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Retrospective study of evaluating the cytokine dynamics in COVID-19 patients who were treated with casirivimab/imdevimab

Akiho Sugita[1], Masahiro Ishikane[1], Noriko Iwamoto[1], Masaya Sugiyama[2], Katsuji Teruya[3], Masayuki Hojo[4], Masashi Mizokami[5], Norio Ohmagari[1]
[1]Disease Control and Prevention Center, National Center for Global Health and Medicine, Tokyo, Japan, [2]Department of Viral Pathogenesis and Controls, Research Institute, National Center for Global Health and Medicine, Tokyo, Japan
[3]AIDS Clinical Center, National Center for Global Health and Medicine, Tokyo, Japan, [4]Department of Respiratory Medicine, National Center for Global Health and Medicine, Tokyo, Japan, [5]Genome Medical Sciences Project, National Center for Global Health and Medicine, Tokyo, Japan

Introduction

- Neutralizing antibody therapy such as casirivimab/imdevimab was approved in Japan for the prevention of severe cases of COVID-19 in 2021.[1] Casirivimab/imdevimab is known to significantly reduce the viral load of SARS-CoV-2.
- Caciriviimab/imdevimab is reported to be effective for Omicron variant due to BA.2,[2] and recently, it is sometimes administered for patients with prolonged active infection of COVID-19 due to the treatment with anti-CD20 antibody for lymphoma.[3]
- This study aimed to evaluate the clinical prognosis, including cytokine dynamics, in COVID-19 patients who were treated with casirivimab/imdevimab.

Methods

Study design: Retrospective observational study

Study patients and samples: medical charts and serum samples of 34 patients with confirmed COVID-19 who received casirivimab/imdevimab at NCGM (Tokyo, Japan) between July 1 and December 31, 2021.

Collected items:
(i) demographic data such as sex and age,
(ii) background and comorbid conditions on admission,
(iii) vaccination, (iv) clinical symptoms on admission,
(v) laboratory and radiological findings, and
(vi) prognosis.
Cytokine dynamics (IFN-λ3, CCL17) were analyzed using serum samples.

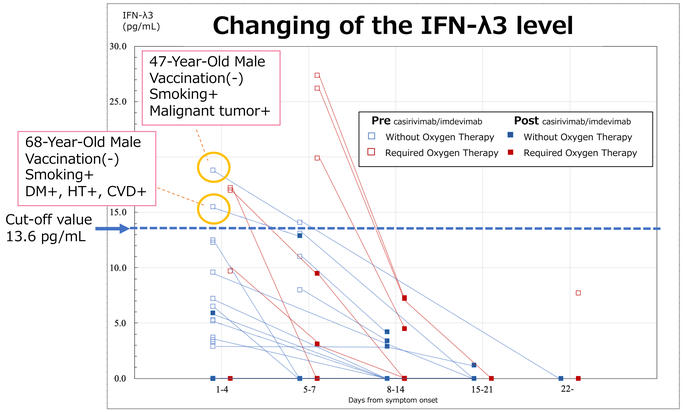
Statistical method: Univariate analysis was performed using Fisher's exact probability test and Mann-Whitney U test
Statistical significance was defined as a two-sided p-value of <0.05, and all statistical analyses were performed with SPSS software (SPSS ver. 27; SPSS, Chicago, IL, USA).

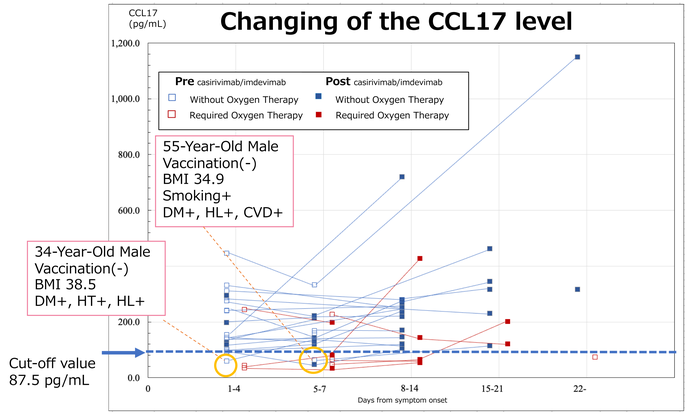
Contact Information

Akiho SUGITA, M.D.
Disease Control and Prevention Center
Department of Infectious Diseases
National Center for Global Health and Medicine
1-21-1 Toyama, Shinjuku-ku, Tokyo 162-8655, Japan
Phone: +81-3-3202-7181
FAX: +81-3-6228-0738
E-mail: asugita@hosp.ncgm.go.jp

Results

Figure 1: The cytokine dynamics in COVID-19 patients who were treated with casirivimab/imdevimab





	Total		Without Oxygen Therapy		Required Oxygen Therapy		
	Median	(IQR)	Median	(IQR)	Median	(IQR)	p value
Pre casirivimab/Imdevimab	9.7	(5.3, 16.3)	7.6	(3.7, 12.7)	17.2	(9.7, 26.2)	0.005
Post casirivimab/Imdevimab	0.0	(0.0, 3.1)	0.0	(0.0, 0.0)	1.6	(0.0, 7.3)	0.203

	Total		Without Oxygen Therapy		Required Oxygen Therapy		
	Median	(IQR)	Median	(IQR)	Median	(IQR)	p value
Pre casirivimab/Imdevimab	138.4	(73.7, 241.2)	148.8	(100.2, 267.1)	64.2	(43.8, 227.0)	0.036
Post casirivimab/Imdevimab	220.3	(135.8, 304.8)	223.4	(141.5, 315.1)	170.6	(61.7, 257.5)	0.158

Table 1: Demographics and characteristics

	Total N=34		Without Oxygen Therapy N=27		Required Oxygen Therapy N=7				
	Median / n	(IQR)/%	Median / n	(IQR)/%	Median /n	(IQR)/%	OR	(95% CI)	p value
Age, years	57.5	(52.8, 67.3)	56.0	(51.0, 63.0)	67.0	(62.5, 70.0)			
Gender									
Male	25	73.5%	22	81.5%	3	42.9%	Ref.		
Female	9	26.5%	5	18.5%	4	57.1%	5.9	(1.0-35.0)	0.04
Race									
Japanese	27	79.4%	21	77.8%	6	85.7%	Ref.		
Non-Japanese	7	20.6%	6	22.2%	1	14.3%	0.6	(0.1-5.8)	0.64
Body mass index	24.0	(22.2, 28.1)	24.0	(22.6, 28.3)	24.8	(19.8, 27.7)			
COVID-19 Vaccination									
Never	23	67.6%	19	70.4%	4	57.1%	0.6	(0.1-4.4)	0.64
Once	3	8.8%	2	7.4%	1	14.3%	1.5	(0.1-26.9)	0.78
Twice	8	23.5%	6	22.2%	2	28.6%	Ref.		
Smoking	15	44.1%	13	48.1%	2	28.6%	0.4	(0.1-2.6)	0.35
Drinking	17	50.0%	15	55.6%	2	28.6%	0.3	(0.1-2.0)	0.20
Variant									
L452R(+) /N501Y(−)	16/23	91.3%	16/18	88.9%	4/5	80.0%			
N501Y(+) /L452R(−)	1/23	4.3%	0/18	0.0%	1/5	20.0%			

	Total N=34		Without Oxygen Therapy N=27		Required Oxygen Therapy N=7	
	n	%	n	%	n	%
Severity at diagnosis						
Asymptomatic	2	5.9%	2	7.4%	0	0.0%
Mild	12	35.3%	12	44.4%	0	0.0%
Moderate I	18	52.9%	13	48.1%	5	71.4%
Moderate II	2	5.9%	0	0.0%	2	28.6%
Severe	0	0.0%	0	0.0%	0	0.0%

* Mild: oxygen saturation (SpO2) ≥96%, no signs of pneumonia
Moderate I: SpO2 < 96% > 93%, Signs of pneumonia, dyspnea
Moderate II: SpO2 < 93%, Oxygen therapy
Severe: ICU Mechanical Ventilation

- The median age of the cohort was 57.5 years (IQR 52.8-67.3), and 25 (73.5%) were male.
- 8 patients (23.5%) had been fully vaccinated and three patients (8.8%) had been vaccinated once.
- The severity of disease before casirivimab/imdevimab was asymptomatic in two (5.9%), mild in 12 (35.3%), moderate in 20 (58.8%)cases.
- Of the 17 cases in which mutant strains were identified, 16 were delta strains.

Table 2:Clinical outcomes

	Total N=34		Without Oxygen Therapy N=27		Required Oxygen Therapy N=7		
	n	%	n	%	n	%	p value
Severity during hospitalization							
Asymptomatic	1	2.9%	1	3.7%	0	0.0%	
Mild	10	29.4%	10	37.0%	0	0.0%	
Moderate I	16	47.1%	16	59.3%	0	0.0%	
Moderate II	7	20.6%	0	0.0%	7	100.0%	
Severe	0	0.0%	0	0.0%	0	0.0%	
Duration of fever	5.0	(3.0, 8.5)	5.0	(3.0, 6.0)	9.0	(6.0, 14.0)	<0.05
Duration of cough	8.0	(6.0, 10.3)	8.0	(6.0, 10.0)	18.0	(9.0, 56.0)	<0.05
Days from symptoms onset to systemic symptoms resolution	7.5	(3.3, 10.8)	6.0	(3.0, 10.0)	10.0	(10.0, 20.0)	<0.05
Days from symptom onset to discharge	10.0	(10.0, 13.8)	10.0	(9.5, 10.5)	16.0	(13.5, 27.0)	<0.05

Patients who required oxygen therapy had prolonged cough and systemic symptoms including fever, and a longer duration from symptom onset to discharge.
None of the patients became seriously ill.

Discussion

- Both IFN-λ3 and CCL17 are reported to be predictive markers for COVID-19 severity.[4] IFN-λ3 is an initial molecule released from immune cells against a pathogen,[5] and CCL17 is a ligand for CCR4 that is involved in Th2 cell recruitment.[6]
- CCL17 The cut-off values of CCL17 and IFN-λ3 to predict the onset of severe/critical symptoms were 87.5 pg/mL, 13.6 pg/mL, respectively.[4]
- IFN-λ3 before casirivimab/imdevimab was significantly higher, while CCL17 was significantly lower in the patients who developed oxygen demand, compared to patients without oxygen demand. After casirivimab/imdevimab was administered, no statistically significant differences were found between both groups
- Our results showed that, even in patients with risk factors for severe COVID-19 (e.g., BMI>30, underlying conditions, smoking, unvaccinated), who were predicted to become severely/critically ill using these cut-off values, caciriviimab/imdevimab may have prevented causing serious symptoms.

Conclusions

There was a statistically significant difference between IFN-λ3 and CCL17 levels before casirivimab/imdevimab in both groups. Our results suggest that casirivimab/imdevimab may improve the clinical prognosis for COVID-19 patients with delta strains.

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