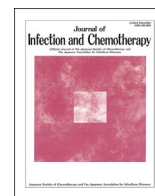




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## Note

## Effectiveness of monoclonal antibody therapy for COVID-19 patients using a risk scoring system



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## ABSTRACT

**Introduction:** Monoclonal antibody therapy has been reported to be highly effective for preventing hospitalisation and severe cases in patients with Coronavirus Disease 2019 (COVID-19). However, since the drug is not readily available, it is important to rapidly and appropriately identify high-risk patients who can benefit most from therapy. Therefore, we designed a risk scoring system to identify at-risk COVID-19 patients in our region during the largest surge of COVID-19, from July to September 2021.

**Methods:** According to the risk scores, confirmed COVID-19 patients were introduced to receive REGN-CoV-2 to our hospital by regional health centre from 18th August (Term 3). The primary outcome was the comparison of the number of hospitalisation and severe condition with other periods, the 4th wave (Term 1) and the early part of the 5th wave (Term 2) in Japan.

**Results:** During Term 3, 115 patients were stratified with the scoring system and administered REGN-COV-2. The number of hospitalisation vs severe cases were 60 (5.2%) vs 14 (1.2%), 8 (1.5%) vs 3 (0.6%) and 21 (1.2%) vs 2 (0.1%), in term 1, 2 and 3, respectively. Among those aged <60 years, compared with term 1, the relative risk of hospitalisation and severe condition were 0.25 (95% CI: 0.12–0.53) and 0.10 (95% CI: 0.01–0.80), respectively, in term 3. Drug adverse events were fever (3: 2.6%), headache (1: 0.9%) and neck rash (1: 0.9%), all events were resolved within 24 h with no serious adverse event.

**Conclusions:** The administration of monoclonal antibody therapy using a risk scoring system significantly reduced the number of hospitalisation and disease severity of COVID-19 without any serious adverse events and avoided regional medical collapse.

The incidence of Coronavirus Disease 2019 (COVID-19) has increased globally, with five waves in Japan [1]. The fifth wave was the largest wave, and the function of many regional hospitals was disrupted, with more than 800,000 confirmed patients between July and September 2021. COVID-19 monoclonal antibody therapy (REGN-COV-2; combination of two monoclonal antibodies, casirivimab and imdevimab) received special emergency approval in Japan at the end of July 2021 and was shown to notably reduce viral load and the number of medical visits [2]. Moreover, it reduced 71.3% of COVID-19-related hospitalisations, with a 4-day-shorter median time to

COVID-19 symptom resolution [3]. In some special settings, such as solid organ transplantation and nosocomial COVID-19 infection, monoclonal antibody therapy showed favourable outcomes [4,5]. However, treatment with REGN-COV-2 compared with usual care showed no significant differences regarding hospital discharge or mechanical ventilation [6]. Since monoclonal antibody therapy has limited supply and most previously healthy patients with COVID-19 including children recover without treatment, drug delivery is crucial for at-risk patients with severe disease progression. Hence, we designed a rapid REGN-COV-2 administration system for high-risk patients with

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**Abbreviations**

COPD	chronic obstructive pulmonary disease
ILD	interstitial lung disease
HIV	human immunodeficiency virus

COVID-19 in our region using a risk scoring system and retrospectively analysed its effectiveness.

REGN-COV-2 is approved for use only COVID-19 patients who present with risk factors for severity in Japan. For prompt the administration of REGN-CoV-2, we stratified each risk factor using risk ratio for severity and mortality of each factor as per previous reports, the underlying medical conditions, such as hypertension, diabetes, chronic pulmonary diseases, and cardiovascular disease are well-known risk factors [7–10]. Renal failure received a higher score than other factors because once the condition of a patient with COVID-19 with renal failure deteriorates, it is difficult to locate hospitals with intensive care units that provide haemodialysis [11]. Moreover, considering the characteristics of previous patients with COVID-19 receiving hospitalisation and the expected medical resource consumption in our region, the highest scores were assigned to obesity and older age subjectively. (Fig. 1).

In Japan, if COVID-19 is confirmed, the diagnosing doctor reports the patient to the regional health centre, which follows up on the daily health status of patients. Therefore, on starting this system, we informed all clinics and medical facilities in our region about our strategy. To rapidly identify patients with the risk of deterioration, doctors record the risk scores at the time of diagnosis and register the patients in the health centre. Also, the health centre then gave the information of the therapy to all patients on the first telephone contact, and they introduced the patients who did not refuse the treatment, to our hospital in the descending order of scores. All patients with one or more risk factors are eligible, and REGN-CoV-2 is then administered for eligible patients in the provided order.

‘COVID-19-confirmed case’ was defined as a positive reverse transcription polymerase chain reaction (RT-PCR) or rapid antigen test for SARS-CoV-2 from a nasopharyngeal swab or saliva, regardless of symptoms. ‘Severe condition’ was defined as requirement for intubation or high-concentration oxygen therapy because of COVID-19 deterioration. Drug adverse events were defined as newly confirmed symptoms or fever with decrease oxygen saturation within 24 h after the

administration of REGN-CoV-2, including infusion reaction. According to the official announcement from our prefecture, Aichi, the 4th wave (Term 1) was defined from 31 March 2021 to 20 July 2021 [12]. Since our hospital initiated REGN-COV-2 from 17 August 2021, term 2 was considered from 21 July to 17 August 2021, and term 3 was from 18 August to 20 September 2021.

We used frequencies and proportions to describe categorical values, and median and interquartile range (IQR) for continuous variables. Chi-square analysis and Mann–Whitney *U* test were used for the univariate analysis as appropriate. Relative risk was calculated with 95% confidence interval (CI). All statistical analyses were performed with SPSS (version 23.0).

During the study period, 115 patients were stratified with the scoring system and administered REGN-COV-2 (Table 1). Their median age was 51 (IQR: 40–54) years, with 81 men (70.4%), 32 current smokers (27.8%) and a median body mass index of 26.7 (IQR 23.0–31.1) kg/m<sup>2</sup>. The median time to REGN-COV-2 administration from symptom onset was 4 (IQR 3–5) days.

There were 1,157, 540 and 1727 confirmed COVID-19 cases in term 1, 2 and 3, respectively.

The number of hospitalisation vs severe cases were 60 (5.2%) vs 14 (1.2%), 8 (1.5%) vs 3 (0.6%) and 21 (1.2%) vs 2 (0.1%), respectively. (Table 2). Compared with term 1, the relative risk of hospitalisation and severe condition was 0.23 (95% CI: 0.14–0.38) and 0.10 (95% CI: 0.02–0.42), respectively, in term 3; and compared with term 2, it was 0.82 (95% CI: 0.35–1.76) and 0.21 (95% CI: 0.03–1.24), respectively, in term 3.

Among those aged <60 years, the number of hospitalisation and severe cases were 23 (2.5%) vs 6 (0.6%), 7 (1.3%) vs 3 (0.6%) and 10 (0.6%) vs 1 (0.06%), respectively. Compared with term 1, the relative risk of hospitalisation and severe condition was 0.25 (95% CI: 0.12–0.53) and 0.10 (95% CI: 0.01–0.80), respectively, in term 3. Compared with term 2, it was 0.46 (95% CI: 0.17–1.20) and 0.11 (95% CI: 0.01–1.02), respectively, in term 3.

In term 3, one patient died of cerebral haemorrhage after a traffic accident. He initially had high fever, with a positive screening rapid antigen test for COVID-19 in the emergency room. However, COVID-19 deterioration was unnoted. Two patients were hospitalised due to deterioration of covid-19 after REGN-COV-2 administration. Due to deterioration of COVID-19, two patients were hospitalised after REGN-COV-2 administration, one was admitted to our hospital and one to another regional hospital; however, for both, the administrations were on day 6 after COVID-19 onset, and their symptoms had worsened before REGN-COV-2 initiation. The other hospitalised patients were elderly people, including 8 fully vaccinated individuals or those without REGN-COV-2 because they had no risk of disease severity and were

Exclusion criteria	
Children (< 18 year old)	
Pregnancy	
Low body weight (< 40kg)	
Fully vaccinated	
High blood antibody titer of SARS-CoV-2 (using rapid antibody test)	



variables	Score
Age ≥ 65 year old	5
Obesity or over weight (Body mass index >30kg/m <sup>2</sup> )	4
Age 50 to 64	3
Chronic kidney disease, including hemodialysis	2
Cardiovascular disease, ex) hypertension	1
Chronic lung diseases, ex) COPD, asthma, ILD	1
Diabetes (HbA1c> 7.0%)	1
Chronic liver diseases, ex) cirrhosis, fatty liver	1
Immunosuppressive diseases	1
Immunosuppressive treatment, ex) malignancy	1
Uncontrolled HIV	1
Current smoker	1

Fig. 1. Patients selection and the risk scoring system

Table 1

Patients characteristics of REGN-COV2 administration (N = 115).

Patients characteristics	
Age, y, median (IQR)	51(40–54)
Sex, Male (n, %)	81 (70.4)
The day of administration of REGN-COV-2 from the onset of symptoms, median (IQR)	4 (3–5)
COVID-19 risk score, median (IQR)	3 (1.5–4)
Vaccine status	
none, (n, %)	100 (87.0)
partially vaccinated, (n, %)	15 (13.0)
fully vaccinated, (n, %)	0 (0.0)
Smoker (n, %)	32 (37.8)
Hypertension (n, %)	21 (18.2)
Diabetes (n, %)	19 (16.5)
Dyslipidemia (n, %)	8 (7.0)
Body mass index, kg/m <sup>2</sup> , median (IQR)	26.7 (23.0–31.1)
>30.0 kg/m <sup>2</sup> (n, %)	36 (31.3)

Abbreviations.

IQR; interquartile range.

**Table 2**  
Incidence and relative risk by terms and age groups.

	Term 1(3/31-7/20)	Term 2(7/21-8/17)	Term 3(8/18-9/20)	Relative risk(Term 1 to Term 3)	Relative risk(Term 2 to Term 3)
all age					
No. of confirmed patients	1157	540	1727		
Sex, Male (n, %)	667 (57.6)	291 (53.9)	1001 (58.0)		
No. of hospitalisation	60	8	21	0.23(95% CI: 0.14–0.38)	0.82(95% CI: 0.35–1.76)
No. of severe condition	14	3	2	0.10(95% CI: 0.02–0.42)	0.21(95% CI: 0.03–1.24)
<60 year					
No. of confirmed patients	942	520	1631		
Sex, Male (n, %)	563 (59.8)	279 (53.7)	952 (58.4)		
No. of hospitalisation	23	7	10	0.25(95% CI: 0.12–0.53)	0.46(95% CI: 0.17–1.20)
No. of severe cases	6	3	1	0.10(95% CI: 0.01–0.80)	0.11(95% CI: 0.01–1.02)

Abbreviations.

CI; confidence interval.

excluded from the scoring system.

Fever, a suspected adverse event, was noted in 3 patients (2.6%) on the day after REGN-COV-2 initiation, and headache and neck rash were found in each patient (0.9%). All symptoms recovered within 24 h without deterioration.

In our investigation, administering monoclonal antibody therapy for high-risk patients with COVID-19 using a regional severity prediction scoring system notably reduced the number of hospitalisations and severe cases. The largest COVID-19 wave occurred from July to August 2021 in Japan and many patients could not reach hospitals and stayed at home with severe conditions. However, our region was able to control the number of hospitalisations and avoided the collapse of medical facilities despite having the highest number of confirmed COVID-19 cases.

The COVID-19 vaccination programme in Japan started from the end of April 2021, for elderly people over 65 years. The rate of elderly patients with COVID-19 was high in the 4th wave. However, in the fifth wave, the number of elderly patients with COVID-19 notably decreased as approximately 80% of elderly people had been vaccinated by the end of July 2021. Nevertheless, the number of confirmed patients was highest in the fifth wave because of the delta variant (B.1.617.2), with most cases involving unvaccinated or partially vaccinated young adults and middle-aged individuals [13].

Our hospital with more than 180 clinics and two regional health centres covers three districts comprising approximately 270,000 residents. Most of the COVID-19 patients are diagnosed and followed at clinics or regional health centres, and if needed, are introduced to our hospital. Since monoclonal antibody therapy should be administered early in COVID-19, the key to decrease hospitalisation and severe conditions is how to refer the patients hospitals where they can receive the necessary care promptly. Moreover, because drug supply is limited, patients at high risk of disease severity should be prioritised; therefore, we constructed a regional monoclonal antibody therapy introduction system. During term 3, all confirmed COVID-19 cases were given scores, all high-risk patients were introduced to our hospital, and then administered REGN-COV-2 unless the patient refused. Although the scores of each factor may be dependent on the region and situation of infection, our system enables the easy selection of high-risk individuals from several confirmed patients, which allows the rapid administration of therapy before COVID-19 progression and helped control the number of hospitalisations and severe cases.

Adverse events, such as nausea, diarrhoea and headache, showed very low rates in a randomised controlled trial, indicating the safety of monoclonal antibody therapy [14]. In addition, only 0.9% of patients who received therapy required emergency room admission because of infusion reaction in a clinical trial [15]. In our study, similar to previous reports, only two patients reported transient adverse events of REGN-CoV-2 (headache and neck rash), and 2.6% of the patients complained of postadministration fever that improved within 24 h. There were no immediate infusion reaction and serious adverse events. Monoclonal antibody therapy seems to be highly effective and safe for

the early stage of COVID-19.

Our research has some limitations. First, the decreased patient numbers may have been due to the vaccination programme. Indeed, we were not able to show the significant differences in both the number of hospitalisation and severe condition in comparison between Term 2 and Term 3, but among those aged <60 years, our system significantly reduced hospitalisation and severe condition when compared between Term 1 and Term 3. The programme is not enough widespread yet for people under 60 years of age even in the middle of August 2021, suggesting that the effect of vaccination program was considerably small on this generation. Additionally, half of the hospitalised patients were under 60 years of age in term 3, and most of them had no risk factors for disease severity, such as diabetes, smoking and obesity.

Second, it is possible that some patients with severe conditions were transferred to hospitals in other regions since the fifth wave was the largest, and the number of patients was more than twice that of the fourth wave although the duration was 50% shorter. The health centre generally introduced patients to other hospitals only when our hospital was unable to accommodate them. However, we could respond to all patients without any medical collapse in this wave and followed up all patients who received REGN-COV-2 in our region.

In conclusion, providing regional monoclonal antibody therapy using a risk scoring system markedly reduced hospitalisation and disease severity even in delta variant-dominant settings. Although additional studies are required, early assessment of at-risk patients and the proactive use of monoclonal antibody therapy may protect health systems in the community.

#### Ethical statement

This study has been approved by the Ethical committee of Tosei general hospital (No.1004).

#### Authors' contributions

YM designed the study, wrote draft of the manuscript and performed statistical analysis. TU and OA prepared and provided drugs. KO, RM, MT, KS, YN, TB, SO, TS, SH, SH, RT, HS, YY, KK, TY, and TM treated and managed the patients received drug, TK, TI and YK supervised the manuscript. All authors critically reviewed and have approved the final version of the manuscript. <a name = "Line\_manuscript\_16">

#### Declaration of competing interest

The authors declare no competing interests.

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