http://www.jhpr.ir
Hosp Pract Res. 2022 Feb;7(1):33-36
doi 10.34172/hpr.2022.07
HPR
Hospital Practices and Research
Case Series

Combination Therapy of ReciGen Interferon, Methylprednisolone, and Sovodak as a Candidate for Treatment of Patients With Severe COVID-19 in Iran: A Case Series

Zahra Kamiab[1,2], **Ali Esmaeili Nadimi**[3,4], **Fatemeh Bahrehmand**[5*]

[1]Clinical Research Development Unit, Ali-Ibn Abi-Talib Hospital, Rafsanjan University of Medical Sciences, Rafsanjan, Iran
[2]Department of Family Medicine, Ali-Ibn Abi-Talib Hospital, School of Medicine, Rafsanjan University of Medical Sciences, Rafsanjan, Iran
[3]Non-Communicable Diseases Research Center, Rafsanjan University of Medical Sciences, Rafsanjan, Iran
[4]Department of Cardiology, School of Medicine, Rafsanjan University of Medical Sciences, Rafsanjan, Iran
[5]Department of Internal Medicine, School of Medicine, Rafsanjan University of Medical Sciences, Rafsanjan, Iran

***Corresponding Author:** Fatemeh Bahrehmand, Department of internal medicine, School of Medicine, Rafsanjan University of Medical Sciences, 7719617996, Rafsanjan, Iran. Tel: +98-3434280185, Fax: +98-3434280185, Email: dr_bahrehmand@yahoo.com

Received July 27, 2021; **Accepted** December 27, 2021; **Online Published** January 19, 2022

Abstract

Introduction: During the current worldwide pandemic of coronavirus disease 2019 (CPVID-19), this disease was first identified in Iran at the end of February. This study was conducted to examine patients with severe COVID-19 disease, who were treated with three medications, namely ReciGen, methylprednisolone, and Sovodak.

Case Presentation: We identified 10 patients (3 males and 7 females) with the mean (±SD) age of 55.70±21.48 years, who were admitted to the only referral hospital in Rafsanjan County (Iran) from March to July 2020 with confirmed infections with severe COVID-19. They were treated with the combination therapy of subcutaneous ReciGen interferon every other day, methylprednisolone at a dose of 250 mg every 6 hours for 5 days, and one tablet of Sovodak daily.

Conclusion: In the series of cases investigated in this study, the general conditions of all patients improved in terms of their clinical parameters after receiving the combination therapy, and all patients were discharged with a blood oxygen level of ≥93% and in good general conditions.

Keywords: COVID-19, Interferon-beta, Methylprednisolone, Therapy

1. Introduction

Coronavirus disease 2019 (COVID-19) that was first identified in Wuhan, China[1] and spread to many countries, including Iran, is a Beta coronavirus that affects the lower respiratory tract and manifests similarly to pneumonia in humans.[2] Pneumonia caused by COVID-19 is a highly contagious disease leading to many deaths worldwide.[3] In terms of severity, there are various types of COVID-19, including mild COVID-19 (no pneumonia manifestations and mild pneumonia) in 81% of cases, severe COVID-19 (shortness of breath, a respiration rate of ≥30 per minute, the blood oxygen saturation level of ≤93%, the partial pressure of arterial oxygen to the inspired oxygen fraction being <300 mm Hg, and/or pulmonary infiltration being >50% within 24 to 48 hours) in 14% of cases, and critical COVID-19 (respiratory failure, septic shock, and/or multi-organ dysfunction or failure) in 5% of cases.[4]

The general mortality rate of COVID-19 is expected to be between 2% and 3%.[5] No deaths were reported among the non-critical cases.[6] Furthermore, the mortality rate in hospitalized adults ranged from 4% to 11%.[7] No specific antiviral treatment has been introduced for definitive treatment of this disease so far[8]; however, earlier research introduced some drugs, such as Remdesivir [9] and Chloroquine,[10] which are antiviral therapies developed for treating the Ebola virus disease and malaria that are active against severe acute respiratory syndrome (SARS) in animal models.[11] ReciGen (interferon beta-1a) was considered the potential drug for the treatment of COVID-19 based on experts' opinions and data available in January 2020, yet it is limited to patients with severe disease.[12] Moreover, evidence shows that methylprednisolone has been used in severe cases of COVID-19, which has had positive effects on the course of treatment.[13] In addition, Sovodak

(sofosbuvir-daclatasvir) has been prescribed for moderate to severe cases of COVID-19 patients in some studies.[14] This study was conducted to examine patients with severe COVID-19 disease, who were hospitalized in the Ali-Ibn Abi-Taleb hospital of Rafsanjan County (Iran) and treated with three medications, namely ReciGen, methylprednisolone, and Sovodak.

2. Case Presentation

This case series investigates 10 nonconsecutive patients with severe COVID-19 retrospectively, who were admitted to the intensive care unit (ICU) in the only referral hospital of Rafsanjan County (Iran). The patients received ReciGen subcutaneously every other day, 250 mg of methylprednisolone four times a day, and one tablet of Sovodak (Abidi Pharmaceuticals, Tehran, Iran), including Sofosbuvir 400 mg and daclatasvir 60 mg daily. They received this combination treatment for five days. In this series of cases, convenience sampling was performed, and a diagnostic strategy was adopted for each patient. Accordingly, sampling was performed on the first day of hospitalization. Nasopharyngeal specimens were taken by swabs and sent to a reference laboratory and evaluated through RT-PCR (Reverse Transcription Polymerase Chain Reaction) for final diagnosis so that COVID-19 was diagnosed decisively. Diagnosis criteria for patients with severe COVID-19 were a respiratory rate of > 30 breaths per minute, and a blood oxygen saturation level of ≤ 93%, or pulmonary infiltration being > 50%.[3] According to the national protocol, criteria for the safe discharge of patients from the recovery room included patients whose symptoms disappeared with a blood oxygen saturation of ≥ 93% and no fever for 72 h.[15,16]

A total of 10 patients (3 males and 7 females) with confirmed severe COVID-19 were reported. The mean (± SD) age of the patients was 55.70 (± 21.48) years. Table 1 shows a summary of the main characteristics and laboratory findings of the patients at the time of ICU admission, and Figure 1 demonstrates the CT scan of the patients at the time of ICU admission.

The most common manifestations were shortness of breath, cough, fever, and myalgia; additionally, the least common symptoms were lack of appetite, fatigue, perspiration, nausea, and vomiting.

Respiratory symptoms of the patients disappeared within an average of 13 days (ranging from 6 to 24 days) after hospitalization and receiving methylprednisolone at a dose of 250 mg every 6 hours for 5 days, subcutaneous ReciGen interferon every other day, and one tablet of Sovodac daily. The treatment continued until the patients met the discharge criteria (the blood oxygen level of ≥ 93% and absence of fever for two days). The oxygen saturation level was considered as the improvement criterion for general conditions. The average recovery time of the patients after receiving the combination therapy was 8.6 days. In this series of cases, the general conditions of all patients improved in terms of their clinical parameters after receiving the combination therapy, and all of them were discharged with a blood oxygen level of ≥ 93% and in good general conditions.

3. Discussion

In this study, the combination therapy of ReciGen interferon and methylprednisolone was prescribed for ten patients. The average recovery time of the patients after receiving this combination therapy was 8.6 days. In addition, the general conditions of all patients improved after receiving this combination therapy, and all of them were discharged in good general conditions. The oxygen saturation level was considered as a criterion for general conditions.

Earlier research studies have shown that SARS-CoV-2 could be more sensitive to interferon compared to other coronaviruses.[17] In this study, interferon was administered on average on the fourth day of hospitalization.

Previous studies on SARS have revealed that administering interferon alfacon-1 along with corticosteroids leads to a disease-related reduction in the oxygen saturation level, accelerates the disappearance of lung involvement on radiography, and lowers the creatine kinase level; however, studies on COVID-19 have not been able to prove the effectiveness of this combination therapy.[18] It seems that a combination of interferon treatment and methylprednisolone could increase the positive effects of interferon treatment.

In this series of cases, rapid improvement was observed in their clinical parameters after receiving methylprednisolone. This finding was consistent with those of other studies that showed the effectiveness of administering corticosteroids in reducing the mortality rate or preventing disease progression.[16,19-20] Combination therapy side effects were not observed in this study.

3.1. Outcome

In the series of cases investigated in this study, the general conditions of all patients improved in terms of their clinical parameters after receiving the combination therapy, and all patients were discharged with a blood oxygen level of ≥ 93% and in good general conditions.

4. Conclusion

In this preliminary case series of 10 patients with severe COVID-19, the administration of interferon, methylprednisolone, and Sovodac was followed by improvement in their clinical status. This combination therapy could be effective in some severe cases of COVID-19 pneumonia. The limited sample size and study design preclude a definitive statement about the potential effectiveness of this treatment and further research is required to demonstrate the efficacy and safety of this combination therapy.

Table 1. Summary of Main Characteristics and Laboratory Findings of Patients at the Time of ICU Admission

	Patient 1	Patient 2	Patient 3	Patient 4	Patient 5	Patient 6	Patient 7	Patient 8	Patient 9	Patient 10
Age (y)	91	31	65	68	57	31	62	63	21	68
Gender	Female	Male	Female	Female	Female	Female	Female	Female	Female	Male
History of medical illness	HTN	Smoking	HTN, DM	DM	-	History of open-heart surgery	-	HTN, Angiography + IHD		HTN
Duration of illness (days)	13	9	31	15	14	14	14	13	8	6
Diagnosis date	7/4/2020	11/4/2020	18/3/2020	31/5/2020	2/7/2020	2/7/2020	2/7/2020	9/7/2020	12/7/2020	7/7/2020
HRCT findings	TCTS	TCTS	TCTS	TCTS	TCTS	Pericardial effusion & TCTS	TCTS	TCTS	TCTS	TCTS
Vital signs										
Temperature	38	39	38.5	38	37.5	36.5	36.5	38	37	38
Heart rate	90	112	100	85	87	110	90	97	104	98
Respiratory rate	23	30	25	24	16	20	20	23	25	22
O2 saturation level	70%	80%	79%	88%	80%	83%	87%	85%	65%	86%
Blood pressure	140/60	130/60	150/70	110/70	110/70	90/50	120/80	130/80	110/70	150/70
Main manifestations										
Fever	+	+	+	+	+	+	+	+	-	+
Chills	-	-	-	+	-	+	-	+	-	+
Perspiration	-	-	-	-	+	-	-	-	-	-
Cough	+	+	+	+	+	+	+	+	+	+
Shortness of breath	+	+	+	+	+	+	+	+	+	+
Chest pain	-	+	-	-	+	-	-	-	+	+
Myalgia	+	+	-	+	+	+	+	-	-	+
Fatigue	+	-	+	-	+	-	-	-	-	-
Lack of appetite	+	-	+	+	-	-	-	-	-	-
Nausea or vomiting	-	-	-	-	-	-	+	-	+	-
Laboratory test										
WBC (x10^6/L)	3900	17300	5900	7100	6600	3600	4300	5600	3500	11900
Neutrophils	65%	80%	69%	79%	79%	58%	65%	90%	60%	90%
Lymphocyte	33%	18%	19%	14%	16%	42%	31%	6%	37%	7%
Hb	13.1	16.5	12.2	10.7	10.8	14.5	11.6	10.8	11.1	16.2
PLT (x106/L)	176	334	166	195	222	142	172	163	215	197
CRP (mg/L)	49	72	63	54	68	56	57	45	70	58
AST (U/L)	67	43	35	40	97	97	40	54	72	55
ALT (U/L)	29	18	24	20	67	67	20	50	49	34
Urea (mg/dL)	24	9	29	23	22	29	31	46	19	49
Creatinine (mg/dL)	1	1.2	1.1	0.9	1	1.1	0.9	1.3	0.9	1.2
Sodium (mEq/L)	135	138	135	137	139	141	139	147	142	136
Potassium (mEq/L)	4.5	4.6	3.5	4	4	4.3	4.2	3.4	4.4	3.9

Abbreviations: HTN, hypertension; DM, diabetes mellitus; IHD, ischemic heart disease; HRCT, High-resolution computed tomography; TCTS, typical computed tomography sign of COVID-19.

Authors' Contributions

ZK developed the study proposal, analysis, and interpretation of data, prepared the draft of the article, critically revised the manuscript, and submitted the final approval of the article. AEN produced the design of the study, revised it critically for important intellectual content, read and approved the final version of the manuscript. FB came up with the design of the study, acquisition of the data, drafting the article, interpreting the data, as well as reading and approving the final manuscript.

Conflict of Interest Disclosures

The authors declare that they have no competing interests.

Ethical Approval

The study was approved by IRB Approval: IR.RUMS.REC.1399.121. Due to its retrospective design, the need for informed consent from

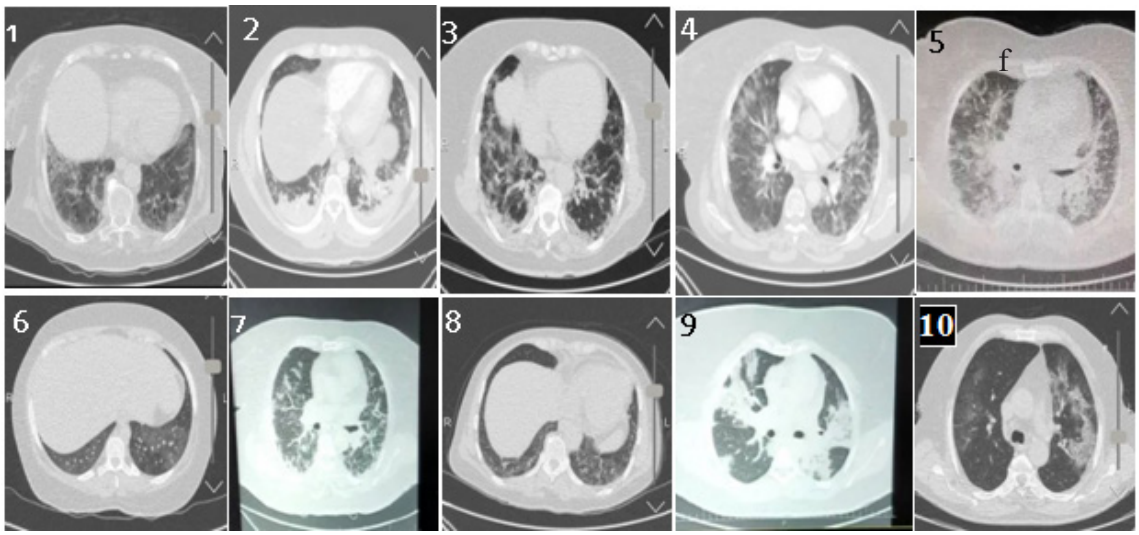

Figure 1. HRCT Scan Images of the Admitted Patients.

individual patients was waived.

Funding/Support

No funding was received in connection with the design or conducting of the study, or the analysis or interpretation of the results.

Acknowledgments

The authors would like to thank the Clinical Research Development Center of Ali-Ibn Abi Talib Hospital, the Rafsanjan University of Medical Science, Kerman, Iran for its cooperation.

References

1. Al-Osail AM, Al-Wazzah MJ. The history and epidemiology of Middle East respiratory syndrome corona virus. Multidiscip Respir Med. 2017;12:20. doi:10.1186/s40248-017-0101-8.
2. Sohrabi C, Alsafi Z, O'Neill N, et al. World Health Organization declares global emergency: a review of the 2019 novel coronavirus (COVID-19). Int J Surg. 2020;76:71-6. doi:10.1016/j.ijsu.2020.02.034.
3. Wang Y, Wang Y, Chen Y, Qin Q. Unique epidemiological and clinical features of the emerging 2019 novel coronavirus pneumonia (COVID-19) implicate special control measures. J Med Virol. 2020;92(6):568-76. doi:10.1002/jmv.25748.
4. Wu Z, McGoogan JM. Characteristics of and important lessons from the coronavirus disease 2019 (COVID-19) outbreak in China: summary of a report of 72 314 cases from the Chinese Center for Disease Control and Prevention. JAMA. 2020;323(13):1239-42. doi:10.1001/jama.2020.2648.
5. Rajgor DD, Lee MH, Archuleta S, Bagdasarian N, Quek SC. The many estimates of the COVID-19 case fatality rate. Lancet Infect Dis. 2020;20(7):776-7. doi:10.1016/s1473-3099(20)30244-9.
6. Tian R, Wu W, Wang C, et al. Clinical characteristics and survival analysis in critical and non-critical patients with COVID-19 in Wuhan, China: a single-center retrospective case control study. Sci Rep. 2020;10(1):17524. doi:10.1038/s41598-020-74465-3.
7. Wu YC, Chen CS, Chan YJ. The outbreak of COVID-19: an overview. J Chin Med Assoc. 2020;83(3):217-20. doi:10.1097/jcma.0000000000000270.
8. Cao YC, Deng QX, Dai SX. Remdesivir for severe acute respiratory syndrome coronavirus 2 causing COVID-19: an evaluation of the evidence. Travel Med Infect Dis. 2020;35:101647. doi:10.1016/j.tmaid.2020.101647.
9. Vincent MJ, Bergeron E, Benjannet S, et al. Chloroquine is a potent inhibitor of SARS coronavirus infection and spread. Virol J. 2005;2:69. doi:10.1186/1743-422x-2-69.
10. Singhal T. A review of coronavirus disease-2019 (COVID-19). Indian J Pediatr. 2020;87(4):281-6. doi:10.1007/s12098-020-03263-6.
11. Wang M, Cao R, Zhang L, et al. Remdesivir and chloroquine effectively inhibit the recently emerged novel coronavirus (2019-nCoV) in vitro. Cell Res. 2020;30(3):269-71. doi:10.1038/s41422-020-0282-0.
12. Zhang L, Liu Y. Potential interventions for novel coronavirus in China: a systematic review. J Med Virol. 2020;92(5):479-90. doi:10.1002/jmv.25707.
13. Wang Y, Jiang W, He Q, et al. A retrospective cohort study of methylprednisolone therapy in severe patients with COVID-19 pneumonia. Signal Transduct Target Ther. 2020;5(1):57. doi:10.1038/s41392-020-0158-2.
14. Eslami G, Mousaviasl S, Radmanesh E, et al. The impact of sofosbuvir/daclatasvir or ribavirin in patients with severe COVID-19. J Antimicrob Chemother. 2020;75(11):3366-72. doi:10.1093/jac/dkaa331.
15. Walsh KA, Jordan K, Clyne B, et al. SARS-CoV-2 detection, viral load and infectivity over the course of an infection. J Infect. 2020;81(3):357-71. doi:10.1016/j.jinf.2020.06.067.
16. Gandhi RT, Lynch JB, Del Rio C. Mild or moderate COVID-19. N Engl J Med. 2020;383(18):1757-66. doi:10.1056/NEJMcp2009249.
17. Sallard E, Lescure FX, Yazdanpanah Y, Mentre F, Peiffer-Smadja N. Type 1 interferons as a potential treatment against COVID-19. Antiviral Res. 2020;178:104791. doi:10.1016/j.antiviral.2020.104791.
18. Loutfy MR, Blatt LM, Siminovitch KA, et al. Interferon alfacon-1 plus corticosteroids in severe acute respiratory syndrome: a preliminary study. JAMA. 2003;290(24):3222-8. doi:10.1001/jama.290.24.3222.
19. Fadel R, Morrison AR, Vahia A, et al. Early short-course corticosteroids in hospitalized patients with COVID-19. Clin Infect Dis. 2020;71(16):2114-20. doi:10.1093/cid/ciaa601.
20. Wu C, Chen X, Cai Y, et al. Risk factors associated with acute respiratory distress syndrome and death in patients with coronavirus disease 2019 pneumonia in Wuhan, China. JAMA Intern Med. 2020;180(7):934-43. doi:10.1001/jamainternmed.2020.0994.