Thalidomide for the treatment of severe Covid-19: A randomized clinical trial

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Abstract

Background Covid-19 pneumonia is the leading cause of death in severe hospitalized patients. Thalidomide has an immunomodulatory and anti-inflammatory effect and thereby decrease lung damage.

Methods This study was a randomized clinical trial that was performed from April 2020 until August 2020 on 60 severe hospitalized Covid-19 pneumonia patients. All patients received the usual care for Covid-19 pneumonia based on our hospital protocols. Patients in the intervention group received thalidomide tablets 100 mg daily for 14 days added to the usual treatment. The primary outcome was the ICU admission rate.

Results Thirty patients were assigned to receive thalidomide and 30 patients usual treatment. Five patients (17.9%) in the thalidomide group required ICU admission and 12 patients (52.2%) in the usual care group (P-value = 0.01). ICU admission hazard ratio was 3.3 higher in the usual care group than the thalidomide group (HR: 3.31 [95% CI: 1.16–9.45]). Hospitalization duration, intubation and mortality showed no significant differences between the two groups (P > 0.05 for all items). No serious and major adverse effects were reported during the trial.

Conclusion The use of thalidomide was associated with a decreased rate of ICU admission in severe hospitalized covid-19 patients.

Introduction

Covid-19 affected more than 117 million patients worldwide until this date and its infectivity and mortality daily increase (1). Respiratory failure, septic shock, and multiple organ dysfunction were symptoms of a critical form of Covid-19 infection (2, 3). A recent study in China reported that almost 81% of Covid-19 patients had mild infection, 14% severe form, and 5% had the critical form of Covid-19 infection (3). Fatality rate of Covid-19 reported 26 % among hospitalized patients and 37 % among intubated patients in United Kingdom (4).

A significant decrease in the mortality rate of hospitalized Covid-19 patients who required supplementary oxygen was observed after administration of dexamethasone in RECOVERY trial (5, 6). Furthermore, usage of remdesivir was associated with reduced disease progression and disease burden in hospitalized Covid-19 patients (7).

Higher levels of cytokines were detected in the severe and critical form of the disease (8, 9). Thalidomide was prescribed during recent years in some groups of diseases such as Hansen disease, multiple myeloma, myelodysplastic syndrome, idiopathic pulmonary fibrosis (IPF), infectious and autoimmune disease (10). Reduction of TNF α , IL1 β , IL6, TGF β and augmentation of peripheral blood CD8 + T cells, plasma interleukin 12 (IL-12) levels and interferon- γ was revealed in in-vitro and in-vivo studies of

thalidomide (11–13). Antifibrotic effects of thalidomide in IPF were proven by preventing the proliferation of type 2 pneumocyte and increasing the type I pneumocyte in the alveolar epithelial cells (14).

Based on documents, hospitalized Covid-19 infected patients had significantly higher levels of IL-6 that was also accounted as one of the predictor markers of the respiratory involvement in Covid-19 patients (15). Thalidomide and low dose corticosteroid had beneficial effects in a severe Covid19 patient in some studies (16, 17). They also believe that further studies are required in this regard. Due to these immunomodulatory and anti-inflammatory effects of thalidomide, we decide to evaluate its effectiveness in the treatment of severe Covid19 pneumonia patients.

Material And Methods

This study was a randomized clinical trial that was performed from April 2020 until August 2020 in Khorshid hospital affiliated with Isfahan University of Medical Sciences. This study was conducted on 60 severe Covid-19 hospitalized patients. The study protocol was approved by Research Committee of Isfahan University of Medical Sciences and the Ethics Committee has confirmed it (IR.MUI.MED.REC.1399.027). Iranian registry for clinical trial code is IRCT20170207032444N3

Hospitalized patients were eligible for the trial if clinical symptoms and signs were compatible with Covid-19 infection and positive PCR test or lung HRCT abnormalities compatible with Covid-19 pneumonia, they were 18-75-year-old men and 50-75-year-old women admitted in hospital and had these criteria, SpO2 less than 85% at admission, no need to intubation in first 24 hours of admission and no multiorgan failure or shock state at presentation

All the patients or their legal representatives, if they were not able to provide consent, signed the informed consent.

Patients were excluded if they had hepatic failure (Child Pugh score $\geq$ C, AST > 5 times of the upper limit normal) or severe renal dysfunction (glomerular filtration rate (GFR) less than 30 CC per min).

Sixty patients were selected based on inclusion criteria. We collected demographic data of all patients including age, gender, the time interval between symptom onset and admission, smoking status, and comorbidities. The mean O2 saturation by the time of admission was also noted. Patients were randomly assigned in 1:1 ratio to 2 groups each containing 30 patients. Randomization was done through random sequence generation by using statistical software. The first group received thalidomide and the other group received the usual care for Covid-19 infection.

Patients in both groups received methylprednisolone 50 mg intravenously every 12 hours for 3 days and then daily for 7 days, hydroxychloroquine 200 mg orally every 12 hours for 5 days.

For symptom control (pain, cough, nausea, and vomiting) acetaminophen codeine, diphenhydramine, dimenhydrinate, and promethazine were prescribed. Antibiotics were administered based on physician

choice (Ceftriaxone, Azithromycin, and Vancomycin). All patients received enoxaparin 40 mg subcutaneously daily during hospitalization.

Patients in the intervention group received thalidomide tablets (Talidex, Alan pharmaceuticals) 100 mg daily for 14 days added to the usual treatment.

All patients were visited daily by an Internist or Pulmonologist and were followed weekly for 4 weeks using phone calls. During follow up adherence to prescribed thalidomide was monitored by a specialized nurse.

ICU admission rate of patients in both groups was assessed as the primary outcome. Rate of intubation and mortality were also evaluated and compared between two groups as the secondary outcomes.

We also evaluated adverse effects related to thalidomide. These adverse effects included peripheral neuropathy, somnolence, constipation, skin rash, neutropenia, weakness, orthostatic hypotension, headache, and peripheral edema (18).

Statistical analysis:

Data were collected and analyzed using SPSS software version 21. Continuous and categorical variables were reported as mean $\pm$ Standard deviation (SD) and frequency (percentage) and compared with independent samples t-test and Chi-squared test, respectively. Kaplan-Meier and log-rank test used for comparing the study outcomes (as the time to event data) and results were reported as hazard ratio and 95% confidence interval (95%CI). P-value < 0.05 was considered as the significance level.

Results

Sixty patients entered the study based on inclusion criteria and were randomized into two groups of 30 patients. Two patients in the intervention group refused to end up with treatment. Loss of follow-up in five patients and consent withdrawal in two patients in the usual care group had occurred. Data of 51 patients were analyzed. The CONSORT flow diagram of patients is shown in Fig. 1.

Demographic characteristics of patients were analyzed and are shown in Table 1. The mean age of the patients was 61 ± 9.6 and 64.1 ± 10.7 years in the thalidomide and the usual care groups respectively. Meantime of starting symptoms until hospitalization in the thalidomide and the usual care group were 7.32 ± 3.60 and 6.78 ± 4.15 days. No significant differences were found between groups regarding the comorbidities and baseline characteristics (Table 1).

Table 1
Demographic and clinical characteristics of the patients at baseline

Variable		Thalidomide (N = 28)	Usual care (N = 23)	P-value
Age		61 ± 9.6	64.1 ± 10.7	0.29
Days since symptom onset till admission		7.32 ± 3.60	6.78 ± 4.15	0.622
Gender	Male	15 (53.6%)	13 (56.5%)	0.83
	Female	13 (46.4%)	10 (43.5%)	
Smoker		3 (10.7%)	4 (17.4%)	0.49
Diabetes mellitus		8 (28.6%)	11 (47.8%)	0.15
Hypertension		8 (28.6%)	9 (39.1%)	0.42
IHD [€]		2 (7.1%)	3 (13%)	0.48
Pulmonary disease		2 (7.1%)	1 (4.3%)	0.67
O2sat at admission		79.2 ± 3.3	79.7 ± 4.3	0.58
Number of Comorbidities	0	12(42.9%)	10(43.5%)	0.61
	1	12(42.9%)	4(17.4%)	
	2	4(14.3%)	7(30.4%)	
	3	0(0%)	2(8.7%)	
*Plus–minus values are means ± SD				
€ Ischemic heart disease				

We observed five (17.9%) ICU admission in the thalidomide group and 12 (52.2%) in the usual care group (P-value: 0.01). (Table 2). ICU admission hazard ratio was 3.3 higher in the usual care group than the thalidomide group (HR: 3.31 [95% CI: 1.16–9.45]) (Fig. 2). Six patients (26.1%) in the usual care group and 4 patients (14.3%) in the thalidomide group underwent intubation during hospitalization (P = 0.29). The intubation hazard ratio was 1.9 higher in the usual care group than the thalidomide group but these data were not significant (HR: 1.95 [95% CI: 0.55–6.29]). Although the mortality rate in the thalidomide group was lower than the usual care group (four patients (14.3%) vs 6 patients (26.1%) ;), however, the difference was not statistically significant (HR: 1.95; 95% CI: 0.55–6.92; P = 0.291) (Fig. 3). No significant differences between the two groups regarding hospitalization duration was found (P > 0.05).

Table 2
Primary and secondary outcomes.

Variable				P value	Time to variable ^ℓ	HR (95% CI)
Primary outcome	ICU admission	Thalidomide	5 (17.9%)	0.01*	4.6 (1.4–7.79)	1
		Usual care	12 (52.2%)		5 (3.79–6.37)	3.31(1.16–9.46)
Secondary outcomes	Intubation	Thalidomide	4 (14.3%)	0.291	9.25(4.36–14.14)	1
		Usual care	6 (26.1%)		8.1 (6-10.27)	1.95(0.55–6.92)
	Mortality	thalidomide	4 (14.3%)	0.291	19.2(17.61–20.79)	1
		Usual care	6 (26.1%)		18.5(16.75–20.35)	1.92(0.53–6.90)
* show significant difference						
ℓ mean time to variable (lower band and upper band)						

No serious and grade 3 and 4 adverse effects were reported during the trial. Grade 2 somnolence in 6 percent of patients and grade 1 and 2 constipation in 10% of patients were reported. Constipation was relieved by laxatives. No thromboembolic events were detected in both groups of patients.

Discussion

Our primary results indicate that among severe hospitalized Covid-19 patients, thalidomide usage for a short duration resulted in lower ICU admission than patients who received usual care. However, there was not a significant difference in mortality and intubation rate among the thalidomide and the usual care groups.

RECOVERY trials show mortality reduction with dexamethasone 6 mg among hospitalized Covid-19 patients who need respiratory supports (6). UK and National Institutes of Health in the United States guidelines recommend the prescription of dexamethasone in hospitalized Covid-19 patients (19, 20). Corticosteroid was used in all of our hospitalized severe Covid-19 patients.

Immune dysfunction plays an important role in Covid-19. IL-2, IL-4, IL-6, IL-10, TNF- α , and IFN- γ had a higher level in Covid-19 patients (21). Thalidomide is an immunomodulatory agent that had promising benefits in pulmonary injuries induced by the H1N1 virus in mice through reduction of IL-6 and TNF- α and some other mechanisms (22, 23). Inhibition of cytokine surge and regulation of immune function with

thalidomide was reported in previous studies (24, 25). Cytokine balance that resulted from thalidomide therapy may affect the clinical course of hospitalized patients. Based on our data, patients who received thalidomide had lower rates of ICU admission.

Thalidomide in combination with low dose corticosteroid-induced gradually reduction of inflammatory markers such as IL6, IL10, and IFN- γ , inhibition of cytokine surge, and improvement of pulmonary effusion symptoms in a patient with severe Covid-19 pneumonia (16). Li and colleagues performed another study in 2021 that evaluated the effects of thalidomide combined with short-term low-dose glucocorticoid therapy for the treatment of severe Covid-19. In this study, six patients received thalidomide along with routine care for Covid-19. In this study combination of thalidomide with a short-term low-dose glucocorticoid was an effective and safe regimen for the treatment of severely ill Covid-19 patients (17). All of our patients in the trial received corticosteroids. Our results were in line with these findings emphasizing the effectiveness of thalidomide therapy in combination with corticosteroids in severe Covid-19 patients.

In our study thalidomide decreased ICU admission but mortality was not significantly different between groups. ICU admission was our endpoint in this study. After admission to ICU, the patients were treated with other modalities such as hemoperfusion, tocilizumab, and hyper-immune plasma. Using such treatments in the ICU may explain statistically insignificant mortality differences.

The mean time of starting symptoms until admission in our patients was about 7 days and so they were admitted in the inflammatory phase of the disease. Effectiveness of thalidomide in Covid-19 has presumably resulted from Immunomodulation so the administration of thalidomide in the inflammatory phase of the disease may be effective.

Because of uncertainty to patient's adherence for staying in quarantine after discharge, our policy in the hospital was a longer duration of hospitalization. This policy may explain the insignificant difference regarding hospitalization duration between the thalidomide and the usual care group.

Thalidomide was prescribed for 14 days in this study and except for some minor complaints; no major adverse effects were reported.

Our small sample size is one of the limitations. We suggest trials with a larger sample size in the future.

Conclusion

The use of thalidomide in severe cases of hospitalized Covid-19 pneumonia was associated with a decreased rate of ICU admission.

Declarations

No acknowledgment

BA contributed in the conception of the work, editing the manuscript, data gathering, and analysis of data and agreed for all aspects of the work.

FA contributed in the conception of the work, editing the manuscript, data gathering, and analysis of data and agreed for all aspects of the work.

FS contributed in, data gathering, editing the manuscript and agreed for all aspects of the work.

AF contributed in, analysis of data and agreed for all aspects of the work.

MS contributed in data gathering, editing the manuscript, and agreed for all aspects of the work.

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Figures

Figure 1

Consort flow diagram of patients.

Figure 2

ICU admission trend among patients

Figure 3

Mortality trend among patients