

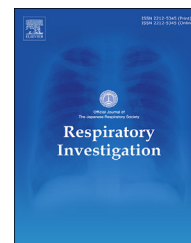


Since January 2020 Elsevier has created a COVID-19 resource centre with free information in English and Mandarin on the novel coronavirus COVID-19. The COVID-19 resource centre is hosted on Elsevier Connect, the company's public news and information website.

Elsevier hereby grants permission to make all its COVID-19-related research that is available on the COVID-19 resource centre - including this research content - immediately available in PubMed Central and other publicly funded repositories, such as the WHO COVID database with rights for unrestricted research re-use and analyses in any form or by any means with acknowledgement of the original source. These permissions are granted for free by Elsevier for as long as the COVID-19 resource centre remains active.

Available online at www.sciencedirect.com

Respiratory Investigation

journal homepage: www.elsevier.com/locate/resinv

Rapid Communication

Report of a combination of remdesivir, intravenous methylprednisolone pulse, and tocilizumab for severe coronavirus disease: 20-case series at a single institution



Takashi Ichiyama^{*}, Masamichi Komatsu, Yosuke Wada,
Masayuki Hanaoka

First Department of Internal Medicine, Shinshu University School of Medicine, 3-1-1 Asahi, Matsumoto, Nagano 390-8621, Japan

ARTICLE INFO

Article history:

Received 7 February 2022

Received in revised form

17 March 2022

Accepted 2 April 2022

Available online 25 April 2022

Keywords:

Coronavirus disease 2019

Remdesivir

Tocilizumab

Methylprednisolone pulse

ABSTRACT

Many drugs have been marketed for treating coronavirus disease 2019 (COVID-19) infection, the disease that has caused a worldwide pandemic. However, in reported clinical trials, almost 30% of patients with COVID-19 did not show any health improvement. The 28-day survival rate was 69.5% when patients who required highflow oxygen therapy (HFNC), ventilation, and extracorporeal membrane oxygenation (ECMO) management were treated with remdesivir. The mortality rate of patients receiving 6 mg dexamethasone was 27%, and that of patients treated with tocilizumab and steroids was 31%. These results are unsatisfactory, and treatment for patients with severe respiratory failure has not yet been established. In our institution, we used remdesivir, methylprednisolone (mPSL) pulse therapy, and tocilizumab in 20 patients with COVID-19 whose PaO₂/FIO₂ (P/F) ratio was <200, and obtained good results for this combination therapy without any adverse events. In this study, we report the possible efficacy and safety of this treatment.

© 2022 The Japanese Respiratory Society. Published by Elsevier B.V. All rights reserved.

1. Introduction

The coronavirus disease (COVID-19) pandemic began in December 2019 and has had a tremendous impact worldwide. New variant strains are continuously discovered, and the end of the pandemic still cannot be foreseen. At our hospital, we were responsible for treating patients with severe respiratory failure who may require treatment with invasive positive

pressure ventilation (IPPV) or extracorporeal membrane oxygenation (ECMO). Although many new drugs have been produced, appropriate treatments for critically ill patients with respiratory failure have not yet been established. Remdesivir was reportedly to be effective in the Adaptive COVID-19 Treatment Trial-1 (ACTT-1) [1]. However, its benefit in patients who require a high-flow nasal cannula (HFNC), mechanical ventilation (MV), or ECMO management has not yet been proven. Dexamethasone has been reported to be

^{*} Corresponding author.

E-mail address: ichiyama@shinshu-u.ac.jp (T. Ichiyama).

<https://doi.org/10.1016/j.resinv.2022.04.001>

2212-5345/© 2022 The Japanese Respiratory Society. Published by Elsevier B.V. All rights reserved.

effective for patients on respirators in the Randomised Evaluation of COVID-19 Therapy (RECOVERY) trial; however, the mortality rate in this study was 27% [2]. More than 50% of the patients experienced worsening respiratory failure with 6 mg of dexamethasone. We had observed an improvement in severe pneumonia caused by the influenza virus with treatment including the methylprednisolone (mPSL) pulse. Hence, we selected mPSL pulse to treat the patients in this study. Tocilizumab is an antibody that targets interleukin (IL)-6, one of the causes of cytokine storms. As of December 2020, tocilizumab has been introduced in the Guide to Pharmacotherapy for COVID-19 by The Japanese Association for Infectious Diseases [3]. We selected tocilizumab because some patients who experienced exacerbation after mPSL pulse and antiviral drug treatment were transferred to our hospital. For patients with severe COVID-19 infection requiring HFNC or MV, we used a combination of remdesivir, mPSL pulse, and tocilizumab and experienced good treatment results.

2. Patients and methods

We analyzed the backgrounds, laboratory data upon admission, previous treatments, and outcomes of patients with COVID-19 treated at Shinshu University Hospital between December 2020 and September 2021.

This study was approved by the Ethics Review Board of Shinshu University School of Medicine (Approval Number: 5107). This was a retrospective, observational study, and an opt-out procedure was used for eligible patients.

3. Results

Remdesivir, tocilizumab, and mPSL pulse therapy were used for 20 patients with severe respiratory failure (15 males and five females). Remdesivir was administered at 200 mg on day 1, and from the next day, it was administered at 100 mg in 13 patients for 9 d. Seven patients ended treatment early due to symptom improvement or minor adverse events. We administered 1000 mg of mPSL for 3 d, starting from day 1, and it was gradually decreased to 250, 125, 80, and finally 40 mg every 2 d. We administered 400 mg of tocilizumab once in 17 patients and at 520, 600, and 680 mg in three patients, respectively, on day 1 or day 2. Table 1 shows the background and laboratory findings of 20 patients upon admission. Individual data are listed in the supplemental table. The median age (interquartile range [IQR]) of the patients was 59.0 (50.9–69.3) y; 11 had an hemoglobin A1C level of $\geq 6.5\%$ upon admission, and six of them were treated for diabetes. Five patients had no prior treatment for COVID-19, and 15 patients were under treatment at their previous hospitals. Among them, six patients had received only dexamethasone, whereas seven had received dexamethasone and antiviral drugs. Two patients initiated mPSL pulse and antiviral drug therapy. One patient was on IPPV combined with ECMO, nine required IPPV, and 10 used HFNC.

Only one patient (5%) who could not receive our prescribed therapy before the time of ECMO introduction died.

All of the patients had positive polymerase chain reaction (PCR) test results up until day 4 of our therapeutic intervention.

Table 1 – Clinical characteristics and clinical laboratory data of the patients.

Age, y	59.0 (50.9–69.3)
Sex	
Male	15 (75)
Female	5 (25)
BMI, kg/m ²	27.4 (25.1–30.2)
WBC count, per mm ³ , median	8575 (6863–11750)
Lymphocyte count, per mm ³ , median	609 (412–760)
Alb g/dL	3.0 (2.8–3.1)
BUN mg/dL	19.9 (15.7–29.1)
Cre mg/dL	0.8 (0.7–1.0)
LDH IFCC U/L	390 (344–508)
CRP mg/dL	8.4 (5.4–11.2)
Ferritin ng/mL	762 (536–1582)
KL-6 U/mL	455 (357–529)
BNP pg/mL	28 (12–57)
HbA1c %	6.7 (6.0–7.0)
P/F ratio at time of medication administration	151 (105–185)
Lowest P/F ratio during treatment	109.5 (94.4–128.3)

Values are given as the number(percentage) or median (25th and 75th percentiles).

BMI, body mass index; WBC, white blood cell; Alb, albumin; BUN, blood urea nitrogen; Cre, creatinine; LDH, lactate dehydrogenase; CRP, C-reactive protein; KL-6, Krebs von den Lungen-6.

The median duration (IQR) of IPPV was 8 d (4–13 d); seven patients were treated with HFNC after extubation, with a median duration (IQR) of 4 d (2–15 d). Ten patients who could be managed with HFNC alone had a median duration (IQR) of HFNC use of 8 d (2–16 d).

Glycemic control was required in 17 patients (85%). Good glycemic control was achieved in two patients with continuous insulin, four patients with oral diabetic agents and insulin using a sliding scale, and 11 patients with insulin only using a sliding scale. An adverse event of secondary infection was a catheter-related infection in only one patient who required ECMO.

4. Discussion

The triple therapy of remdesivir, mPSL pulse, and tocilizumab for COVID-19 with severe respiratory failure showed good results. All of the patients with IPPV at the time of treatment were extubated, and all of the patients who required HFNC were not prescribed IPPV.

Various drugs have become available for use in clinical practice as a result of randomized control trials (RCTs); however, the treatment results are not satisfactory. Remdesivir has been reported to be effective in the ACTT-1 trial [1]; however, the 28-d survival rate of patients who required HFNC, MV, or ECMO was 69.5%, which was not significantly different from the placebo rate of 70.2%. Notably, all of our patients were PCR-positive; thus, the possibility of residual viral infection cannot be ruled out. We believe that the concomitant use of antiviral drugs is desirable for strong immunosuppressive therapy.

The RECOVERY trial has reported that 6 mg of dexamethasone significantly reduced the mortality in patients with MV,

though the mortality rate was 27% [2]. Thirteen of our patients had worsened respiratory failure after initiating dexamethasone treatment at their previous hospitals. Treatment with only 6 mg of dexamethasone, which was used in the RECOVERY trial, might be insufficient. However, treatment guidelines for influenza virus infection do not recommend the routine use of steroid pulse therapy for viral pneumonia [4]. This evidence is based on some reviews of low-quality observational studies, and the appropriate timing and mPSL dosing have not yet been established [5]. The dose for mPSL pulse should be considered. In vitro, mitogen-induced lymphocyte proliferation was reportedly maximally inhibited at 1000 mg intravenous mPSL [6]. In our report, two patients also experienced worsened respiratory failure while using mPSL pulse and antiviral drugs. Thus, the addition of tocilizumab may also be a crucial factor.

Tocilizumab is an IL-6 receptor antagonist that is expected to improve the prognosis by suppressing inflammatory cytokines, and a significant reduction in mortality was reported in the RECOVERY trial [7]. The mortality rate was even lower in the combined steroid group, though it was still high at 31%. The patient who received our prescribed treatment, which occurred at the time ECMO was introduced, died without improvement due to lung fibrosis. We believe that adequate anti-inflammatory treatment before the development of irreversible lung fibrosis is crucial. We suggest that our treatment should be introduced before the P/F ratio falls below 150 after standard therapy.

Our patients' adverse events were manageable. The blood glucose level could be controlled well. The patients with improvement had short intubation and central venous catheterization periods and could achieve early mobilization; therefore, they did not develop infections caused by our treatment.

This report was a single-center, retrospective, observational study with fewer patients. RCTs are necessary to prove that this treatment should be the standard of care, but it will be difficult to develop an appropriate study design.

5. Conclusion

The triple therapy of remdesivir + mPSL pulse + tocilizumab may be a promising treatment option for COVID-19 infections with severe respiratory failure.

Conflict of Interest

The authors state that they have no conflicts of interest.

Acknowledgements

We would like to thank Enago (www.enago.jp) for the English language review and editing.

Appendix A. Supplementary data

Supplementary data to this article can be found online at <https://doi.org/10.1016/j.resinv.2022.04.001>.

REFERENCES

- [1] Beigel John H, Tomashek Kay M, Dodd Lori E, Mehta Aneesh K, Zingman Barry S, Kalil Andre C, et al., ACTT-1 Study Group Members. Remdesivir for the treatment of covid-19 - final report. *N Engl J Med* 2020;383(19):1813–26.
- [2] Horby Peter, Lim Wei Shen, Emberson Jonathan R, Mafham Marion, Bell Jennifer L, Linsell Louise, et al., RECOVERY Collaborative Group. Dexamethasone in hospitalized patients with Covid-19. *N Engl J Med* 2021;384(8):693–704.
- [3] The Guide to Pharmacotherapy for COVID-19 by the Japanese Association for Infectious Diseases. sixth ed. 2020. https://www.kansensho.or.jp/uploads/files/topics/2019ncov/covid19_drug_200817.pdf. [Accessed 17 March 2022].
- [4] Treatment guidelines for adult new Influenza. second ed. 2017. <https://www.mhlw.go.jp/file/06-Seisakujouhou-10900000-Kenkoukyoku/0000190793.pdf>. [Accessed 17 March 2022].
- [5] Rodrigo Chamira, Leonardi-Bee Jo, Nguyen-Van-Tam Jonathan, Lim Wei Shen. Corticosteroids as adjunctive therapy in the treatment of influenza. *Cochrane Database Syst Rev* 2016 Mar 7;3:CD010406.
- [6] Fan PT, Yu DT, Targoff C, Bluestone R. Effect of corticosteroids on the human immune response. Suppression of mitogen-induced lymphocyte proliferation by “pulse” methylprednisolone. *Transplantation* 1978;26(4):266–7.
- [7] RECOVERY Collaborative Group. Tocilizumab in patients admitted to hospital with COVID-19 (RECOVERY): a randomised, controlled, open-label, platform trial. *Lancet* 2021;397(10285):1637–45.