak a pandemic on March 11, 2020. Until October 26, 2020, the confirmed number of cases surpassed 43 million including

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more than 1,162,000 deaths across the world.[4] Fortunately, this infectious disease despite its highly contagious nature infects only about 20% of patients severely. Severity of the disease includes severe respiratory failure, septic shock, and multi-organ dysfunction. Acute inflammatory disease and fatal manifestations of this viral infection are much more common in older adults, particularly in those with underlying diseases.[3]

This pathogen usually targets the upper and lower respiratory systems; accordingly, respiratory symptoms and signs are highly detected in COVID-19 patients.

Coronavirus pathogens primarily target the respiratory system and pathological changes in pulmonary involvement include edema and proteinaceous exudate with globules, patchy inflammatory cellular infiltration, and formation of hyaline membranes.[5]

Among patients with severe infection in the lung lesions, extensive infiltration of neutrophils and macrophages but minimal lymphocyte infiltration is detected. Neutrophils and monocytes in the peripheral blood increase, whereas CD4 and CD8 and natural killer (NK) cells are reduced.[3,6]

Cytokine storm refers to uncontrolled release of pro-inflammatory cytokines initiate in the infected lungs and spread all over the body through systemic circulation.[7]

Multi-organ damage is mainly caused by the unregulated circulating cytokines and the over-expression of inflammatory mediators in the interstitial space of various organs that induce universal endothelium and parenchyma injuries.[8-10] This viral infection might be hypothetically controlled by anti-viral and supportive care, but cytokine storm as a severe body challenge should be restricted using anti-inflammatory drugs.[3] Immunotherapies by targeting inflammatory mediators or passively neutralizing the SARSCoV2 or preventing its entry to the host as an adjunct therapy in severe cases are being considered.[11]

Thalidomide is approved for multiple myeloma and erythema nodosum leprosum (ENL) treatment. This drug is immunomodulatory and has anti-inflammatory effects, T-cell stimulation ability, and cell proliferation inhibition ability; hence it is a promising candidate for lung injury and pulmonary fibrosis reduction.[12]

Thalidomide can speed up the degradation of mRNA in blood cells and thus decreases tumor necrosis factor-α (TNF-α), and it increases the secretion of interleukins, such as IL-12, and activates NK cells, and was shown to down-regulate the phagocytic activity of immune cells. These anti-inflammatory actions help to improve lung injury, increase survival, reduce inflammatory cell infiltration, and inhibit cytokines against the H1N1 influenza virus in vivo.[13,14] Also, thalidomide's anti-inflammatory properties treated acute cutaneous manifestations of moderate to severe cases of ENL.[15]

Preclinical studies tested thalidomide's effectiveness in several pulmonary diseases and lung injuries.[15] There is only one clinical study that treated 23 patients who were suffering from idiopathic pulmonary fibrosis with thalidomide. This study reported improvement in cough and respiratory signs and tolerable side effects such as constipation, dizziness, and malaise.[15]

In accordance with the above, based on potent anti-inflammatory properties of thalidomide and its potential ability to control inflammation and cytokine storms, this drug can be considered in treating respiratory complications associated with COVID-19. However, thalidomide's side effects including peripheral neuropathy, anemia, thrombocytopenia, and venous thromboembolism should be noted. COVID-19-infected patients require anti-inflammatory treatment for a short period, whereas the side effects of thalidomide, apart from sleepiness, usually appear after prolonged use.[16]

This study evaluated thalidomide's effectiveness and safety as an adjuvant therapy to routine treatment for moderate COVID-19-induced pneumonia.

Methods

Ethics approval

The study was approved by the Ethics Committee of the research center of Isfahan University of Medical Science (ethical code: IR.MUI.MED.REC.1399.048).

This trial was conducted as an open-labeled, randomized, controlled trial In Amin General Hospital, Isfahan University of Medical Science.

Written informed consent was obtained from all of the patients or a legal representative if they were unable to provide consent.

Patients selection

Patients with COVID-19 signs and symptoms and compatible lung high-resolution computed tomography (HRCT) scan with or without positive COVID-19 nasopharyngeal reverse-transcriptase polymerase chain reaction test who were hospitalized from April to August 2020 and fulfilled the inclusion criteria were assigned to this trial.

Inclusion criteria

(1) 18–75-year-old men and 50–75-year-old women who were hospitalized.
(2) SpO2: 85–89% on admission time (if correct with O_2 nasal maximum 6 l/min to SpO2> = 90%) or SpO2: 90–93% and RR >30 (considered as moderate pneumonia).

Exclusion criteria

(1) Needed intubation in the first 24 hours of admission
(2) Multi-organ failure at presentation
(3) Hepatic failure (Child-Pugh score ≥C, AST >5 times the upper limit normal)
(4) Severe renal dysfunction (GFR less than 30 cc per min)
(5) Women of childbearing age (less than 50 years old) excluded from this study.

Study design

In this randomized, controlled, open-label platform trial, eligible patients enrolled to study and investigator fulfilled a form with the following information: demographic characteristics, symptoms at presentation, COVID-19 symptoms onset date, date of hospitalization, first O_2 saturation percentage, respiratory rate and temperature, major comorbidity (e.g., heart disease, diabetes, and hypertension), date of ICU admission or discharge from the hospital, whichever happened sooner.

Patients were randomized in two treatment arms (control arm and thalidomide arm) using random numbers generated by randomizer.org.

The usual treatment prescribed for all patients included tab. hydroxychloroquine, 200 mg, BID for 5 days, OR dexamethasone, 8 mg, intravenously for 10 days (according to the national protocol), enoxaparin, 40 mg, subcutaneously, daily during hospitalization, and tab. acetaminophen PRN for symptom control and diphenhydramine syrup for cough. Tab. thalidomide, 100 mg, PO daily for 14 days was added to the usual treatment in the thalidomide arm.

Collecting follow-up information included daily O_2 saturation percentage, respiratory rate, and temperature that were recorded by the clinician on a daily visit, as well as discharge date and ICU admission date.

The following parameters were evaluated at first: Cell blood count (CBC), Blood urea nitrogen (BUN), creatinine (Cr), Sodium (Na), Potassium (K), Aspartate aminotransferase (AST), Alanine aminotransferase (ALT), Alkaline phosphatase (ALP), Venous blood gas (VBG), C-reactive protein (CRP), Prothrombin time (PT), Partial thromboplastin time (PTT), International normalized ratio (INR), Creatine phosphokinase (CPK), Lactate dehydrogenase (LDH), Calcium, Phosphorous, Bilirubin, Albumin, Troponin, Magnesium and Ferritin. During discharge time, CBC, LDH, AST, ALT, bilirubin, BUN, Cr, and CRP were requested. Electrocardiogram (ECG) was obtained on the first, third, and fifth days of hydroxychloroquine prescription.

The patients were visited daily by an intern, and patients were followed up by phone visits weekly for up to 4 weeks for any readmission.

Outcomes

Primary Outcome

1. Time to clinical recovery (TTCR) means days from admission until body temperature <38°C, respiratory rate <24, and SpO2 >90% on room air without supplementary oxygen
2. ICU admission (meeting any of the following criteria): Progression to severe pneumonia (SpO2 <85%), occurrence of respiratory failure (requiring mechanical ventilation), and occurrence of organ failure.

Secondary outcome

1. 28 days survival rate
2. 14 days readmission rate.

Thalidomide was administrated for 14 days even if patients were discharged. Thalidomide was discontinued if the patients progress to severe pneumonia that needed ICU admission or intubation or developed organ failure or if any complication of thalidomide occurred.

Safety

Any suspected adverse reactions and side effects of thalidomide were recorded by clinicians. All patients were also monitored closely for any signs of ECG rhythm abnormality or clinical features of cardiac arrhythmia.

Methods of analysis

Data were entered into the SPSS software (version 21) and analyzed. The mean and standard deviation (SD) were used to describe the quantitative data, and frequency and frequency percentages were used for the qualitative data. Chi-square analysis was used to compare qualitative data between control and intervention groups, and the Mann–Whitney U was used for the quantitative data. Also, to compare the changes in the respiratory rate, O_2 saturation, and temperature over time between the control and intervention groups, analysis of variance (ANOVA) repeated measure was used. Linear regression was used to evaluate the effect of thalidomide on TTCR as well as control the effect of the prescribed treatment (dexamethasone or hydroxychloroquine). To assess the effect of thalidomide on TTCR, ICU admission, and hospitalization days, linear or logistic regression was used. A significance level of 5% was considered for all analyses.

Results

Patients characteristics

From April 25 to August 8, 2020, based on the inclusion criteria and after excluding 32 cases, 47 cases were included in the study, which were randomized and allocated to two treatment groups the case (n = 27) and control (n = 20) patients.

Except for one patient who was excluded on the second day of the study because of nausea and vomiting starting before the study, all thalidomide group patients completed their 14-day treatment duration.

The mean (±SD) age of the patients in the thalidomide and control group was 53.6_+12.7 years and 55.6_+13.4 years, respectively. 67% of the patients were male. History of IHD was present in 13% of the patients, diabetes mellitus in 26%, and hypertension in 28%.

78% of the patients had laboratory-confirmed SARS-CoV-2 infection (positive PCR) and all of the patients had lung HRCT highly suggestive of COVID-19 pneumonia.

The mean O_2 saturations (SpO2) before intervention in the thalidomide and control groups were 86% and 87% respectively.

58% of the patients received hydroxychloroquine in the thalidomide group and 70% in the control group.

50% of the patients received dexamethasone in the thalidomide group and 30% in the control group [Table 1].

Primary outcomes

The results showed that in both groups, decreasing changes in RR and T and increasing changes in O_2 saturation before the study up to three times after the initiation of the study were significant, but these changes were not significantly different between the intervention and control groups ($P > 0.05$).

Table 1: Demographic and baseline clinical data of the patients in the two groups

	Intervention ($n=26$)	Control ($n=20$)	P*
Gender: male: *n* (%)	21 (80.8)	10 (50.0)	0.027*
Age: yr.: Mean (SD)	53.6 (12.7)	55.6 (13.4)	0.969
Smoking: *n* (%)	7 (26.9)	6 (30.0)	0.818
Addiction: *n* (%)	4 (15.4)	3 (15.0)	0.971
Medical history: *n* (%)			
No history	16 (61.5)	10 (50.0)	0.434
Ischemic heart disease	2 (7.7)	4 (20.0)	0.380
Diabetes mellitus	6 (23.1)	6 (30.0)	0.596
Hypertension	6 (23.1)	7 (35.0)	0.373
Drug history: *n* (%)	17 (65.4)	13 (65.0)	0.987
PCR positive: *n* (%)	20 (76.9)	16 (80.0)	0.802
Symptoms onset days before admission: Mean (SD)	7.5 (3.7)	7.6 (3.8)	0.921
Fibrinogen: Mean (SD)	326.8 (82.5)	361.6 (114.1)	0.461
Ferritin: Mean (SD)	654.6 (121.5)	615.9 (182.4)	0.858
D-dimer: Mean (SD)	527.1 (255.7)	611.1 (445.0)	0.467
Erythrocyte sedimentation rate	34.2 (14.1)	40.0 (28.1)	0.406
Hydroxychloroquine	15 (57.7)	14 (70.0)	0.540
Dexamethasone	13 (50.0)	6 (30.0)	0.232

The Chi-square/Fisher exact test for categorical variables and the Mann-Whitney test for continuous variables were significant if P value<0.05

Tables 2 and 3 show the treatment outcomes in both treatment groups.

TTCR did not have a statistical difference between the thalidomide group and the usual treatment group (5.5 days versus 5.3 days P: 0.8).

27% of patients in the thalidomide group and 20% in the control group progressed to severe pneumonia and were admitted to the ICU.

Lymphocyte count and LDH in both groups, after treatment, did not show a significant difference (mean lymphocyte count after treatment 2019 versus 1750 P: 0.372; mean LDH after treatment 594 versus 486 P: 0.14).

Mean CRP after treatment in thalidomide and control patients was 31.7 versus14 (P-value: 0.015) [Table 4].

The length of stay in hospital in both groups was 10 days.

One patient after the 10th day in the thalidomide group suddenly exhibited a drop in the SpO2 level and became tachypneic with pulmonary thromboembolism diagnosis; subsequently, thalidomide was discontinued, and therapeutic anticoagulation was prescribed.

Secondary outcome

There was no mortality in both groups, and no patients were readmitted in 28 days of follow-up.

Discussion

COVID-19 pandemic with serious and multiple peaks worldwide has caused severe morbidity and mortality, and it is important to investigate an effective and safe treatment plan. Many drugs have been studied, but none of them have proven to be effective significantly.

Table 2: Determination and comparison of main outcomes in the two groups

	Intervention ($n=26$)	Control ($n=20$)	P*	$P^{\&}$
TTCR: Days: Mean (SD)	5.5 (2.4)	5.3 (1.8)	0.807	-
ICU: *n* (%)	7 (26.9)	4 (20.0)	0.425	-
Length of stay (days): mean (SD)	10.5 (3.8)	10.9 (6.8)	0.713	-
Respiratory Rate[b]: Mean (SD)	25.2 (7.3)	26.9 (4.4)	0.766	0.631
Respiratory Rate[a.1]: Mean (SD)	24.0 (6.0)	25.4 (4.6)	0.249	
Respiratory Rate[a.5]: Mean (SD)	21.3 (5.6)	22.8 (6.3)	0.639	
Respiratory Rate[a.16]: Mean (SD)	18.5 (2.2)	18.3 (2.6)	0.885	
Temperature[b]: Mean (SD)	37.7 (0.72)	37.6 (0.65)	0.490	0.612
Temperature[a.1]: Mean (SD)	37.7 (0.83)	37.3 (0.56)	0.219	
Temperature[a.5]: Mean (SD)	36.9 (0.63)	37.0 (0.63)	0.617	
Temperature[a.16]: Mean (SD)	36.7 (0.43)	36.9 (0.64)	0.814	
O_2sat percentage[b]: Mean (SD)	0.86 (0.03)	0.87 (0.03)	0.081	0.691
O_2sat percentage[a.1]: Mean (SD)	0.88 (0.03)	0.88 (0.03)	0.825	
O_2sat percentage[a.5]: Mean (SD)	0.90 (0.04)	0.89 (0.04)	0.885	
O_2sat percentage[a.16]: Mean (SD)	0.92 (0.03)	0.92 (0.03)	0.845	

b: before intervention; a. 1: one day after intervention; a. 5: 5 days after the intervention, a. 16: 16 days after intervention. *Chi-square test for categorical variables and Mann-Whitney test for continuous variables were significant if P value <0.05. ANOVA repeated-measure test, adjusting gender difference, was significant if P value <0.05. (Power>0.66)

Table 3: Determination and comparison of laboratory tests in the two groups

	Before intervention			After Intervention		
	Mean (SD)		*P**	Mean (SD)		*P**
	Intervention (*n*=26)	Control (*n*=20)		Intervention (*n*=26)	Control (*n*=20)	
WBC count ($\times 10^3$)	6453 (2661)	6390 (3797)	0.234	9536 (3865)	6788 (1799)	0.084
Lymphocyte count ($\times 10^3$)	1637 (1390)	1735 (1063)	0.137	2019 (1303)	1750 (1030)	0.372
Platelet count ($\times 10^3$)	188.1 (56.5)	204.8 (67.5)	0.372	309.5 (135.8)	297.9 (154.9)	0.615
AST (u/l)	47.3 (21.2)	42.8 (17.5)	0.616	43.8 (15.0)	43.1 (20.1)	0.227
ALT (u/l)	35.3 (20.6)	34.3 (14.5)	0.969	88.8 (70.7)	94.4 (104.9)	0.687
Bilirubin (mg/dl)	0.76 (0.35)	0.65 (0.31)	0.991	0.46 (0.33)	0.46 (0.30)	0.802
LDH (u/l)	650.5 (189.3)	646.1 (260.5)	0.766	594.2 (180.2)	486.2 (130.2)	0.141
CRP (mg/dl)	52.5 (38.2)	54.6 (37.2)	0.861	31.7 (28.9)	14.0 (20.4)	0.015
BUN (mg/dl)	16.2 (3.1)	16.8 (9.3)	0.372	20.2 (7.7)	18.4 (8.5)	0.256
Cr (mg/dl)	1.25 (0.21)	1.23 (0.31)	0.219	1.19 (0.28)	1.07 (0.14)	0.295

*Mann-Whitney test was significant if *P* value<0.05

Table 4: Determination and comparison of main outcomes in the two groups adjusted for the type of standard drug, gender, and underlying disease

Clinical outcome	Beta/Odds Ratio of thalidomide (0.95% CI)	
	Crude	Adjusted*
TTCR[&]	0.21 (−1.71,1.28)	0.01 (−1.58,1.59)
Length of stay (days)[&]	−0.48 (−3.63, 2.7)	−1.14 (−4.88, 2.60)
ICU admission[^]	1.47 (0.36,5.97)	3.89 (0.55-27.4)

[&]Beta estimated by linear regression and [^]odds ratio estimated by logistic regression; considering 5% for significant level*. TTCR: Time to clinical recovery; ICU: Intensive-care unit. (Power=0.69)

Thalidomide, because of its known immunomodulatory actions, has been noticed for the treatment of diseases with an inflammatory phase. Our study is the first to evaluate the effects of thalidomide on non-critically ill COVID-19 patients with moderate pneumonia and evaluate its role in controlling disease progression.

In one study, thalidomide reduced damage to the lungs of mice infected with the H1N1 influenza virus and improved survival, reduced inflammatory cell infiltration in the lungs, and inhibited the production of cytokines.[13]

A case-series study result revealed that thalidomide significantly shortened the duration time to obtain a negative SARS-CoV-2 test, and hospital stay days were shorter in the thalidomide group. In addition, in their study, patients with critical COVID-19 infection in the thalidomide group needed less mechanical ventilation than in the control group. These pieces of evidence showed that dual treatment of thalidomide with a low dose of glucocorticoids improved the prognosis of patients with life-threatening COVID-19-induced pneumonia effectively.[17] It is noteworthy that their patients were critically ill, and the sample size was very small.

The present study is the first randomized, controlled trial designed to assess the effect of thalidomide treatments for moderate COVID-19 pneumonia on TTCR and the need for ICU admission and 28-day mortality.

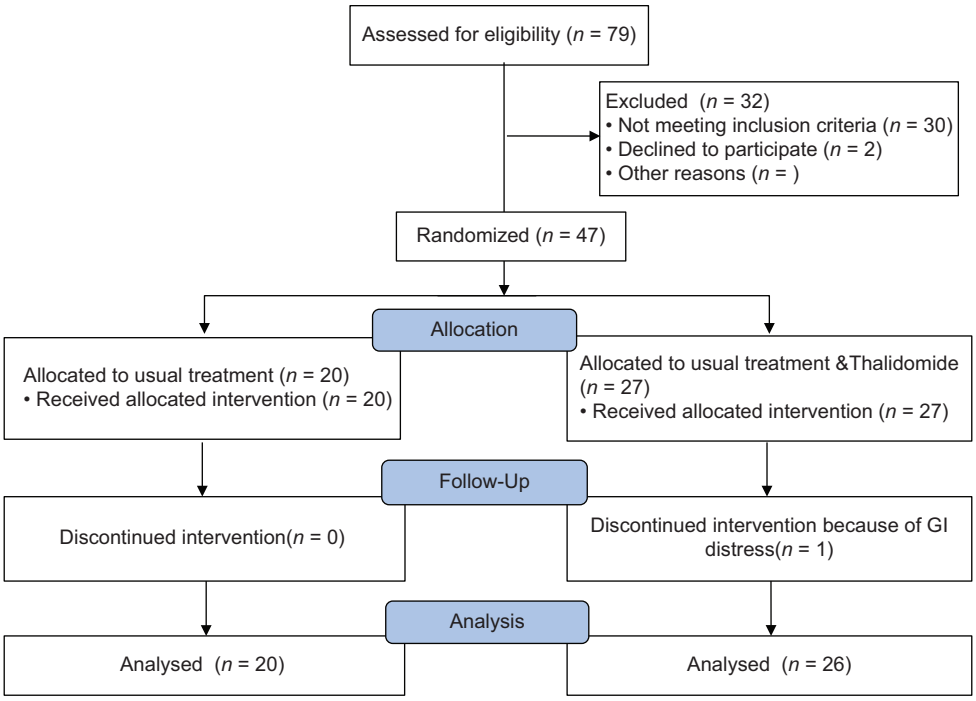
Data analysis on the severity and inflammatory factors such as CRP, ferritin, LDH, ESR, and lymphocytopenia in the thalidomide and control groups before intervention showed no significant difference. After treatment, CRP, ESR, lymphopenia, and LDH improved but without statical value comparing groups except for CRP that was higher in the thalidomide group.

Clinical signs assessed in this study (SpO2, respiratory rate, and temperature) alleviated in the first, fifth, and 16th days after treatment in both groups, but thalidomide did not show superiority.

In our trial, 7 patients in the thalidomide group and 4 patients in the control group showed worsening of clinical conditions (decreasing SpO2) and were admitted to the ICU, with a *P* value of 0.425. There were more cases in the thalidomide group (27 versus 21).

The usual treatment for hospitalized moderate pneumonia according to the first edition of the health ministry flowchart for COVID-19 was hydroxychloroquine, but the next

CONSORT 2010 Flow Diagram



flowcharts recommended against the prescription of hydroxychloroquine in hospitalized patients and counseled corticosteroids (dexamethasone: 8 mg) for moderate pneumonia with SpO2 <90%. After adjusting for the type of standard drug, gender, and underlying disease, the odds ratios for TTCR and ICU admission rates were 0.01 (95% CI, −1.58, 1.59) and 3.89 (0.55–27.4), respectively.

From the analysis of the trial, we determined that thalidomide was not an effective treatment for patients hospitalized with moderate COVID-19 pneumonia compared to usual standard treatment, but we do not address its use in patients with more severe SARS-CoV-2 infection managed in hospitals and ICUs.

All patients recovered and were discharged from the hospital and after 28 days of phone follow-up were not readmitted. The findings suggested each anti-inflammatory agent (dexamethasone or hydroxychloroquine alone or combined with thalidomide) may alleviate the clinical progression of COVID-19.

Symptom onset duration before admission was approximately 7 days, and the time of starting treatment in our study was the second week, in the inflammatory phase of the disease, which is a suitable time for thalidomide's role in inflammation control.

We did not observe any adverse effects of the drug in the thalidomide group as expected for low dose and short duration of thalidomide.

For better evaluation of thalidomide efficacy in moderate COVID-19 infection, it seems that a larger sample size and multicenter trials are needed. Another limitation was the low cost for the evaluation of other inflammatory factors such as IL6 and interferons.

Conclusion

In summary, this study investigated the effects of thalidomide to treat moderate COVID-19 clinical outcomes. The results established that this drug regimen did not add more effect to usual treatment for moderate COVID-19 pneumonia. However, additional studies are warranted to validate these effects.

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Declaration of patient consent

The authors certify that they have obtained all appropriate patient consent forms. In the form, the patient(s) has/have given his/her/their consent for his/her/their images and other clinical information to be reported in the journal. The patients understand that their names and initials will not be published and due efforts will be made to conceal their identity, but anonymity cannot be guaranteed.

Trial registration number: IRCT20200428047232N1

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Nil.

Conflicts of interest

There are no conflicts of interest.

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