Severity-Adjusted Dexamethasone Dosing and Tocilizumab Combination for Severe COVID-19

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Purpose: Real-world experience with tocilizumab in combination with dexamethasone in patients with severe coronavirus disease (COVID-19) needs to be investigated.

Materials and Methods: A retrospective cohort study was conducted to evaluate the effect of severity-adjusted dosing of dexamethasone in combination with tocilizumab for severe COVID-19 from August 2020 to August 2021. The primary endpoint was 30-day clinical recovery, which was defined as no oxygen requirement or referral after recovery.

Results: A total of 66 patients were evaluated, including 33 patients in the dexamethasone (Dexa) group and 33 patients in the dexamethasone plus tocilizumab (DexaToci) group. The DexaToci group showed a statistically significant benefit in 30-day clinical recovery, compared to the Dexa group (p=0.024). In multivariable analyses, peak FiO_2 within 3 days and tocilizumab combination were consistently significant for 30-day recovery (all p<0.05). The DexaToci group showed a significantly steeper decrease in FiO_2 (-4.2±2.6) than the Dexa group (−2.7±2.6; p=0.021) by hospital day 15. The duration of oxygen requirement was significantly shorter in the DexaToci group than the Dexa group (median, 10.0 days vs. 17.0 days; p=0.006). Infectious complications and cellular and humoral immune responses against severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) in the convalescence stage were not different between the two groups.

Conclusion: A combination of severity-adjusted dexamethasone and tocilizumab for the treatment of severe COVID-19 improved clinical recovery without increasing infectious complications or hindering the immune response against SARS-CoV-2.

Key Words: Dexamethasone, tocilizumab, COVID-19, immune response

INTRODUCTION

Unlike fatal beta-coronavirus infections that have previously emerged, severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection shows a discordant course of viral kinetics and disease severity.[1] The deterioration of oxygenation despite a reduced viral load suggests that the critical pathophysiology of severe coronavirus disease (COVID-19) may be associated with an immune response induced by SARS-CoV-2, and low-dose dexamethasone treatment has become a mainstay of COVID-19 therapy after the RECOVERY dexamethasone trial suggested a survival benefit for 6 mg-dexamethasone treatment.[2,3] However, a certain proportion of severe COVID-19 patients progress despite the fixed dose of dexamethasone

treatment, and the optimal dose and duration of dexamethasone for severe COVID-19 remain unclear.[4]

Tocilizumab, a monoclonal antibody agent against interleukine-6 receptor, was also investigated as a potential therapeutic for severe COVID-19. Although early studies evaluating tocilizumab treatment for COVID-19 showed controversial results,[5-8] recent randomized controlled trials (RCTs) and a large cohort study reported a survival benefit for tocilizumab treatment, especially in combination with corticosteroids.[9-11] Based on this research, the United States National Institutes of Health recommended early tocilizumab treatment for severe COVID-19 in combination with dexamethasone in April 2021,[12] although real-world experiences in individual countries still need to be assessed.

Herein, we report our experience with severity-adjusted dosing of dexamethasone in combination with tocilizumab for severe COVID-19 and compared this with a regimen of dexamethasone monotherapy.

MATERIALS AND METHODS

Study design and population
This study was conducted as a retrospective cohort study of data from a tertiary care hospital designated for severe COVID-19 patient care between August 2020 and August 2021. Dexamethasone was routinely administered from August 2020, and tocilizumab was subsequently added to the regimen beginning in April 2021 at our center. COVID-19 patients who required more than 5 L of oxygen (O_2) per minute via a facial mask were referred to or hospitalized directly in the intensive care unit (ICU) for COVID-19. The diagnosis of COVID-19 was made based on a real-time polymerase chain reaction (RT-PCR) test for SARS-CoV-2 using test kits given emergency use authorization by the Korean Ministry of Food and Drug Safety.[13] During the study period, patients with severe COVID-19 were screened and defined as COVID-19 patients requiring high-flow oxygen support, including high-flow nasal cannula (HFNC), non-invasive mechanical ventilation, or invasive mechanical ventilation. This definition is equivalent to an ordinal severity scale score of five points or higher[13,14] and a World Health Organization Clinical Progression Scale (WHO-CPS) of six points or higher.[15]

Patients who did not need high-flow oxygen supplementation, who had been intubated for more than 5 days before referral, who received tocilizumab for more than 5 days after hospitalization, and those with a do not resuscitate status were excluded from the analysis. Enrolled patients were classified into either a dexamethasone (Dexa) group or dexamethasone plus tocilizumab (DexaToci) group, and the clinical outcomes of study participants were followed until their date of discharge or referral after recovery.

Institutional treatment protocol for severe COVID-19
HFNC was primarily used for oxygen supplementation, starting from a fraction of inspired oxygen (FiO_2) of 40% to 90% and an oxygen flow of 40 L/min to 60 L/min, with a target saturation of percutaneous oxygen (SpO_2) of at least 93%. Endotracheal intubation with mechanical ventilator support was considered when the target SpO_2 was not stably maintained or respiratory distress progressed despite HFNC support. An oxygen supplementation device was step-downed to nasal prongs when the target SpO_2 was stably maintained with a FiO_2 of 30% and oxygen flow of 30 L/min after improvement.

Dexamethasone or an equivalent dose of methylprednisolone was administered to all patients with severe COVID-19. After experiencing clinical deterioration despite low-dose dexamethasone treatment, we used an adjusted dose of dexamethasone according to the oxygen requirements of individual patients. Doses of dexamethasone were 0.1 mg/kg/day for patients requiring oxygen supplementation of FiO_2 40% to 50%, 0.15 mg/kg/day for patients requiring oxygen supplementation of FiO_2 60% to 70%, and 0.2 mg/kg/day for patients requiring oxygen supplementation more than FiO_2 80%. The dose of dexamethasone was reduced according to improvements in oxygenation and tapered off for 7 to 14 days after oxygen supplementation was no longer required. A proton-pump inhibitor or histamine H_2 receptor antagonist (H_2 blocker) was administered for ulcer prevention in all patients. Trimethoprim/sulfamethoxazole for Pneumocystis jirovecii pneumonia prophylaxis was given after 10 to 14 days of steroid administration.

Tocilizumab was administered in addition to dexamethasone to all patients with severe COVID-19 after April 2021. A single dose of tocilizumab of 8 mg/kg (maximum: 800 mg) was administered within 1 to 3 days after admission, and the second dose of tocilizumab was considered if an oxygen requirement of more than FiO_2 80% persisted and the clinical course did not improve within 5 days after the first dose. Anti-mold prophylaxis using itraconazole syrup (100 mg twice a day) was performed when the second dose of tocilizumab was administered.

Remdesivir was administered over a 5-day regimen to all patients with severe COVID-19, except in the case of shortages. From June 2021, remdesivir was administered for up to 10 days. Patients who underwent endotracheal intubation before admission were not indicated for remdesivir treatment.[13] Antibiotics were not routinely given and only considered when a bacterial infection was suspected. Enoxaparin (1 mg/kg per day) was routinely administered for deep vein thrombosis prophylaxis unless contraindicated.

Data collection and outcome assessment
Baseline characteristics, treatment modalities, and outcome data were retrospectively collected from electronic medical records. Demographic data included age, sex, body mass index, and the interval between symptom onset and ICU admis-

sion. Initial status at the time of ICU admission was assessed by initial cycle threshold (Ct) values of RT-PCR, endotracheal intubation, and peak FiO_2 within 3 days from admission. Initial laboratory test results and underlying diseases were also recorded. Concerning treatment modalities, treatment duration and the cumulative dose of dexamethasone, administration interval of tocilizumab, and administration of other treatment modalities were collected. The primary endpoint was clinical recovery by hospital day (HD) 30, defined as no O_2 requirement (WHO-CPS of four points or lower) or referral to a mild COVID-19 patient care hospital with minimal O_2 support (<5 L per minute via nasal prongs, equivalent to WHO-CPS of five points). Infectious complications, the slope of FiO_2 until HD 15, endotracheal intubation, extracorporeal membrane oxygenation (ECMO), continuous renal replacement therapy, duration of oxygen requirement, and death were investigated as secondary outcomes.

Sero-immunologic response against SARS-CoV-2

To investigate the potential effect of immunomodulatory therapy on sero-immunologic responses against SARS-CoV-2, cellular and humoral immune responses were measured among patients who agreed to undergo the relevant tests. Sero-immunologic investigation was performed during the convalescent stage, at least more than 2 weeks after the onset of symptoms.[16] For the evaluation of humoral immune responses, a quantitative anti-SARS-CoV-2 spike protein antibody test kit (Elecsys Anti-SARS-CoV-2 S; Roche Diagnostics, Basel, Switzerland) was used.[17] Cell-mediated immunity was evaluated by measuring interferon-gamma (IFN-γ) secreted by T-cells in response to SARS-CoV-2-specific antigens using a SARS-CoV-2-specific IFN-γ release assay (IGRA) kit with enzyme-linked immunosorbent assay (ELISA) (Covi-FERON ELISA; SD Biosensor, Suwon, Republic of Korea).[18] The test kit consists of nil, SARS-CoV-2 spike protein antigen (Sp)1, Sp2, mitogen tubes, and IFN-γ ELISA. The Sp1 tube contained spike protein antigens derived from the original SASR-CoV-2 strain and its alpha variant, and the Sp2 tube contained those derived from the beta and gamma variants.[19]

Statistical analysis

To compare clinical variables, either Student's t-test or Mann–Whitney U test was used for continuous variables, and the chi-squared or Fisher's exact test was used for categorical variables. Slopes of FiO_2 were calculated by linear regression. Additionally, the Kaplan-Meier method was used to calculate the 30-day probability of recovery, and Cox proportional hazards models were used to evaluate the potential effects of each variable on clinical recovery by HD 30. Univariable analysis included all factors with significant differences in baseline characteristics between the two groups. To lower the risk of overfitting in regression analysis with a limited number of patients included,[20] multivariable analyses were conducted in separate sets to ad-

just the effect of the tocilizumab combination on the probability of 30-day recovery. Each statistically significant factor was included in the adjusted analyses in addition to peak FiO_2 within 3 days and tocilizumab combination. All p-values were two-tailed, and those less than 0.05 were considered to be statistically significant. IBM SPSS Statistics version 20.0 (IBM Corporation, Armonk, NY, USA) and R software (version 4.0.0 with packages; The R Foundation for Statistical Computing, Vienna, Austria) were used for all statistical analyses.

Ethics statement

The present retrospective cohort study was approved by the Institutional Review Board (IRB) of Samsung Medical Center (IRB no. SMC 2021-09-080), and the requirement for informed consent was waived because de-identified retrospective data were used for analysis. The sero-immunologic investigation was conducted among patients who agreed to undergo the test and was approved by the Institutional Review Board of Samsung Medical Center (IRB no. SMC 2020-03-113), with written informed consent obtained from each of these patients.

RESULTS

Study population and baseline characteristics of patients with severe COVID-19

Between August 2020 and August 2021, 71 patients with severe COVID-19 were screened. After excluding five patients, a total of 66 patients were included in the study cohort and classified into a Dexa group (n=33) or DexaToci group (n=33) (Fig. 1A). The institutional treatment protocol for severe COVID-19 is summarized in Fig. 1B.

The baseline characteristics of the cohort patients are presented in Table 1. Patients in the Dexa group were older (69.2± 7.9 years) than those in the DexaToci group (59.1±13.0 years; p<0.001). There were no significant differences in the duration of symptom onset to admission and peak FiO_2 within the first 3 days between the two groups. Albumin levels were significantly lower in the Dexa group (3.4±0.3 g/dL) than in the DexaToci group (3.7±0.4 g/dL; p=0.010), while C-reactive protein levels were significantly higher in the Dexa group (11.2±7.4 mg/dL) than in the DexaToci group (7.5±5.7 mg/dL; p=0.027). Diabetes mellitus was more common in the Dexa group (60.6%) than in the DexaToci group (21.2%; p=0.003) and more patients had hypertension in the Dexa group (60.6%) than in the DexaToci group (33.3%; p=0.048).

Treatment and clinical outcomes of the cohort patients

We investigated the duration and dose of dexamethasone for individual patients. The tapering dose of dexamethasone after recovery to room air was not included. Patients in the DexaToci group had shorter treatment durations of dexamethasone than
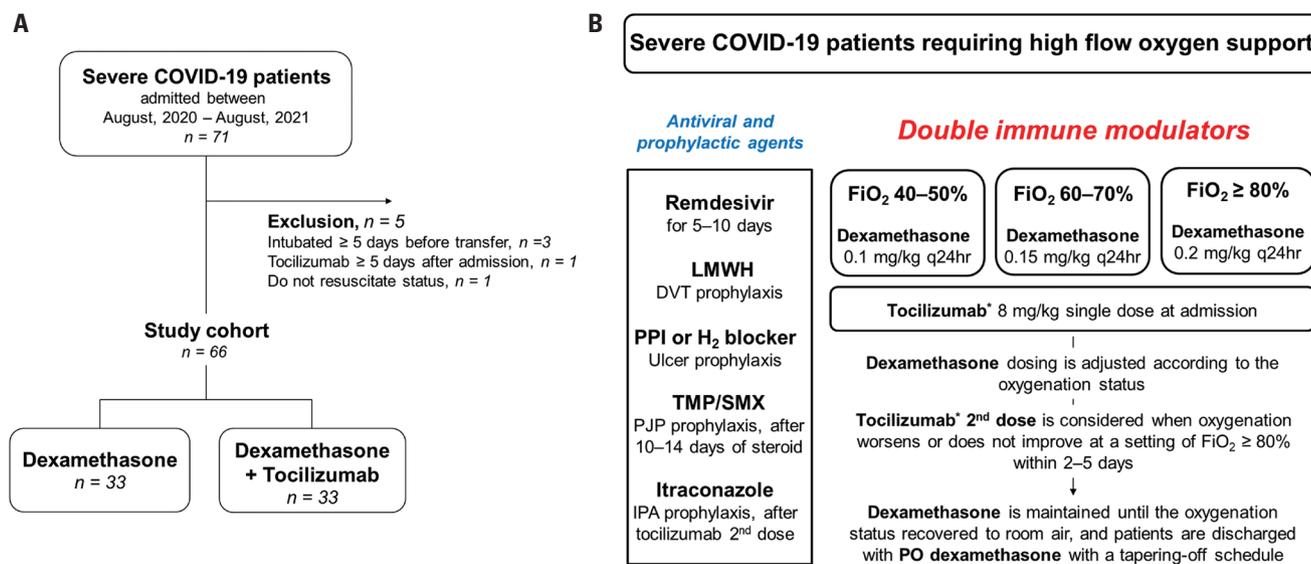
Fig. 1. Study population of the cohort and institutional treatment protocol. The study population of the retrospective cohort study (A) and institutional treatment protocol applied to the cohort (B) are presented. *Tocilizumab combination was applied after April 2021. COVID-19, coronavirus disease; FiO_2, fraction of inspired oxygen; LMWH, low-molecular-weight heparin; DVT, deep vein thrombosis; PPI, proton-pump inhibitor; TMP/SMX, trimethoprim/sulfamethoxazole; PJP, Pneumocystis jirovecii pneumonia; IPA, invasive pulmonary aspergillosis; PO, per os.

patients in the Dexa group, although statistical significance was not observed (median, 10.0 days vs. 14.0 days; $p=0.088$). Cumulative doses of dexamethasone were lower in the DexaToci group than in the Dexa group, without statistical significance (average, 145.6 mg vs. 217.1 mg; $p=0.166$). Patients in the DexaToci group were administered the first dose of tocilizumab on average 0.8 days after admission. Four patients in the DexaToci group (12.1%) received a second dose of tocilizumab, and the interval between admission and the second dose of tocilizumab was, on average, 5.0 days. Other treatment modalities led to no significant difference between the two groups, except for camostat use.

The primary endpoint was calculated using the Kaplan-Meier method, and significantly more patients in the DexaToci group than in the Dexa group recovered within 30 days ($p=0.024$) (Fig. 2A). To compare the rate of oxygenation improvement, we calculated the slope value of daily FiO_2 until HD 15. The DexaToci group experienced a significantly steeper decrease in FiO_2 (-4.2± 2.6) than the Dexa group (-2.7±2.6; $p=0.021$) (Fig. 2B). The duration of oxygen requirement was significantly shorter in the DexaToci group than in the Dexa group (median, 10.0 days vs. 17.0 days; $p=0.006$). There were five cases of referral to a mild COVID-19 patient care hospital with minimal O_2 support, accounting for 7.6% of the total cohort, two in the Dexa group (6.1%) and three in the DexaToci group (9.1%). In these cases, the duration of oxygen requirement was estimated as the date predicted by extrapolating the individual's FiO_2 improvement slope. There was no significant difference between the two groups in the frequency of requiring endotracheal intubation, ECMO support, or continuous renal replacement therapy support. Also, the distribution of WHO-CPS at HD 30 showed no significant difference between the two groups (Table 2).

There were eight in-hospital deaths, accounting for 12.1% of the total cohort. The DexaToci group had a lower in-hospital mortality rate (9.1%) than the Dexa group (15.2%), without statistical significance ($p=0.706$). There was no significant difference between the two groups in terms of infectious complications, including culture-proven bacterial infection, invasive candidiasis, invasive pulmonary aspergillosis, and cytomegalovirus reactivation requiring treatment.

Univariable and multivariable analyses for the probability of 30-day recovery in the total cohort

To identify potential confounding factors for the probability of 30-day recovery, univariable analysis was conducted for individual variables. Given the small sample size of the study cohort, statistically significant variables were individually included in each adjusted analysis, in addition to peak FiO_2 within 3 days and the addition of tocilizumab. In the three adjusted analyses, peak FiO_2 within 3 days and the addition of tocilizumab were consistently significant factors for 30-day recovery (all $p<0.05$) (Table 3).

Cellular and humoral immune responses against SARS-CoV-2

Cellular immune responses in the convalescent stage were measured in nine patients of the Dexa group and 17 patients of the DexaToci group using a SARS-CoV-2-specific IGRA test (Fig. 3). The median interval from symptom onset to testing was 57 days [interquartile range (IQR), 48–66 days] in the Dexa group and 41 days (IQR, 25–55 days) in the DexaToci group ($p= 0.055$). Overall, IFN-γ responses against SARS-CoV-2 Sp1 (4.07± 4.23 IU/mL), Sp2 (3.06±4.09 IU/mL), and mitogen (11.53±5.21 IU/mL) were robust, compared to the IFN-γ concentration of nil

Table 1. Baseline Characteristics of the Cohort Patients

Variables	Dexa group (n=33)	DexaToci group (n=33)	*p* value
Demographics			
Age, yr	69.2±7.9	59.1±13.0	<0.001
Male sex	22 (66.7)	19 (57.6)	0.612
BMI, kg/m^2	25.1±4.5	25.4±4.9	0.790
Sx onset to ICU admission, days	7.9±3.9	8.1±3.0	0.832
Initial presentations at ICU admission			
Initial Ct value (LRT, RdRp, or ORF1ab)*	25.3±4.7	24.3±4.4	0.365
Severity at admission			
HFNC (WHO-CPS 6)	30 (90.9)	32 (97.0)	0.606
Endotracheal intubation (WHO-CPS 7)	3 (9.1)	1 (3.0)	0.606
Peak FiO$_2$ within 3 days	69.1±19.9	67.1±17.5	0.670
Initial laboratory tests			
WBC count, /μL	8304.9±3616.5	7493.3±2997.9	0.325
Leukopenia (<4000 /μL)	6 (18.2)	5 (15.2)	>0.999
Lymphocyte count, /μL	759.4±439.4	730.0±373.2	0.771
Lymphopenia (<1000/μL)	23 (69.7)	26 (78.8)	0.573
Platelet count, ×10^3/μL	199.7±84.7	228.2±92.5	0.197
Thrombocytopenia (<150×10^3/μL)	11 (33.3)	8 (24.2)	0.587
Albumin, g/dL	3.4±0.3	3.7±0.4	0.010
BUN, mg/dL	20.5±11.6	18.0±12.0	0.384
Creatinine, mg/dL	0.9±0.5	0.8±0.6	0.396
LDH, IU/L	597.5±318.8	545.2±159.9	0.403
CRP, mg/dL	11.2±7.4	7.5±5.7	0.027
Underlying diseases			
Cardiovascular diseases	2 (6.1)	6 (18.2)	0.258
Respiratory diseases	3 (9.1)	2 (6.1)	>0.999
Diabetes mellitus	20 (60.6)	7 (21.2)	0.003
Hypertension	20 (60.6)	11 (33.3)	0.048
Liver diseases	1 (3.0)	1 (3.0)	>0.999
Renal diseases	5 (15.2)	1 (3.0)	0.199
Charlson Comorbidity Index	1 (0–2)	0 (0–1)	0.007

Dexa, dexamethasone; DexaToci, dexamethasone plus tocilizumab; BMI, body mass index; Sx, symptom; ICU, intensive care unit; Ct, cycle threshold; LRT, lower respiratory tract; RdRp, RNA-dependent RNA polymerase; ORF1ab, open reading frame 1ab; HFNC, high-flow nasal cannula; WHO-CPS, World Health Organization Clinical Progression Scale; FiO$_2$, fraction of inspired oxygen; WBC, white blood cell; BUN, blood urea nitrogen; LDH, lactate dehydrogenase; CRP, C-reactive protein; SD, standard deviation; IQR, interquartile range.
Data are expressed as the number (%) of patients, means±SD, or medians (IQR) unless indicated otherwise.
*LRT specimen included either sputum or aspirates from the endotracheal tube. From the end of January 2021, the manufacturer changed the SARS-CoV-2-specific target region from the RdRp to the ORF1ab gene (PowerCheck™ 2019-nCoV RT-PCR kit; KogeneBiotech, Seoul, Korea).

tubes (0.15±0.11 IU/mL). Two patients (2/9, 22.2%) in the Dexa group (0.55 and 1.98 IU/mL) and three (3/17, 17.6%) in the DexaToci group (1.29, 1.65, and 4.96 IU/mL) showed decreased responses to mitogen, less than half of the average value. IFN-γ responses were not significantly different between the two groups in the values of Sp1-nil (3.7±3.8 vs. 4.0±4.5; *p*=0.853), Sp2- nil (2.7±2.8 vs. 3.0±4.6; *p*=0.856), and mitogen- nil (11.1± 5.8 vs. 11.5±5.0; *p*=0.842) (Fig. 3A).

Humoral immune responses in the convalescence stage were measured in 22 patients of the Dexa group and 16 patients of the DexaToci group using a quantitative anti-SARS-CoV-2 S antibody test kit. The median interval from symptom onset to the test date was 28.5 days (IQR, 21–38 days) in the Dexa group and

40.5 days (IQR, 28–55 days) in the DexaToci group (*p*=0.056). The S antibody concentrations between the Dexa (777.84± 528.79 U/mL) and DexaToci (669.83±634.47 U/mL) groups were not significantly different (*p*=0.571) (Fig. 3B).

DISCUSSION

During the COVID-19 pandemic, numerous clinical studies have been conducted, and scientific evidence has rapidly accumulated. However, the wide disease spectrum of COVID-19 and the limited research resources due to the pandemic situation and associated restrictions have hindered the production of
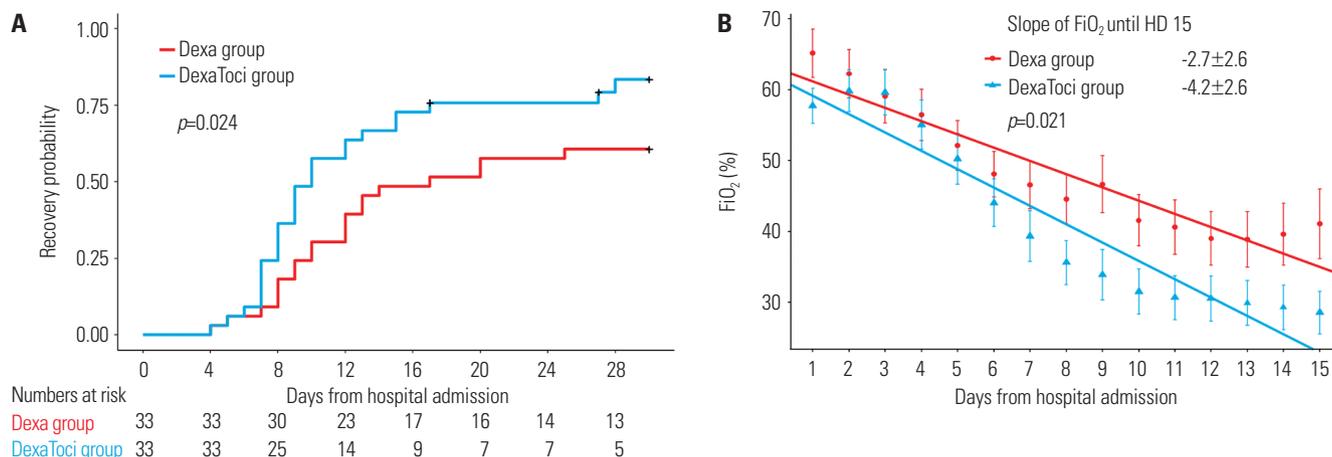
Fig. 2. Clinical outcomes of the Dexa and DexaToci groups. (A) Thirty-day recovery probabilities of the Dexa and DexaToci groups were compared using the Kaplan-Meier method. (B) The oxygenation improvement between the two groups were compared by calculating the slope of FiO_2 until HD 15. Dexa, dexamethasone; DexaToci, dexamethasone plus tocilizumab; FiO_2, fraction of inspired oxygen; HD, hospital day.

qualified study data, and many studies have led to heterogeneous outcomes. For example, the ACTT-1 trial showed a clinical benefit for remdesivir (n=1062),[21] but the Solidarity trial did not (n=5451).[22] As the Solidarity trial was designed quite practically and did not assess the time interval between symptom onset and treatment, subgroup analysis according to treatment timing could not be conducted despite the huge study population. Recommendations regarding remdesivir use in COVID-19 patients are also heterogeneous among the authorities,[23,24] and clinicians need to interpret the data based on their own situation.[13] Similarly, clinical studies assessing tocilizumab treatment for COVID-19 have proven controversial, while recent RCTs have suggested a survival benefit.[9,10] Therefore, retrospective cohort studies in real-world settings of each country are necessary to ensure a detailed analysis and document experiences of patient management.

As previous large RCTs exhibited, the tocilizumab combination strategy in the present cohort was also effective in terms of clinical recovery. Although a limited number of variables were included, the combination of tocilizumab was significantly associated with 30-day recovery in multivariate analyses. Decreases in oxygen requirement were faster and durations of oxygen requirement were shorter in the DexaToci group than in the Dexa group. Infectious complications were not statistically different between the two groups; however, among four patients who received a second dose of tocilizumab, three experienced culture-proven bacterial pneumonia, and two were diagnosed with probable invasive pulmonary aspergillosis. Although these patients showed deteriorating courses before the second dose of tocilizumab and were at high risk for infectious complications, we think a second dose of tocilizumab should be carefully given. We investigated cellular and humoral immune responses against SARS-CoV-2 in the convalescent stage, and the results suggested that the additional combination of tocilizumab may not hinder the immune response against SARS-CoV-2. On the other hand, both COVID-19 infection itself and immune modulation therapies can cause dysfunction of the immune system in the acute phase of critically ill COVID-19 infection. It was noticed that 19.2% of cohort patients showed decreased INF-γ responses to mitogen stimulation in the convalescent stage. Further studies are needed to ascertain the degree of immunosuppression during the acute phase of COVID-19.

Of note, the in-hospital mortality rate of the present cohort was lower than rates in previously reported RCTs. Because outcomes data based on the scope of COVID-19 intensive care in Korea are lacking, such could be compared with those of the RECOVERY trial, a large RCT. The in-hospital mortality rate of the Dexa group was 15.2% (5/33) and the 30-day mortality rate was 0.0% (0/33) in the present study. Two patients expired despite ECMO support, and all five patients who died did so after 30 days (median, 62 days; range, 34–117 days). In the RECOVERY dexamethasone trial, the 29-day mortality rate of the oxygen-only group was 23.3% in the dexamethasone arm and 26.2% in the usual care arm.[9] In the present cohort, the in-hospital mortality rate of the DexaToci group was 9.1% (3/33), and the 30-day mortality rate was 6.1% (2/33). These three fatal cases did not receive ECMO support due to the limited probability of recovery (due to old age, TB-destroyed lung, and massive stroke). In the RECOVERY tocilizumab trial, the 28-day mortality rate of the non-invasive ventilation subgroup (including HFNC) was 38% in the tocilizumab group and 42% in the usual care group.[10] The low mortality of our cohort could be associated with various factors. First, the outbreak situation may have been worse in the United Kingdom, where the RECOVERY trials were mainly conducted. In an overwhelming outbreak situation, medical resources would be limited for critical patient care. Second, we administered remdesivir for most indicated patients, while other countries have tended to use remdesivir less. Third, dexamethasone dosing according to disease severity might be effective. As a limitation of this single-center study, we did not compare severity-adjusted dosing with a fixed-dosing regimen. Nevertheless, we experienced recovery cases af-

Table 2. Treatment and Outcomes of the Cohort Patients

Variables	Dexa group (n=33)	DexaToci group (n=33)	p value
Dexamethasone			
Duration of treatment	14.0 (9.0–20.0)	10.0 (8.0–15.0)	0.088
The cumulative dose of dexamethasone	217.1±261.6	145.6±123.9	0.166
The average dose of dexamethasone per day	9.4±3.5	9.9±3.1	0.521
Tocilizumab			
Single-dose treatment	NA	29 (87.9)	NA
The interval from admission to the first dose of tocilizumab, days	NA	0.8±0.9	NA
Second dose treatment	NA	4 (12.1)	NA
The interval from admission to the second dose of tocilizumab, days	NA	5.0±2.2	NA
Other treatment modalities			
Remdesivir	29 (87.9)	33 (100.0)	0.525
Camostat	19 (57.6)	0 (0.0)	<0.001
Nafamostat	3 (9.1)	7 (21.2)	0.303
Antibiotics	19 (57.6)	16 (48.5)	0.622
Clinical outcomes during hospitalization			
Endotracheal intubation during ICU care	10 (30.3)	9 (27.3)	>0.999
ECMO support	3 (9.1)	2 (6.1)	>0.999
CRRT support	1 (3.1)	0 (0.0)	>0.999
The slope of FiO$_2$ until HD 15	-2.7±2.6	-4.2±2.6	0.021
Duration of oxygen requirement, days	17.0 (10.0–56.0)	10.0 (8.0–18.0)	0.006
In-hospital mortality	5 (15.2)	3 (9.1)	0.706
Clinical outcomes by HD 30			
Dead (WHO-CPS 10)	0 (0.0)	2 (6.1)	0.473
MV with CRRT or ECMO (WHO-CPS 9)	3 (9.1)	1 (3.0)	0.606
MV with P/F ratio <150 (WHO-CPS 8)	1 (3.0)	1 (3.0)	>0.999
MV with P/F ratio ≥150 (WHO-CPS 7)	1 (3.0)	0 (0.0)	>0.999
HFNC (WHO-CPS 6)	5 (15.2)	2 (6.1)	0.424
Nasal prong (WHO-CPS 5)	3 (9.1)	0 (0.0)	0.237
No oxygen (WHO-CPS 4)*	20 (60.6)	27 (81.8)	0.103
Infectious complications			
Bacterial infection, culture-proven	10 (30.3)	10 (30.3)	>0.999
Pneumonia	3 (9.1)	7 (21.2)	0.303
Urinary tract infection	6 (18.2)	2 (6.1)	0.258
Others	1 (3.0)	2 (6.1)	>0.999
Invasive candidiasis	1 (3.0)	0 (0.0)	>0.999
Invasive pulmonary aspergillosis	3 (9.1)	2 (6.1)	>0.999
CMV reactivation requiring treatment	2 (6.1)	0 (0.0)	0.473

Dexa, dexamethasone; DexaToci, dexamethasone plus tocilizumab; CMV, cytomegalovirus; ICU, intensive care unit; ECMO, extracorporeal membrane oxygenation; CRRT, continuous renal replacement therapy; FiO$_2$, fraction of inspired oxygen; WHO-CPS, World Health Organization Clinical Progression Scale; HD, hospital day; NA, not applicable; HFNC, high-flow nasal cannula; SD, standard deviation; IQR, interquartile range; MV, mechanical ventilation; P/F ratio, the ratio of the partial pressure of oxygen in arterial blood (PaO$_2$) to the inspired oxygen fraction (FiO$_2$).
Data are expressed as the number (%) of patients, means±SD, or medians (IQR) unless indicated otherwise.
*Including continuously improving patients with minimal O$_2$ support who were referred to mild COVID-19 patient care hospitals.

ter increasing the dexamethasone dose among patients who were referred to the ICU of our center due to worsening progress despite a 6-mg dose of dexamethasone. The potential effect of severity-adjusted dosing of dexamethasone needs to be further investigated in a multi-center retrospective cohort study.

The present study has several limitations. First, the baseline characteristics were not balanced due to the retrospective design, and the number of study participants was limited. Patients in the Dexa group were older than those in the DexaToci group, but this reflects the real-world outbreak situation in Korea. The domestic COVID-19 pandemic situations in 2020 and 2021 were different due to various factors. The dominant clades of SARS-CoV-2 were different, and the COVID-19 vaccination be-

Table 3. Univariable and Adjusted Analyses for 30-Day Recovery

Variables	Univariable analysis		Adjusted analysis 1		Adjusted analysis 2		Adjusted analysis 3	
	HR (95% CI)	*p* value	HR (95% CI)	*p* value	HR (95% CI)	*p* value	HR (95% CI)	*p* value
Age	0.969 (0.948–0.990)	0.003	0.990 (0.968–1.012)	0.347				
Male sex	0.799 (0.444–1.438)	0.455						
BMI	0.999 (0.936–1.066)	0.983						
Sx onset to ICU admission	1.038 (0.961–1.121)	0.345						
Initial Ct value (LRT, RdRp, or ORF1ab)	1.046 (0.980–1.117)	0.174						
Endotracheal intubation at admission	0.334 (0.081–1.381)	0.130						
Peak FiO₂ within 3 days	0.944 (0.926–0.963)	<0.001	0.941 (0.921–0.961)	<0.001	0.942 (0.921–0.964)	<0.001	0.940 (0.920–0.961)	<0.001
WBC count	0.986 (0.907–1.072)	0.742						
Albumin	1.557 (0.744–3.257)	0.240						
Thrombocytopenia (<150×10³/μL)	0.531 (0.263–1.070)	0.076						
BUN	0.976 (0.943–1.009)	0.155						
Creatinine	0.805 (0.419–1.547)	0.516						
LDH	0.997 (0.995–0.999)	0.002			0.999 (0.998–1.001)	0.413		
CRP	0.913 (0.865–0.964)	0.001					0.944 (0.900–0.991)	0.020
Diabetes mellitus	0.651 (0.361–1.175)	0.154						
Hypertension	0.716 (0.402–1.275)	0.257						
Charlson Comorbidity Index	0.830 (0.639–1.078)	0.163						
Tocilizumab combination	1.930 (1.078–3.455)	0.027	2.045 (1.040–4.021)	0.038	2.377 (1.301–4.343)	0.005	1.925 (1.052–3.522)	0.034

HR, hazard ratio; CI, confidence interval; BMI, body mass index; Sx, symptom; ICU, intensive care unit; Ct, cycle threshold; LRT, lower respiratory tract; RdRp, RNA-dependent RNA polymerase; ORF1ab, open reading frame 1ab; FiO₂, fraction of inspired oxygen; WBC, white blood cell; BUN, blood urea nitrogen; LDH, lactate dehydrogenase; CRP, C-reactive protein.
Univariable analyses for 30-day recovery were conducted for each variable. Since the sample size of the cohort was limited, statistically significant variables were individually included in each adjusted analysis, in addition to peak FiO₂ within 3 days and tocilizumab combination treatment.
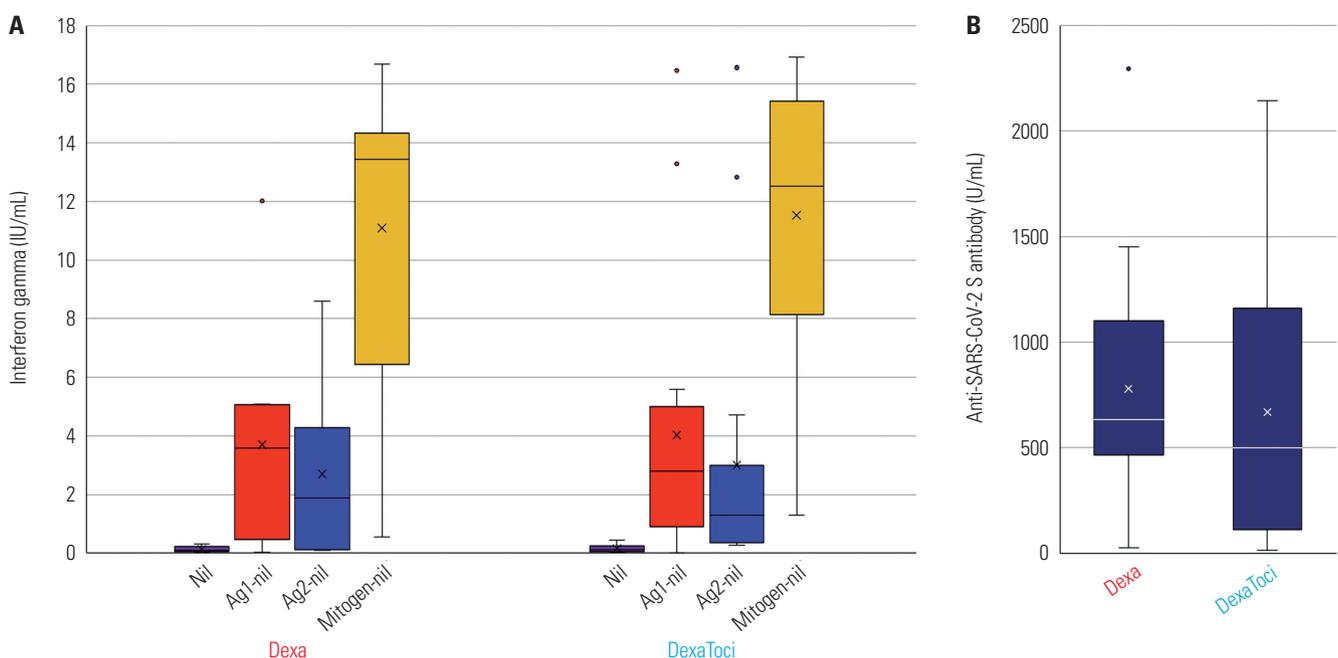

Fig. 3. Cellular and humoral immune responses against SARS-CoV-2 among the cohort patients. Cellular and humoral immune responses against SARS-CoV-2 were measured in the convalescent stage. Cellular responses were measured in nine patients of the Dexa group and 17 patients of the DexaToci group using SARS-CoV-2-specific IGRA test (A). Humoral responses were measured in 28 patients of the Dexa group and 19 patients of the DexaToci group using a quantitative anti-SARS-CoV-2 S antibody test kit (B). SARS-CoV-2, severe acute respiratory syndrome coronavirus 2; Dexa, dexamethasone; DexaToci, dexamethasone plus tocilizumab; IGRA, interferon-gamma release assay; Ag, antigen.

gan with older adults first in February 2021. Dexamethasone has already been proven as a treatment of COVID-19, while subsequent studies have suggested the benefit of tocilizumab, so this study was designed as a pre-and post-cohort study by tocilizumab administration since April 2021. As these various factors would induce the two groups to be unbalanced, we tried to adjust potential biases by multivariable analysis. Although minor treatment protocols, such as the use of camostat or nafamostat, were altered, other treatment protocols were relatively consistent during the study period because this was a single-center study. Second, the effect of immune modulators on viral load was not investigated. It has been reported that tocilizumab treatment may be associated with prolonged shedding of SARS-CoV-2.[25] There were changes in the dominant strain of SARS-CoV-2 in the Republic of Korea during the study period. The delta variant is known to be associated with a higher viral load and poorer outcomes,[26] although details on infections by variants of SARS-CoV-2 in each case were limited. Therefore, it was difficult to reflect the effect of individual SARS-CoV-2 variants on viral load kinetic analysis in the present analysis. In addition, it has been suggested that infectivity of SARS-CoV-2 would be associated with the production of neutralization antibodies rather than viral load per se.[27] Although we suggested that immune responses to SARS-CoV-2 in the convalescent stage are not impaired, further studies of neutralizing antibody production and viral culture need to be performed. Third, immune responses to SARS-CoV-2 were measured only in some patients in the study cohort and need to be investigated in a larger population.

In conclusion, the combination of severity-adjusted dexamethasone and tocilizumab for severe COVID-19 improved the probability of clinical recovery without increasing infectious complications or hindering the immune response against SARS-CoV-2.

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