GHM Open. 2022; 2(1):38-43.

BRIEF REPORT

DOI: 10.35772/ghmo.2022.01002

Safety of convalescent plasma therapy for COVID-19 patients and analysis of viral kinetics: A single-center, open-label, single-arm, interventional study in Japan

Satoshi Kutsuna[1,2,§,*], Sho Saito[1,§], Yuki Takamatsu[3], Mari Terada[1,4], Tomiteru Togano[5], Noriko Kinoshita[1], Kenji Maeda[3], Akihiro Matsunaga[6], Masahiro Satake[7], Keiji Matsubayashi[7], Nelson Hirokazu Tsuno[8], Makiko Kojima[7,8], Madoka Kuramitsu[9], Kenta Tezuka[9], Emi Ikebe[9], Kazu Okuma[9], Isao Hamaguchi[9], Yumiko Shimanishi[1], Akira Hangaishi[5], Yukihito Ishizaka[6], Norio Ohmagari[1], Hiroaki Mitsuya[3]

[1] Disease Control and Prevention Center, National Center for Global Health and Medicine, Tokyo, Japan;
[2] Department of Infection Control, Graduate School of Medicine Faculty of Medicine, Osaka University, Osaka, Japan;
[3] Department of Refractory Viral Infections, National Center for Global Health and Medicine Research Institute, Tokyo, Japan;
[4] Center for Clinical Sciences, National Center for Global Health and Medicine, Tokyo, Japan;
[5] Department of Hematology, National Center for Global Health and Medicine, Tokyo, Japan;
[6] Department of Intractable Diseases, National Center for Global Health and Medicine, Tokyo, Japan;
[7] Japanese Red Cross Central Blood Institute, Tokyo, Japan;
[8] Japanese Red Cross Kanto-Koshinetsu Block Blood Center, Tokyo, Japan;
[9] Department of Safety Research on Blood and Biological Products, National Institute of Infectious Diseases, Tokyo, Japan.

Abstract: Convalescent plasma therapy is an important treatment method for patients with severe coronavirus disease (COVID-19). This study was conducted to confirm the safety of this therapy. We conducted an open-label clinical trial to administer convalescent plasma transfusion in a small Japanese cohort. Blood was collected from the recovered COVID-19 patients with high anti-severe acute respiratory syndrome coronavirus 2 (anti-SARS-CoV-2) spike IgG titer and high neutralizing activity and stored in the National Center for Global Health and Medicine Hospital until use. Convalescent plasma was administered to COVID-19 patients who required supplemental oxygen within 3 days of hospitalization. Convalescent plasma was administered to 11 patients with moderate to severe COVID-19. One patient experienced an adverse event, such as redness of the skin around the intravenous injection site within 3 hours after transfusion. Ten patients (91%) showed clinical improvement within 28 days, and one patient died of causes unrelated to plasma therapy. The data suggest that patients with COVID-19 examined in the present study received convalescent plasma without having any significant adverse effects. We plan to conduct a randomized controlled trial to examine the clinical effectiveness of convalescent plasma transfusion in a large Japanese COVID-19 cohort.

***Keywords*:** SARS-CoV-2, hospitalization, safety study, adverse event, Japan

Introduction

The coronavirus disease (COVID-19) epidemic began in December 2019, and as of November 2021, more than 250 million infections and 5 million deaths have been reported (*1*). Although some standard treatments such as remdesivir and dexamethasone have been established (*2*), resistance to remdesivir has been reported (*3*), and therapeutic agents with antiviral activity, in particular, continue to be in demand.

Convalescent plasma therapy was classically used to treat patients with the Spanish flu and has been reported to be effective (*4*). More than 40 years ago, a randomized controlled trial conducted on cases of Argentine hemorrhagic fever (*5*), one of the South American hemorrhagic fevers, revealed that the therapy reduced the fatality rate. In recent years, convalescent plasma therapy has been used for severe infections such as H5N1 avian influenza and Ebola hemorrhagic fever (*6,7*), as well as severe acute respiratory syndrome and Middle East respiratory syndrome (*8-10*), which are infections caused by the same coronavirus as the new coronavirus.

Several clinical studies of convalescent plasma therapy for COVID-19 have been reported in China (*11*), India (*12*), the United States (*13*), and South America (*14*), but it has never been implemented in Japan. This is the first report on convalescent plasma therapy in Japan,

and we conducted a safety evaluation and virological analysis.

Materials and Methods

This study was designed as an open-label, single-arm, interventional study with only the convalescent plasma group and was conducted at the National Center for Global Health and Medicine (NCGM) in Tokyo, Japan.

Recruitment of COVID-19 convalescent patients was performed for plasma collection (*15*). Blood samples were taken from COVID-19 recovering patients who were at least 3 weeks from the date of onset for measurement of laboratory data. Hemoglobin, spike protein antibodies, and neutralizing activity were examined at the National Center for Global Health and Medicine Research Institute. Screening for infectious diseases (hepatitis B virus (HBV) surface antigen (Ag), HBV core antibody (Ab), HBV surface Ab, hepatitis C virus (HCV) Ab, human immunodeficiency virus (HIV)-1 Ab, HIV-2 Ab, HBV DNA, HCV RNA, hepatitis E virus RNA, HIV-1 RNA, HIV-2 RNA, *Treponema pallidum* Ab, human T-cell lymphoma virus 1 Ab, human T-cell lymphoma virus 2 Ab, and human parvovirus B19 Ag), blood type tests, and irregular antibody testing were performed at the Japanese Red Cross Central Blood Institute, while severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) PCR tests in plasma were performed at the National Institute of Infectious Diseases, Department of Safety Research on Blood and Biological Products (*16*). Spike protein was measured based on the methods previously reported (*17,18*), and patients whose plasma sample, absorbance value at optical density (OD) 450 nm was > 1, were considered to be eligible as donors. As a neutralizing activity, the concentration of IgG required for 50% inhibition of viral infection (IC_{50}) was evaluated according to the methods reported previously (*19*). Plasma with less than 50 μg/mL of IC_{50} was considered eligible. Cases with positive infectious disease screening tests or irregular antibodies were excluded, as were cases with positive polymerase chain reaction (PCR) tests for SARS-CoV-2 in serum. Four hundred mL of plasma was collected from eligible convalescent patients using a blood cell separator, and the plasma was stored below -20°C in a freezer at the National Center for Global Health and Medicine Research Institute. Plasma to be administered to the patient was obtained from plasma that was compatible with the patient's and donor's blood types, starting with the oldest date of collection.

The patients to whom plasma was administered were diagnosed with COVID 19 by PCR or antigen testing, and required supplemental oxygen. Patients aged under 20 years, pregnant or lactating women, those whose religious beliefs do not allow for the administration of blood transfusions, those participating in other treatment studies for COVID-19, and those whose physicians deemed inappropriate for inclusion in the study were excluded. Eligible patients were given 200 mL plasma within 3 days of admission after providing written consent. The plasma to be administered was matched to the blood type of the recipient patient. Plasma was thawed spontaneously, cross-matching was performed, and plasma was administered after confirming the cross-matching results. Convalescent plasma was administered *via* a peripheral vein starting at 10 mL/15 min and then increasing the flow to 100 mL/h.

Initially, the primary endpoint was set as the absence of ventilatory management or death by day 14 of treatment, but this was judged to be difficult to evaluate because of the small number of participants in this study due to the planned start of a randomized controlled trial, so the aim was changed to an evaluation of the safety of convalescent plasma therapy. The primary endpoint was the presence or absence of adverse events within 28 days of plasma administration. An adverse event was defined as any unwanted or unintended symptom (including abnormal laboratory test results), condition, or illness that occurred within 28 days after convalescent plasma administration. The presence of adverse events was assessed daily during hospitalization and on days 3, 7, 14, and 28 after plasma administration, which was the day of the outpatient visit after discharge. Secondary endpoints included changes in SARS-CoV-2 viral load in nasopharyngeal swabs (pre-dose to day 14) and clinical improvement was monitored up to 28 days using an 8-point scale and the National Early Warning Score. Nasal swabs were collected before and 3, 7, 14, and 28 days after plasma administration. The SARS-CoV-2 viral copy number in each sample was determined as previously described and the threshold cycle (Ct) values were obtained (*20*). To calculate the copy numbers of SARS-CoV-2 from the Ct values, a standard curve was generated with 10-fold serial dilutions of a reference SARS-CoV-2 viral RNA (*19*), and the Ct values for each sample were converted to SARS-CoV-2 copy numbers. The 8-point scale was: 1. Dead; 2. Hospitalized and using invasive mechanical ventilation or extracorporeal membrane oxygenation; 3. Hospitalized and using noninvasive ventilation or high-flow oxygenation; 4. Hospitalized and needing oxygen supplementation; 5. Hospitalized and needing no oxygen supplementation – requiring continuation of treatment (COVID-19-related or other); 6. Hospitalized and needing no oxygen supplementation – needing no continuation of treatment; 7. Not hospitalized and needing limitation of activities and/or oxygen therapy at home; 8. Not hospitalized, and no limitation of activities.

This study was approved as a specified clinical trial in October 2020 in the NCGM and registered in the Japanese Register of Clinical Trials (jRCTs031200124).

Table 1. The characteristics, COVID-19 treatment, plasma side effects and outcome of 11 COVID-19 patients who received a convalescent plasma transfusion

	Age (years)	Sex	Underlying diseases	Treatment for COVID-19	Days from COVID-19 onset to plasma administration	Oxygen dose at the time of plasma administration	Oxygen dose at the worst point of respiratory condition	Intubation or death	Adverse event	Outcome
1	46	M	HIV infection	REM/DEX	10	1 L/min	4 L/min	None	None	Recovery
2	59	M	Diabetes, hypertension, COPD, hyperlipidemia	REM/DEX	8	NHF	NHF	None	None	Recovery
3	46	M	Hypertension, obesity	REM/DEX	7	1 L/min	2 L/min	None	None	Recovery
4	39	M	None (Previous history of hepatitis B)	DEX	12	2 L/min	5 L/min	None	None	Recovery
5	61	M	Membranous nephropathy, bronchial asthma, hyperuricemia, dyslipidemia	REM/DEX	12	4 L/m	5 L/min	None	None	Recovery
6	61	M	Interstitial pneumonia	REM/DEX	7	2 L/m	2 L/min	None	None	Recovery
7	60	M	Hypertension	REM/DEX	8	2 L/m	2 L/min	None	None	Recovery
8	64	F	Osteoporosis	REM/DEX	10	4 L/min	NHF	None	Erythema at the infusion site	Recovery
9	90	F	Interstitial pneumonia, hypertrophic heart disease, hypertension	REM/DEX	9	5 L/min	NHF	Yes	None	Death
10	66	M	Hypertension	REM/DEX	7	3 L/min	NHF	None	None	Recovery
11	86	F	Hypertension, dyslipidemia	REM/DEX	6	1 L/min	1 L/min	None	None	Recovery

COVID-19, coronavirus disease; HIV, human immunodeficiency virus; COPD, chronic obstructive pulmonary disease; REM, remdesivir; DEX, dexamethasone; F, female; M, male; NHF, nasal high-flow therapy.

Results and Discussion

From October 1, 2020, to December 31, 2020, 11 patients were enrolled in the study (Table 1). Eight (72.7%) patients were men, and the median age was 61 years. All patients had underlying medical conditions. The median day from onset to plasma administration was 8 days. All patients received dexamethasone during the study, and all but one received remdesivir. All patients were on oxygen at the time of enrollment. One patient died and the other ten were discharged. The data and safety monitoring committee determined that the patient's death was not causally related to the plasma administration. One patient developed erythema at the puncture site the plasma transfusion. Of the 11 COVID-19 patients who received convalescent plasma, five underwent infectious disease screening tests 90 days after administration, and all were negative.

Figure 1 shows the relationship between the number of days elapsed from the date of administration of the convalescent plasma and the percentage of recovered COVID-19 patients, defined as the criteria for category 6, 7, or 8 on the 8-point scale. Four patients (36%) recovered within 7 days of treatment, 7 (64%) within 14 days, and 10 (91%) within 28 days.

Figure 2 shows the trend of SARS-CoV-2 viral load in nasal swabs as a function of the number of days elapsed from the onset date. Counting from the date of onset, none of the patients had the virus undetectable within 10 days of onset, three patients (27%) had the virus below the detection limit within 20 days, 7 (64%) patients within 30 days, and 9 (82%) patients within 40 days, and two patients (18%) did not disappear until 30 or 34 days after onset. Starting from the administration of plasma, two patients (18%) disappeared within 7 days after plasma administration, 7 (64%) within 14 days, 9

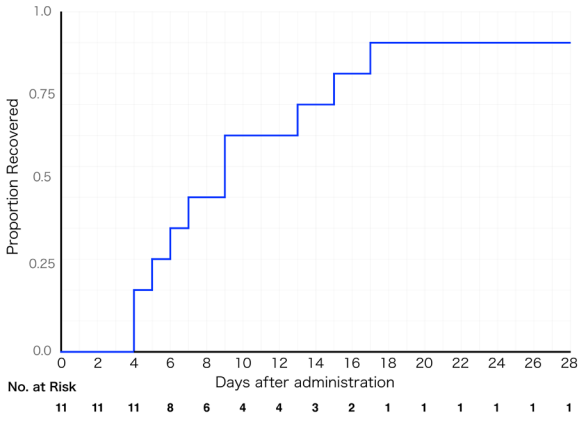

Figure 1. The relationship between the number of days elapsed from the date of administration of the convalescent plasma and the percentage of COVID-19 patients discharged from the hospital. No, number; COVID-19, coronavirus disease.

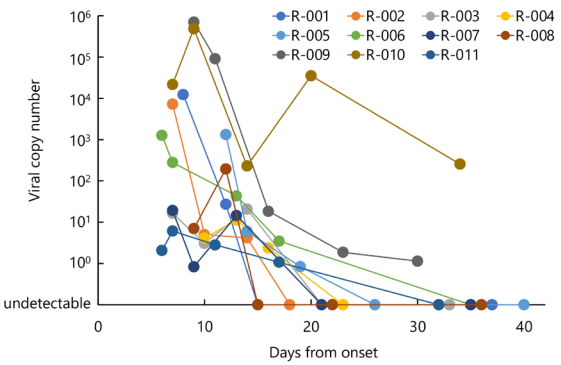

Figure 2. The trend of SARS-CoV-2 viral load in nasal swabs as a function of the number of days elapsed from the onset date. SARS-CoV-2, severe acute respiratory syndrome coronavirus.

(82%) within 28 days, and two patients (18%) still had detectable virus 28 days after administration.

Eleven COVID-19 patients received convalescent plasma, and no adverse events related to plasma administration were identified, except for redness at the site of intravenous injection after administration. Although convalescent plasma therapy for COVID-19 has been used overseas, this is the first time that this therapy has been implemented in Japan. The establishment of a system for the safe administration of convalescent plasma in Japan is considered significant.

Although the number of COVID-19 patients to whom we have administered convalescent plasma is small (11 patients), a larger number of patients have been administered COVID-19 overseas, and the safety of COVID-19 has been verified. In the United States, 22,000 COVID-19 patients have been treated with convalescent plasma and analyzed for adverse effects (*21*). In this analysis, complications included the following: transfusion reactions in 89 (< 1%), thromboembolic complications in 87 (< 1%), cardiac events in 680 (approximately 3%), and the majority of thromboembolic and cardiac events were judged to be unrelated to the plasma. These results show that the incidence of transfusion reactions with convalescent plasma appears to be comparable with that of standard plasma when applied to a patient population with similar illness severity.

In our study, 10 of 11 patients recovered, and one died (mortality rate 9.1%). According to data from COVID-19 Registry Japan (COVIREGI-JP) (*22*), a Japanese registry of COVID-19 hospitalized patients, the mortality rate for patients requiring oxygen or ventilatory management on admission is 17.7%. It is difficult to simply compare the results of this study with those of COVIREGI-JP because of the two studies used different definitions of disease severity. Randomized controlled trials (RCTs) to determine the efficacy of convalescent plasma therapy have been conducted in other countries, and the results of some RCTs have been reported to date. Multiple RCTs have shown that the administration of convalescent plasma to hospitalized patients who require oxygenation or who are severely ill with COVID-19 is not expected to be effective (*11,12,23*). This may be because in patients with advanced disease, viral replication has ceased and the focus of the disease is on an excessive inflammatory response, so the time when convalescent plasma, whose mechanism of action is to neutralize the virus, is no longer effective.

In contrast, an RCT in which convalescent plasma was administered within 3 days of disease onset to older patients and patients at high risk of severe disease with underlying disease showed that it prevented severe disease (*14*). Furthermore, Sullivan *et al.* reported that early administration of high-titer SARS-CoV-2 convalescent plasma reduced outpatient hospitalizations by more than 50% (*24*). However, in another RCT, convalescent plasma was administered within 7 days of onset, but no efficacy was demonstrated (*25*). These results suggest that convalescent plasma is unlikely to be effective in already severe disease, and that administration of plasma with high antibody titers as soon as possible after the onset of disease is most likely to be effective. In addition, in the RCTs conducted to date, the neutralizing activity of the collected plasma was not assessed prior to administration, but only the IgG titer was assessed. In fact, it has been reported that plasmas or purified-IgG with high-neutralizing activity significantly reduced the viral induced lung lesions in SARS-CoV-2 infected Syrian hamsters (*26*).

We have reported that IgG titer and neutralizing activity can sometimes deviate in convalescent patients, and neutralizing activity may not be accurately assessed by measuring IgG titers alone (*19*). In this study, we assessed the neutralizing activity in the collected plasma, in order to assess the plasma quality more accurately. In the future, the efficacy of convalescent plasma therapy could be validated by conducting a randomized controlled trial in high-risk patients with early onset of disease, using plasma that has been previously evaluated for neutralizing activity to be administered. The antibodies possessed by the convalescent patients are a wide variety of polyclonal ones, only a few of which have neutralizing activity against the virus. A homogeneous monoclonal antibody preparation with high neutralizing activity has been shown to be effective in patients with early-onset COVID-19 (*27,28*). Now that monoclonal antibody products are available, the role of convalescent plasma therapy is limited, but it remains a potential treatment option in developing countries and could be a treatment option for the next emerging infectious disease.

In this study, we also observed changes in the viral load of SARS-CoV-2 in the nasal swabs of 11 patients. In a study analyzing the viral load of SARS-CoV-2 in 655 COVID-19 patients (40% of whom required oxygen administration), the median time for the virus

to fall below the limit of detection in patients older than 65 years was 16 days after onset, and 12 days in those younger than 65 years (*29*). In our study, the median time for viral load to fall below the detection limit in nine patients was 21 days, and two patients virus was still detectable 28 days after transfusion. With these results, it is not possible to show the effect of the administration of convalescent plasma on the reduction of viral load. The fact that the 11 patients in our study had a higher severity of illness than the COVID-19 patients in the study by Néant *et al.* may be related to the longer viral disappearance time. In addition, since this study did not examine the efficacy of convalescent plasma, but rather focused on evaluating safety, it is not possible to determine the efficacy of convalescent plasma because of the disparate neutralizing activities of the plasma administered.

In conclusion, this is the first study of plasma therapy for COVID-19 patients to be conducted in Japan. No treatment-related adverse events were observed in the 11 patients who received plasma therapy. A randomized controlled trial using plasma with pre-evaluated neutralizing activity is needed to determine the efficacy of plasma therapy in patients with moderately severe COVID-19.

Funding: This work was supported by the Health, Labor, and Welfare Policy Research Grants, Research on Emerging and Re-emerging Infectious Diseases and Immunization (grant number 20HA1006) and NCGM Intramural Research Fund (20A2003D).

Conflict of Interest: The authors have no conflicts of interest to disclose.

References

1. World Health Organization. Weekly epidemiological update - 30 November 2021. *https://www.who.int/publications/m/item/weekly-epidemiological-update-on-covid-19---30-november-2021* (accessed February 9, 2022).
2. Kutsuna S. Coronavirus disease 2019 (COVID-19): research progress and clinical practice. Glob Health Med. 2020; 2:78-88.
3. Martinot M, Jary A, Fafi-Kremer S, Leducq V, Delagreverie H, Garnier M, Pacanowski J, Mékinian A, Pirenne F, Tiberghien P, Calvez V, Humbrecht C, Marcelin AG, Lacombe K. Emerging RNA-dependent RNA polymerase mutation in a remdesivir-treated B-cell immunodeficient patient with protracted coronavirus disease 2019. Clin Infect Dis. 2021; 5;73:e1762-e1765.
4. Luke TC, Kilbane EM, Jackson JL, Hoffman SL. Meta-analysis: convalescent blood products for Spanish influenza pneumonia: a future H5N1 treatment? Ann Intern Med. 2006; 17;145:599-609.
5. Maiztegui JI, Fernandez NJ, de Damilano AJ. Efficacy of immune plasma in treatment of Argentine haemorrhagic fever and association between treatment and a late neurological syndrome. Lancet. 1979; 2:1216-1217.
6. Zhou B, Zhong N, Guan Y. Treatment with convalescent plasma for influenza A (H5N1) infection. N Engl J Med. 2007; 357:1450-1451.
7. van Griensven J, Edwards T, de Lamballerie X, *et al.* Evaluation of convalescent plasma for Ebola virus disease in Guinea. N Engl J Med. 2016; 374:33-42.
8. Cheng Y, Wong R, Soo YO, Wong WS, Lee CK, Ng MH, Chan P, Wong KC, Leung CB, Cheng G. Use of convalescent plasma therapy in SARS patients in Hong Kong. Eur J Clin Microbiol Infect Dis. 2005; 24:44-46.
9. Arabi Y, Balkhy H, Hajeer AH, *et al.* Feasibility, safety, clinical, and laboratory effects of convalescent plasma therapy for patients with Middle East respiratory syndrome coronavirus infection: a study protocol. Springerplus. 2015; 4:709.
10. Ko JH, Seok H, Cho SY, *et al.* Challenges of convalescent plasma infusion therapy in Middle East respiratory coronavirus infection: a single centre experience. Antivir Ther. 2018; 23:617-622.
11. Shen C, Wang Z, Zhao F, *et al.* Treatment of 5 critically Ill patients with COVID-19 with convalescent plasma. JAMA. 2020; 323:1582-1589.
12. Agarwal A, Mukherjee A, Kumar G, Chatterjee P, Bhatnagar T, Malhotra P. Convalescent plasma in the management of moderate covid-19 in adults in India: open label phase II multicentre randomised controlled trial (PLACID Trial). BMJ. 2020; 371:m3939.
13. Joyner MJ, Carter RE, Senefeld JW, *et al.* Convalescent plasma antibody levels and the risk of death from Covid-19. N Engl J Med. 2021; 384:1015-1027.
14. Libster R, Pérez Marc G, Wappner D, *et al.* Early high-titer plasma therapy to prevent severe Covid-19 in older adults. N Engl J Med. 2021; 384:610-618.
15. Terada M, Kutsuna S, Togano T, *et al.* How we secured a COVID-19 convalescent plasma procurement scheme in Japan. Transfusion. 2021; 61:1998-2007.
16. Nomoto H, Kutsuna S, Okuma K, *et al.* No SARS-CoV-2 RNA detected in the convalescent plasma of COVID-19 patients with different disease severity. J Infect Chemother. 2021; 27:653-655.
17. Kutsuna S, Asai Y, Matsunaga A. Loss of anti-SARS-CoV-2 antibodies in mild Covid-19. N Engl J Med. 2020; 383:1695-1696.
18. Kutsuna S, Asai Y, Matsunaga A, *et al.* Factors associated with anti-SARS-CoV-2 IgG antibody production in patients convalescing from COVID-19. J Infect Chemother. 2021; 27:808-813.
19. Maeda K, Higashi-Kuwata N, Kinoshita N, Kutsuna S, Tsuchiya K, Hattori S, Matsuda K, Takamatsu Y, Gatanaga H, Oka S, Sugiyama H, Ohmagari N, Mitsuya H. Neutralization of SARS-CoV-2 with IgG from COVID-19-convalescent plasma. Sci Rep. 2021; 11:5563.
20. Hattori SI, Higashi-Kuwata N, Hayashi H, *et al.* A small molecule compound with an indole moiety inhibits the main protease of SARS-CoV-2 and blocks virus replication. Nat Commun. 2021; 12:668.
21. Joyner MJ, Bruno KA, Klassen SA, *et al.* Safety update: COVID-19 convalescent plasma in 20,000 hospitalized patients. Mayo Clin Proc. 2020; 95:1888-1897.
22. Matsunaga N, Hayakawa K, Terada M, *et al.* Clinical epidemiology of hospitalized patients with COVID-19 in Japan: report of the COVID-19 Registry Japan. Clin Infect Dis. 2021; 73:e3677-e3689.
23. Simonovich VA, Burgos Pratx LD, Scibona P, *et al.* A Randomized trial of convalescent plasma in Covid-19

severe pneumonia. N Engl J Med. 2021; 384:619-629.
24. Sullivan DJ, Gebo KA, Shoham S, *et al.* Randomized controlled trial of early outpatient COVID-19 treatment with high-titer convalescent plasma. medRxiv [Preprint]. 2021; 2021.12.10.21267485.
25. Korley FK, Durkalski-Mauldin V, Yeatts SD, *et al.* Early convalescent plasma for high-risk outpatients with Covid-19. N Engl J Med. 2021; 385:1951-1960.
26. Takamatsu Y, Imai M, Maeda K, Nakajima N, Higashi-Kuwata N, Iwatsuki-Horimoto K , Ito M, Kiso M, Maemura T, Takeda Y, Omata K, Suzuki T, Kawaoka Y, Mitsuya H. Highly neutralizing COVID-19 convalescent plasmas potently block SARS-CoV-2 replication and pneumonia in Syrian hamsters. J Virol. 2022; 96:e0155121.
27. Weinreich DM, Sivapalasingam S, Norton T, *et al.* REGEN-COV antibody combination and outcomes in outpatients with Covid-19. N Engl J Med. 2021; 385:e81.
28 Gupta A, Gonzalez-Rojas Y, Juarez E, *et al.* Early treatment for Covid-19 with SARS-CoV-2 neutralizing antibody sotrovimab. N Engl J Med. 2021; 385:1941-1950.
29 Néant N, Lingas G, Le Hingrat Q, *et al.* Modeling SARS-CoV-2 viral kinetics and association with mortality in hospitalized patients from the French COVID cohort. Proc Natl Acad Sci U S A. 2021; 118:e2017962118.

Received February 9, 2022; Revised March 8, 2022; Accepted March 12, 2022.

Released online in J-STAGE as advance publication March 18, 2022.

[§]*These authors contributed equally to this work.*
**Address correspondence to*:
Satoshi Kutsuna, Department of Infection Control, Graduate School of Medicine Faculty of Medicine, Osaka University, 2-2 Yamadaoka, Suita, Osaka 565-0871, Japan.
E-mail: kutsuna@hp-infect.med.osaka-u.ac.jp