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.

International Journal of Infectious Diseases 117 (2022) 189–194

Contents lists available at ScienceDirect

International Journal of Infectious Diseases

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

Impact of Antibody Cocktail Therapy Combined with Casirivimab and Imdevimab on Clinical Outcome for patients with COVID-19 in A Real-Life Setting: A Single Institute Analysis

Yasutaka Kakinoki [1,*], Kazuki Yamada [1], Yoko Tanino [1], Keiko Suzuki [1], Takaya Ichikawa [1], Naoki Suzuki [2], Go Asari [2], Ai Nakamura [1], Shin Kukita [1], Akito Uehara [1], Seisuke Saito [1], Shohei Kuroda [1], Hidemitsu Sakagami [1], Yuuki Nagashima [1], Kae Takahashi [1], Satoshi Suzuki [1]

[1] *Division of Internal Medicine, Asahikawa City Hospital, Asahikawa, Japan*
[2] *Asahikawa City Health Center, Asahikawa, Japan*

ARTICLE INFO

Article history:
Received 10 December 2021
Revised 18 January 2022
Accepted 30 January 2022

Keywords:
COVID-19
SARS-CoV-2
Cocktail
Ronapreve
REGEN-COV

ABSTRACT

Background: Recent data from clinical trials suggest that antibody cocktail therapy, which combined casirivimab and imdevimab, is linked to the reduction of the risk of hospitalization or death among high-risk patients with COVID-19. However, it remains unclear how effective the therapy is in a real-life clinical practice.

Methods: We retrospectively analyzed patients with COVID-19 with high-risk factors who underwent the antibody cocktail therapy, compared with those who were not given the cocktail therapy while being isolated in nonmedical facilities during the same period.

Results: Data from 55 patients who received the antibody cocktail therapy and 53 patients with initial isolation in nonmedical facilities were analyzed. A total of 22 (41.5 %) of 53 patients staying in isolation facilities were eventually hospitalized and received medical interventions. By contrast, 13 (23.6 %) of 55 patients who received the antibody cocktail therapy subsequently underwent further medical interventions. In multivariate analysis, the antibody cocktail therapy significantly reduced the need for further medical interventions by 70 % compared with isolation (odds ratio=0.30, 95%CI [0.10-0.87], p=0.027). Patients with percutaneous oxygen saturation 96% or higher were significantly favoured for the therapy and had an advantage.

Conclusion: The results of this study indicate that the antibody cocktail therapy is associated with reducing burden on hospitals during the COVID-19 pandemic.

© 2022 The Author(s). Published by Elsevier Ltd on behalf of International Society for Infectious Diseases.
This is an open access article under the CC BY-NC-ND license (http://creativecommons.org/licenses/by-nc-nd/4.0/)

Introduction

COVID-19, caused by SARS-CoV-2, was first detected in December 2019 and was declared a global pandemic in March 2020 (Zhu et al., 2019 WHO, 2020; Wu et al., 2020;). In Japan, as of September 22, 2021, approximately 1.68 million people have been infected and approximately 17 000 have died, and only about 55% of the population is fully vaccinated (MHLW of Japan, 2020). Although the records regarding infected figures appear to be fewer than in Western countries, there are several challenging issues in hospitals including unavailability of hospital beds and shortages of hospital staff, mostly nurses. To resolve these issues, Japan's Ministry of Health, Labour and Welfare (MHLW) has approved the antibody cocktail of casirivimab and imdevimab, under the brand name of Ronapreve™ (provided from Roche globally, and CHUGAI Pharmaceutical in Japan), for the treatment of mild to moderate COVID-19 patients with high-risk factors through intravenous infusion, which was granted a Special Approval Pathway under article 14-3 of the Pharmaceuticals and Medical Devices Act on July 19, 2021 (MHLW of Japan, 2021). The approval by the MHLW is

* Corresponding author: Yasutaka Kakinoki, MD, PhD. Asahikawa City Hospital, 1-1-65, Kinseicho, Asahikawa, 070-8610, Japan.
E-mail address: y_kakinoki@ach.hokkaido.jp (Y. Kakinoki).

https://doi.org/10.1016/j.ijid.2022.01.067
1201-9712/© 2022 The Author(s). Published by Elsevier Ltd on behalf of International Society for Infectious Diseases. This is an open access article under the CC BY-NC-ND license (http://creativecommons.org/licenses/by-nc-nd/4.0/)

based on results from the global phase 3 REGN-COV2067 trial (Weinreich et al., 2021) in high-risk nonhospitalized patients with COVID-19, which showed that the cocktail therapy reduced hospitalization or any-cause death by 70% and COVID-19-related symptom duration by 4 days, as well as a phase 1 clinical study with safety, tolerability, and pharmacokinetics in the Japanese population. (Regeneron, 2020). In addition, the ability of the cocktail to retain activity against the emerging variants including the Delta variant has been demonstrated in an in vitro study (Baum et al., 2020 Copin et al., 2021; Wang et al., 2021;). However, these results are from randomized clinical trials and experimental studies, and, therefore, application in daily clinical practice of the cocktail therapy needs to be observed. In this study, we describe the clinical benefits of Ronapreve in a real-life clinical practice at our institute.

Methods

Patients

Eligible patients were aged 20 years or older, with a SARS-CoV-2 infection confirmed by a real-time reverse transcription-polymerase chain reaction (RT-PCR) test, a COVID-19-related fever (≧37.5°C) in mild to moderate condition, and the presence of risk factors meeting the criteria for severe COVID-19 (Weinreich et al., 2021) during June 2021 through early September 2021. The local public health center made allocation decisions based on several factors such as severity and urgency to deliver patients to hospitals or nonmedical facilities for isolation. The use of the patient's clinical information was approved by the Research Ethics Committee of Asahikawa City Hospital which oversaw the study conduct and documentation. The chief officer of the local public health center authorized the use of the data collected from nonmedical facilities under fully anonymized conditions. This study was conducted in accordance with the principles of the Declaration of Helsinki.

Medical intervention

Patients assigned to our institute were first reviewed for eligibility for the use of Ronapreve according to the criteria (Weinreich et al., 2021). Ronapreve was given at equal doses of 600 mg of casirivimab and imdevimab combined in a 100 ml normal saline solution through intravenous infusion over 30 minutes, if applicable (Ronapreve group). Afterward, if necessary, patients received additional therapy such as oxygen support, steroids, or antiviral drugs. Patients assigned to nonmedical facilities were under watch-and-wait intervention to see if they progress to the point where they need hospitalization (watchful observation group). When the patients' condition worsened, they were immediately transferred to hospitals to receive treatment for COVID-19.

Key and other outcomes

Key outcomes were designated to the difference between the Ronapreve and watchful observation groups in terms of the necessity of additional treatment such as oxygen support, steroid administrations, or antiviral drugs. In the Ronapreve group, any additional treatment after Ronapreve administration indicated the failure of the cocktail therapy by definition. In the watchful observation group, the transfer of patients to hospitals to receive additional therapies indicated that patients were under intractable or deteriorating conditions. Other outcomes were designated in the Ronapreve group to investigate the duration of fever and adverse events after Ronapreve administration.

Statistical analysis

Logistic regression models for multivariate analysis were applied to evaluate the proposed significant factors in terms of the efficacy of Ronapreve, using age, body mass index (BMI), high-risk factors, and percutaneous oxygen saturation (SpO2) as explanatory variables. Receiver operating characteristic (ROC) curves were used to determine the cut-off value for SpO2. All p-values were two-sided and p-values of 0.05 or less were considered statistically significant. All statistical analyses were performed with EZR Version 1.50 (Saitama Medical Center, Jichi Medical University, Saitama, Japan), which is a graphical user interface for R (The R Foundation for Statistical Computing, Vienna, Austria). More precisely, it is a modified version of R commander designed to add statistical functions frequently used in biostatistics (Kanda, 2013).

Results

Patients' characteristics

Patients' characteristics were collected consecutively during the period from June 2021 through early September 2021, when the Delta variant was widely spreading in our community. As a result, 55 patients were given Ronapreve first in our institute (Ronapreve group) and 53 patients were initially assigned to nonmedical isolation facilities to observe the situation (watchful observation group) (Table 1).

In the Ronapreve group, the median age was 51 years, 69.1% were male, and the median BMI score was 27.5. Among those patients with high-risk factors, 30.9% possessed 1 factor, 32.7% possessed 2 factors, and 36.4% possessed 3 or more factors. SpO2 tests revealed 67.3% of patients to be 96% or higher and 43.6% of patients have pneumonia detected by CT scan, X-ray imaging, or stethoscopic findings. In contrast, in the watchful observation group, although distributions of age and gender were similar, the proportion of high-risk factors and BMI scores regarding disease progression was significantly lower ($p<0.001$ and $p=0.01$, respectively), than the Ronapreve group. Details of the high-risk factors patients in both groups have been provided in the Supporting Information (Table S1).

Clinical efficacy

Key outcomes

In the Ronapreve group, 23.6% (13 of 55) of patients eventually needed further medical interventions after Ronapreve administration, such as oxygen support, steroid administrations, or antiviral drugs (Figure 1). However, no deterioration was found beyond 5 days after Ronapreve administration, meaning the remaining 76.4% (42 of 55) of patients in this group fully recovered from COVID-19 (Figure 1A). In contrast, patients in the watchful observation group showed that those who got progressively worse were increasingly transferred to hospitals until 12 days after the disease onset, eventually reaching 41.5% (22 of 53) of patients (Figure 1B). In multivariate analysis with age, BMI, and high-risk factors as explanatory variables, Ronapreve significantly reduced the need for additional treatments by 70% compared with the watchful observation group patients (odds ratio=0.301, 95%CI [0.104-0.869], $p=0.026$) (Figure 2). Furthermore, in Ronapreve group, patients with 96% or higher SpO2, the SpO2 cutoff value was established by ROC curves, showed a 97% reduction on additional treatment compared with patients with 95% or lower SpO2, which was significant (odds ratio=0.03, 95%CI [0.01-0.22], $p<0.001$) (Figure 3).

Table 1
Patients' Demographic and Epidemiological Characteristics.

Characteristics	Ronapreve (n=55)	Watchful observation (n=53)	p value
Median age (IQR), yr	51.0 (20.0, 94.0)	52.0 (20.0, 68.0)	0.939
Male sex, no. (%)	38 (69.1)	30 (56.6)	0.232
Median BMI (IQR)	27.5 (17.2, 47.5)	23.5 (14.7, 38.6)	0.011
Patients with high-risk factors#, no. (%)			<0.001
1 factor	17 (30.9)	41 (77.4)	
2 factors	18 (32.7)	6 (11.3)	
3 or more factors	20 (36.49)	6 (11.39)	
SPO2, no. (%)			0.169
≧96%	37 (67.3)	28 (52.8)	
≦95%	18 (32.7)	25 (47.2)	
Pneumonia, no. (%)			
yes	24 (43.6)	N.E	
no	31 (56.4)	N.E	

Abbreviations: IQR, interquartile range; BMI, body mass index; SpO2, Percutaneous oxygen saturation; N.E, not evaluated.
#High-risk factors for severe COVID-19 include the age of more than 50 years, obesity (BMI≧30), cardiovascular disease (including hypertension), chronic lung disease (including asthma), chronic metabolic disease (including diabetes), chronic kidney disease (including receipt of dialysis), chronic liver disease, and immunocompromised.

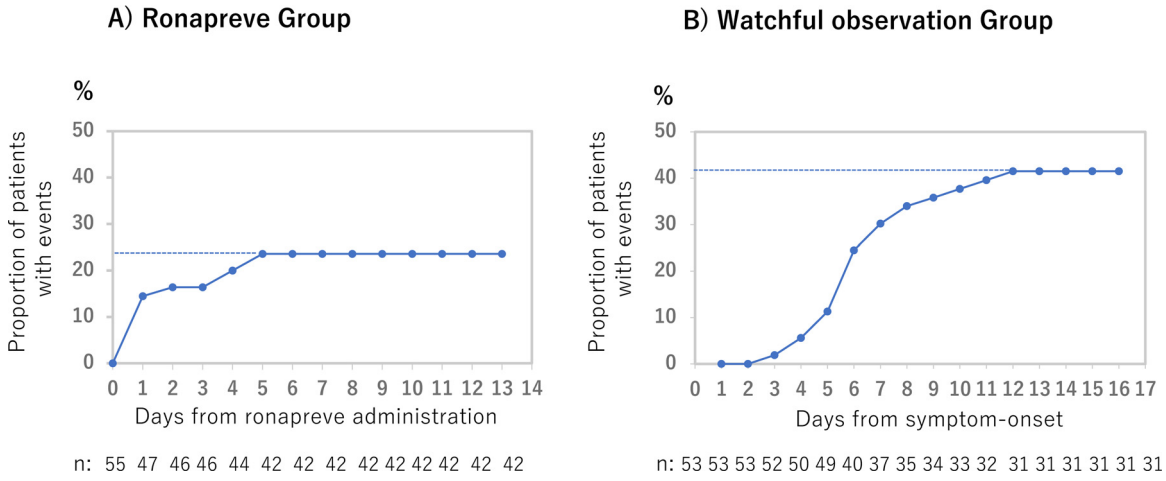

Figure 1. Time to additional treatment.
Event indicates that additional treatments are started.
A) shows time (day) to the next additional treatment after Ronapreve administration (date of the dripping indicates day 0). B) shows time (day) to be hospitalized to receive medical interventions from disease onset.

Other outcomes

Ronapreve was started at a median time of 3 days from the onset of symptoms (range; 0-7 days) (Figure S1). Ronapreve treatment was associated with quick relief from COVID-19-related fever. Of 27 in-patients, 14 patients (51.9%) had a reduced fever the following day, and all 27 patients achieved afebrile state 4 days after the administration. Although, this result is based on data from limited numbers, 27 in-patients, owing to missing data from another 28 outpatients (Figure 4). Regarding vaccinated patients who were enrolled, out of 3 patients with 1 dose and 5 patients with 2 doses, 1 and 4 patients, respectively, were shown to have fever reduction(Table S2). Concerning adverse events, 1 patient showed a reaction to the infusion in the form of mild swelling of eyelids and urticaria in the upper arms during the administration of Ronapreve drip, resulting in stopping the administration, and 2 patients showed skin eruption around 2-3 hours after the administration (Table S3).

Discussion

Ronapreve (also known as REGEN-COV in clinical trials) is a cocktail made up of 2 noncompeting neutralizing human IgG1 monoclonal antibodies, casirivimab and imdevimab, which target the receptor-binding domain of the SARS-CoV-2 spike protein, thereby preventing viral entry into human cells through the angiotensin-converting enzyme 2 (ACE2) receptor (Baum et al., 2020 Hansen et al., 2020;). This cocktail therapy retains its neutralization potency against circulating SARS-CoV-2 variants of concern, including B.1.1.7 (or Alpha), B.1.351 (or Beta), B.1.617.2 (or Delta), and so forth, in vitro and in vivo (Baum et al., 2020 Copin et al., 2021; Wang et al., 2021;). However, more recently, some reports have shown that the B.1.1.529 (or Omicron) variant reduced the neutralization by the cocktail antibodies in an in vitro study (Ikemura et al., 2021 Wilhelm et al., 2021;).

In a real-life practice setting, we described that the administration of Ronapreve was associated with a 70% reduction in uptake of additional treatment, compared with watchful observation in isolation facilities where patients are under a watch-and-wait situation to see if they progress to the point where they need hospitalization to receive treatments (Figure 2). Moreover, we showed that a 97% reduction of additional treatments in patients who had a SpO2 of 96% or higher, compared with those who had a SpO2 of 95% or lower was observed(Figure 3). This result may be associated with the suppression of SARS-CoV-2 itself by Ronapreve before a surge of inflammation in the lungs. In addition, Ronapreve was related to substantially speeding up recovery from COVID-19-

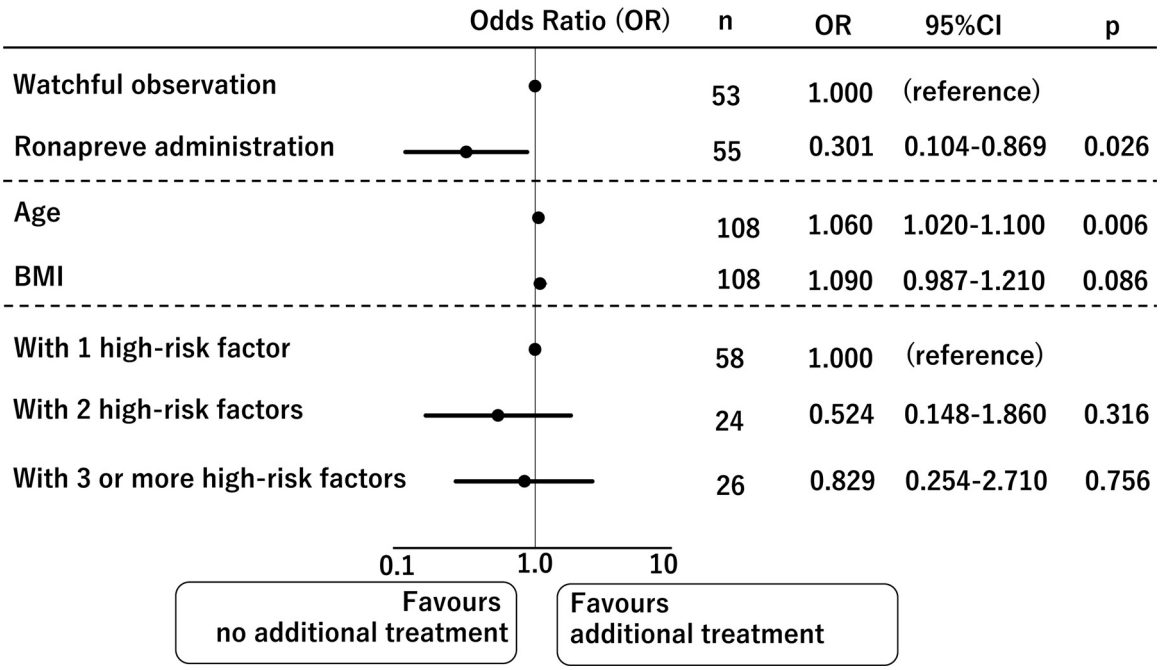

Figure 2. Multivariate analysis for the efficacy of Ronapreve using variables of age, BMI, and high-risk factors. Forest plots depict the comparison of the incidences between watchful observation and Ronapreve groups.

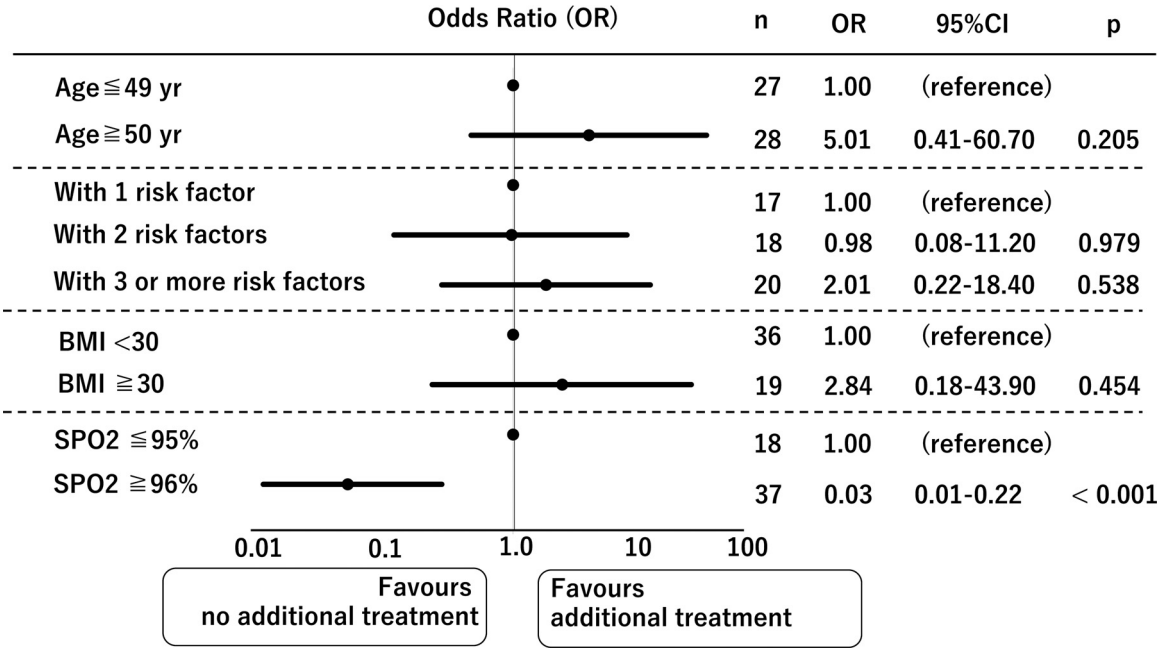

Figure 3. Multivariate analysis for age≧50 years, 1, or 2, or 3 or more high-risk factors, BMI≧30, and SpO2≧96% in the Ronapreve group. Forest plots depict the comparison of the incidences.

related fever at a median time of just 1 day within the administration (Figure 4), which probably represents an additional benefit for patients with COVID-19. Moreover, it is worth noting that patients in the Ronapreve group had worse conditions for the disease progression than those in the watchful observation group based on high-risk factors and BMI (Table 1).

Our data in a real-life setting suggest that Ronapreve has the potential to prevent patients with mild to moderate COVID-19 with high-risk factors from receiving additional treatments, such as supplemental oxygen, dexamethasone, or antiviral therapies owing to the disease progression, in hospitals in Japan. This result indicates that Ronapreve is associated with reducing the burden of care of patients with COVID-19 in hospital beds, which is related to returning the use of public health care resources to normal.

Overall, our findings described previously are consistent with data from previous clinical trials regarding Ronapreve. The phase 1 and 2 trial data showed that REGEN-COV for patients with COVID-19 lowered viral load, reduced the need for medical attention, and was highly suggestive of a reduced risk for hospitalization (Weinreich et al., 2021). The phase 3 clinical trial confirmed that early treatment with REGEN-COV in outpatients with high-risk factors for severe COVID-19 dramatically reduced the risk of hospi-

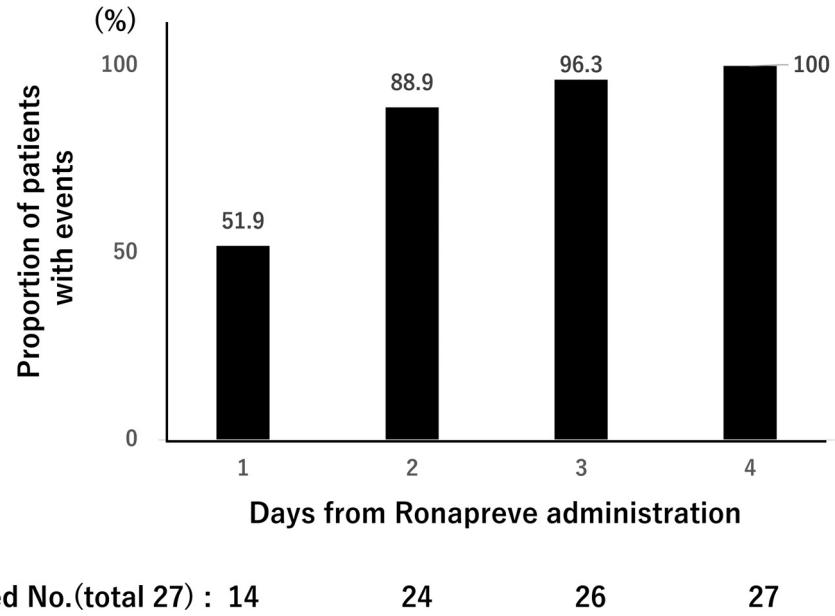

Figure 4. Accumulation of patients with events from Ronapreve administration.
The date of the Ronapreve dripping indicates day 0.
Event indicates that the fever is reduced.

talization or all-cause death by 70.4% and the symptom duration by 4 days at equal doses of 600 mg of casirivimab and imdevimab (Weinreich et al., 2021). In addition, the phase 3 trial for the prevention of COVID-19 in household contacts of infected individuals showed that subcutaneous administration of REGEN-COV reduced the risk of symptomatic COVID-19 infections by 81.4% (O'Brien et al., 2021). These findings suggest that REGEN-COV therapy in outpatients with COVID-19 has the potential to improve patient outcomes and substantially reduce the health care burden by lowering morbidity and mortality.

The important point for Ronapreve treatment we mentioned previously is that the efficacy for patients is diminished under the condition of SpO2 of 95% or lower. Because low SpO2 or pneumonia is probably associated with cytokine-storm-induced hyperinflammation caused by SARS-CoV-2, steroids such as dexamethasone will be more effective to suppress the storm rather than Ronapreve, because the antibody treatment probably affects the virus itself.

In conclusion, Ronapreve, also known as REGEN-COV, is thought to be closely linked to a reduction in the risk of hospitalization or the need for additional treatment, along with a potential benefit of prompt recovery from COVID-19-related fever. Although our data provided from daily practice is small-sized and limited, the antibody cocktail therapy in the early phase of the disease suggests a promising way to minimize the serious impact of COVID-19 on the public health care system.

Financial disclosure

I have no financial support.

Conflict of interest

All authors have no conflicts of interest to disclose.

Ethical approval

The use of patients' clinical information was approved by the Research Ethics Committee of Asahikawa City Hospital which oversaw the study conduct and documentation (No.7 of the fiscal year 2021). The chief officer of the local public health center authorized the use of the data collected from nonmedical facilities under fully anonymized conditions. This study was conducted following the principles of the Declaration of Helsinki.

Acknowledgment

All authors thank all the participating physicians and comedical staff for their care of patients with COVID-19.

Author contributions

Design of research studies: YK and KY.
Data acquisition: TK, KY, GA, and NS.
Data analysis: YK and KY.
Writing the manuscript: YK.
All authors worked hard to take care of patients with COVID-19.

Supplementary materials

Supplementary material associated with this article can be found, in the online version, at doi:10.1016/j.ijid.2022.01.067.

References

Baum A, Fulton BO, Wloga E, et al. Antibody cocktail to SARS-CoV-2 spike protein prevents rapid mutational escape seen with individual antibodies. Science 2020;369:1014–18.
Copin R, Baum A, Wloga E, et al. The monoclonal antibody combination REGEN–COV protects against SARS-C0V-2 mutational escape in preclinical and human studies. Cell 2021 June 5 (Epub ahead of print).
Hansen J, Baum A, Pascal KE, et al. Studies in humanized mice and convalescent humans yield a SARS-CoV-2 antibody cocktail. Science 2020;369:1010–14.
Ikemura N, Hoshino A, Higuchi Y, et al. SARS-CoV-2 Omicron variant escapes neutralization by vaccinated and convalescent sera and therapeutic monoclonal antibodies. December 14, 2021 (10.1101/2021.12.13.21267761). preprint.
Kanda Y. Investigation of the freely-available easy-to-use software"EZR" (Easy R) for medical statistics. Bone Marrow Transplant 2013;48:452–8 advance online publication 3 December 2012. doi:10.1038/bmt.2012.244.
Ministry of Health, Labour and Welfare. Approval for RonapreveTM (casirivimab and imdevimab) for the treatment of patients with mild to moderate COVID-19. Available at: https://www.mhlw.go.jp/stf/newpage_19940.html. Accessed 20 July 2021.

Ministry of Health, Labour and Welfare. Current status of the novel coronavirus infection and the response of the MHLW. 2020. Available at: https://www.mhlw.go.jp/stf/newpage_12312.html. Accessed 22 September 2021.
O'Brien MP, Forleo-Neto E, Musser BJ, et al. Subcutaneous REGEN-COV antibody combination to prevent COVID-19. N Engl J Med 2021 August 4 (Epub ahead of print).
Regeneron's COVID-19 outpatient trial prospectively demonstrates that REGN-COV2 antibody cocktail significantly reduced virus levels and need for further medical attention. Regeneron, October 28, 2020 (https://investor.regeneron.com/news-releases/news-release-details/regenerons-covid-19-outpatient-trial-prospectively-demonstrates).
Wang P, Nair MS, Liu L, et al. Antibody resistance of SARS-CoV-2 variants B.1.351 and B.1.1.7. Nature 2021;593:130–5.
Weinreich DM, Sivapalasingam S, Norton T, et al. REGN-COV2, a neutralizing antibody cocktail, in outpatients with COVID-19. N Engl J Med 2021;384:238–51.
Weinreich DM, Sivapalasingam S, Norton T, et al. REGEN-COV antibody cocktail clinical outcomes study in COVID-19 outpatients. June 6, 2021 (https://www.medrxiv.org/content/10.1101/2021.05.19.21257469v2). preprint.
Wilhelm A, Widera M, Grikscheit K, et al. Reduced neutralization of SARS-CoV-2 omicron variant by vaccine sera and monoclonal antibodies. December 13, 2021 (10.1101/2021.12.07.21267432). preprint.
World Health Organization. WHO Director-General's opening remarks at the media briefing on COVID-19—11 March 2020. 2020 (https://www.who.int/director-general/speeches/detail/who-director-general-s-opening-remarks-at-the-media-briefing-on-covid-19—11-march-2020).
Wu F, Zhao S, Yu B, et al. A new coronavirus associated with human respiratory disease in China. Nature 2020;579:265–9.
Zhu N, Zhang D, Wang W, et al. A novel coronavirus from patients with pneumonia in China, 2019. N Engl J Med 2020;382:727–33.