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Special Article

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Korean Society of Infectious Diseases/National Evidence-based Healthcare Collaborating Agency Recommendations for Anti-SARS-CoV-2 Monoclonal Antibody Treatment of Patients with COVID-19

OPEN ACCESS

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ABSTRACT

Neutralizing antibodies targeted at the receptor-binding domain of severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) spike protein have been developed and now under evaluation in clinical trials. The US Food and Drug Administration currently issued emergency use authorizations for neutralizing monoclonal antibodies in non-hospitalized patients with mild to moderate coronavirus disease 2019 (COVID-19) who are at high risk for progressing to severe disease and/or hospitalization. In terms of this situation, there is an urgent need to investigate the clinical aspects and to develop strategies to deploy them effectively in clinical practice. Here we provide guidance for the use of anti-SARS-CoV-2 monoclonal antibodies for the treatment of COVID-19 based on the latest evidence.

Keywords: COVID-19; Anti-SARS-CoV-2 monoclonal antibody; Korea

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Conflict of Interest
No conflicts of interest.

Author contributions
Conceptualization: SBK, WSC, JSY, KRP, MYC. Data curation: MYC, SYY, JMK. Formal analysis: MYC, SYY, JMK. Funding acquisition: MYC. Investigation: MYC, SYY, SER, SBK, KMH, JYH, JEJ, YJK, WSC, YJK, YKY, SJJ, KRP, JSY. Methodology: MYC, SYY, JMK. Project administration: SBK, KMH, JYH, JEJ, YJK, WSC, YJK, YKY, SJJ. Resources: MYC, SYY, JMK. Software: SBK, KMH, JYH, JEJ, YJK, WSC, YJK, YKY, SJJ. Supervision: JSY, KRP, MYC. Validation: JSY, KRP, MYC. Visualization: MYC, SYY, JMK. Writing - original draft: SBK, KMH, JYH, JEJ, YJK, WSC, YJK, YKY, SJJ, MYC. Writing - review & editing: SBK, KMH, JYH, JEJ, YJK, WSC, YJK, YKY, SJJ, MYC, SER, KRP, JSY.

Background

Neutralizing antibodies against coronavirus are detected approximately 10 days after infection. These antibodies mainly target trimeric spike glycoproteins on the virus's surface that mediate its entry into host cells. The spike glycoproteins have two functional subunits that mediate cell attachment (S1 subunit that forms the four main domains from $S1_A$ to $S1_D$) and fusion of viral and cellular membranes (S2) [1]. Neutralizing activity of the plasma of patients with coronavirus disease 2019 (COVID-19) correlates with the magnitude of antibody response against the spike glycoprotein and nucleocapsid protein of severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2). This has led to the development of anti-SARS-CoV-2 monoclonal antibodies against the receptor-binding domain of the spike glycoprotein to treat COVID-19 infection at the early stages of the disease [2]. Based on this, bamlanivimab (LY-CoV555 and LY3819253, Eli Lily and Company, Indianapolis, IN, USA) and etesevimab (LY-CoV016 and LY3832479) (Eli Lily and Company, USA) REGN-COV2, a combination of casirivimab (REGN10933) and imdevimab (REGN10987) (Regeneron Pharmaceuticals, Tarry Town, NY, USA), and regdanvimab (CT-P59) (Celltrion, Yeonsu, Incheon, Korea) were developed and under evaluation in clinical trials. This article is an update to the previous guideline on treatment of patients with COVID-19, which was published by Korean Society of Infectious Diseases/National Evidence-based Healthcare Collaborating Agency in March of 2021 [3].

CQ. Anti-SARS-CoV-2 monoclonal antibody

* Clinical question

1. Is anti-SARS-CoV-2 monoclonal antibody effective for patients with mild-to-moderate COVID-19 compared to placebo?
2. Is anti-SARS-CoV-2 monoclonal antibody effective for patients with severe COVID-19 compared to placebo?

* Recommendations

1. Anti-SARS-CoV-2 monoclonal antibody may be considered in patients with mild to moderate COVID-19 who are at high risk of progression to severe COVID-19 (level of evidence: low, grade of recommendation: B, conditional recommendation).
*Refer to **Table 1** for patients who are at high risk of progression to severe COVID-19.

2. Anti-SARS-CoV-2 monoclonal antibody is not recommended for patients with severe COVID-19; however, these treatments may be considered for clinical trials of patients with severe COVID-19 requiring supplementary oxygen but not high flow oxygen or invasive mechanical ventilation (level of evidence: low, grade of recommendation: C, not recommended).

Evidence summary

A total of 372 articles were identified through literature and manual search between June 2020 and March 5, 2021. Three additional articles were additionally identified on April 5, 2021. We excluded duplicates and the remaining 277 articles were screened for their title, abstract, and main text. A total of four main texts and two abstracts (three clinical trials) were

Table 1. High-risk groups for progressing to severe COVID-19 are defined as patients who meet at least one of the following criteria according to the FDA's Emergency Use Authorization Standards

[1] Patients with a body mass index (BMI) ≥35
[2] Patients with chronic kidney disease/diabetes
[3] Patients with immune deficiencies (*i.e.*, immunocompromised) or those currently taking immunosuppressants
[4] Patients older than age 65
[5] Patients older than age 55 with: - cardiovascular disease or - hypertension or - chronic respiratory diseases
[6] Patients between ages 12 and 17 who: - have a BMI ≥85th percentile for their age and gender based on - have sickle cell anemia or - have congenital/acquired heart disease or - have neurodevelopmental disorders or - underwent tracheostomy/gastrostomy or - are currently under mechanical ventilation or - have asthma/chronic respiratory diseases that require medication

COVID-19, coronavirus disease 2019.

selected. The two abstracts were not included in the meta-analysis as the denominator value for each group was not clearly indicated.

The three clinical trial studies are as follows. Two papers have been published from the BLAZE-1 clinical trial of patients with mild and moderate COVID-19 [4, 5]. The intervention groups included bamlanivimab monotherapy and bamlanivimab/etesevimab combination therapy; the control group received a placebo. In the Activ-TicoCoV555 clinical trial, bamlanivimab monotherapy was provided to the intervention group, while a placebo was administered to the control group. However, most controls were receiving remdesivir. A clinical trial on COVID-19 in outpatient settings was also conducted [6]. In this study, the intervention drug was cocktail therapy casirivimab/imdevimab, and the control group was provided with a placebo.

The results of the meta-analysis of the three clinical trial studies are shown in the tables. Five outcomes were compared to assess the effects of antibody monotherapy; however, the number of compared studies was limited, and there were no statistically significant differences between the two groups (**Table 2**).

In comparison between combination therapy and placebo, the average viral load reduction during the first 7 days after administration was significantly greater in the combination therapy group; however, this was observed in only one study. There were no significant differences in clinical recovery, number of hospital visits, or adverse events (**Table 3**).

Table 2. Comparison of monotherapy versus placebo

Outcome	Number of studies	Study name (clinical trial or intervention)	Sample size	Estimated effect size
1.1 Viral load (Ct value) at 11 days	1	Gottlieb 2021 (BLAZE-1)	461	MD = 0.13 [−0.21, 0.47]
1.2 Clinical recovery	2	Activ-TicoCoV5552020 Gottlieb2021(BLAZE-1)	583	RR = 1.10 [0.93, 1.30]
1.3 All-cause mortality	1	Activ-TicoCoV555 2020	314	RR = 1.67 [0.57, 4.86]
1.4 Hospitalization or hospital visit in 29 days	1	Gottlieb 2021 (BLAZE-1)	461	RR = 0.27 [0.09, 0.80]
1.5 Treatment-emergent adverse event	1	Gottlieb 2021 (BLAZE-1)	465	RR = 0.90 [0.65, 1.25]

Ct, cycle threshold of the reverse-transcriptase–polymerase-chain-reaction assay; MD, mean difference; RR, risk ratio.

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Table 3. Comparison of combination therapy versus placebo

Outcome	Number of studies	Study name (clinical trial or intervention)	Sample size	Estimated effect size
2.1 Time-weighted average change in viral load (in log10 copies per milliliter) during 1st 7days	1	Weinreich 2021 (REGN-COV2)	221	MD = −0.40 [−0.43, −0.37]
2.2 Clinical recovery	1	Gottlieb 2021 (BLAZE-1)	229	RR = 1.24 [0.98, 1.57]
2.3 Hospital visit within 29 days	1	Weinreich 2021 (REGN-COV2)	275	RR = 0.51 [0.17, 1.54]
2.4 Treatment-emergent adverse event	1	Gottlieb 2021 (BLAZE-1)	268	RR = 0.63 [0.39, 1.02]

MD, mean difference; RR, risk ratio.

Table 4. Comparison of combination therapy versus monotherapy

Outcome	Number of studies	Study name (clinical trial or intervention)	Sample size	Estimated effect size
3.1 Viral load Change (Ct value) from baseline to day 11 *vs.* placebo	1	Gottlieb2021 (BLAZE-1) bamlanivimab/ etesevimab *vs.* bamlanivimab	418	MD = −0.61 [−1.11, −0.11]

Ct, cycle threshold of the reverse-transcriptase–polymerase-chain-reaction assay; MD, mean difference; RR, risk ratio.

The BLAZE-1 study compared the change in viral load relative to placebo in combination therapy and monotherapy groups; viral loads were significantly more decreased in the combination therapy group than in the monotherapy group (**Table 4**).

Data obtained from abstracts included the effects of CT-P59 (regdanvimab), published by Celltrion in Korea, and the results of the BLAZE-2 clinical trial of the residents and staffs in nursing homes. CT-P59 significantly shortened the clinical recovery period compared to placebo. In the BLAZE-2 study, the frequency of symptomatic COVID-19 infection and the number of deaths was significantly decreased in the intervention group compared to the control group.

The level of evidence was determined using GRADE methodology [7] (**Table 5, 6**). The level of evidence regarding monotherapy versus placebo was graded as 'moderate' based on the low incidence and wide confidence interval (CI). The level of evidence regarding combination therapy versus placebo was graded as 'low' based on the wide CI and small sample size.

Table 5. Certainty of evidence

Grade	Definition
High	We are very confident that the true effect lies close to that of the estimate of the effect.
Moderate	We are moderately confident in the effect estimate: The true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different.
Low	Our confidence in the effect estimate is limited: The true effect may be substantially different from the estimate of the effect.
Very Low	We have very little confidence in the effect estimate: The true effect is likely to be substantially different from the estimate of effect.

Table 6. Definition of recommendation grading

Grade of recommendations		Explanation
A	Strong recommendation	The intervention can be strongly recommended in most clinical practice, considering greater benefit than harm, evidence level, value and preference and resources.
B	Conditional recommendation	The intervention can be conditionally recommended in clinical practice considering balance of benefit and harm, evidence level, value and preference and resources.
C	Not recommended	The harm of the intervention maybe greater than the benefit. Also considering evidence level, value and preference and resources, the intervention should not be recommended.
I	Inconclusive	Considering of very low or insufficient evidence level, uncertain or variable in balancing of benefit and harm, value and preference, and resources, it is not possible to determine the strength and direction of recommendation It means that intervention cannot be recommended or opposed and the decision depends on clinician's judgement.
Expert Consensus		There is not enough evidence to give an evidence-based recommendation but a consensus-based recommendation can be given based on clinical experiences and expert consensus methods under considering given the benefit and harm, preference and value, and resources.

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Lastly, a comparison of monotherapy versus combination therapy was graded as 'very low' for inaccuracy with a significantly wide CI as only one study was analyzed. The overall level of evidence was assessed as 'low'.

Considerations for recommendations

The high-risk group for progression to severe COVID-19 was defined in the US Food and Drug Administration (FDA)'s Emergency Use Authorization criteria for neutralizing antibodies against SARS-CoV-2 [8, 9]. These criteria were used to select patients with mild and moderate COVID-19 with a high risk of developing severe COVID-19 in Section 1 of this recommendation (**Table 1**).

1. Benefit and harm

1) Benefit

- In a randomized controlled (clinical) trial (RCT) of patients at high risk of developing severe COVID-19 that did not require hospitalization, no deaths were observed in 518 patients treated with bamlanivimab /etesevimab compared to 10 deaths in 517 patients who received placebo. Thus, bamlanivimab /etesevimab resulted in an absolute reduction in mortality of 1.9%, and also reduced the risk of COVID-19-related hospitalization by day 29 (risk ratio [RR]: 0.30; 95% confidence interval [CI]: 0.16 – 0.59) and the risk of developing a high viral load on day 7 compared to placebo (RR: 0.34, 95% CI: 0.25 – 0.46) [4].
- In patients with one or more risk factors for serious COVID-19 that did not require hospitalization, those who received casirivimab/imdevimab had a relatively lower mortality rate (RR: 0.28, 95% CI: 0.05 – 1.40) and risk of hospitalization (RR: 0.45; 95% CI: 0.30 - 0.67) compared to the placebo group [6].
- Regdanbimab reduced the incidence of severe COVID-19 requiring inpatient treatment by 54% and 68% in all COVID-19 patients and patients with moderate COVID-19 over the age of 50, respectively. Additionally, time to clinical recovery was shorted by 3.4 days in the regdanvimab- treated group [95% CI, 5.35 [3.97 - 6.78] - 8.77 [6.72 - 11.73], log-rank $P = 0.0097$] [5].

2) Harm

- According to the FDA's Emergency Use Authorization fact sheet for bamlanivimab/etesevimab, the adverse events included nausea, dizziness, rashes, pruritus, and pyrexia. In the BLAZE-1 phase 3 study, 1% of the participants experienced hypersensitivity reactions such as infusion-related reactions, rashes, and inflammation; however, these events were resolved [9].
- According to the fact sheet for Emergency Use Authorization of casirivimab/imdevimab by the FDA, 1 out of 533 participants who received casirivimab/imdevimab in the R10933-10987-COV-2067 study had an anaphylactic reaction that required treatment with epinephrine. Four participants who received 4,000 mg of casirivimab/imdevimab showed grade 2 or higher infusion-related reactions, and administration was permanently discontinued in two [8].
- In a clinical trial of 325 patients with mild and moderate COVID-19 treated with regdanvimab or placebo, adverse events were observed in 27% of the regdanvimab group and 31% of the placebo group. Regdanvimab-related adverse events were observed in 5.6%, with no serious adverse events, deaths, or other events leading to study discontinuation [10].

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2. Patients' values and preferences

Few treatments exist for patients with COVID-19 and only a few drugs have shown therapeutic effects. Vaccination for COVID-19 started worldwide in 2021. In Korea, vaccination was started in February; however, more time is required to reach a satisfactory coverage rate. On February 5, 2021, the Korean Ministry of Food and Drug Safety (mFDS) has approved the administration of regdanvimab in high-risk mild patients over the age of 60 with underlying medical conditions (diabetes, hypertension, cardiovascular and chronic respiratory disease, etc.) and patients over the age of 18 with moderate COVID-19, subject to the submission of phase 3 clinical trial results. Patients who meet the indications for administration are expected to prefer treatment with monoclonal antibodies.

3. Resources (including cost)

The price of therapeutic antibody products developed by Eli Lily and Company and Regeneron is $2,400 (approximately 2.7 million Korean won, KRW), and the price of regdanvimab is about 600,000 KRW which is close to the production cost. Bamlanivimab/etesevimab and REGN-COV2 are expected to be preferred by patients at risk of developing severe COVID-19; however, the relatively high cost of those agents calls for an in-depth discussion of the acceptability of these agents in Korea - including insurance coverage - is necessary.

4. Comparison of recommendations with clinical practice guidelines in other countries

The United States National Institutes of Health classification of the severity of illness was adopted after a review of similar classifications from various guidelines (**Table 7**) [11].

- The FDA guidelines state that, for patients with mild-to-moderate COVID-19 who do not require hospitalization and have a high risk of developing severe COVID-19, bamlanivimab monotherapy is not recommended. Combination therapy of bamlanivimab 700 mg/etesevimab 1,400 mg or casirivimab 1,200 mg/imdevimab 1,200 mg is recommended for these patients; however, this combination therapy is not recommended for patients who require inpatient treatment, except in clinical trials.
- According to the Infectious Disease Society of America (IDSA) guidelines, administration of bamlanivimab/etesevimab or casirivimab/imdevimab is recommended in patients with moderate COVID-19 who do not require hospitalization and have a risk of developing severe COVID-19. However, administration of bamlanivimab alone is not recommended for patients with severe COVID-19 who require hospitalization.
- The Australian guidelines do not recommend the administration of bamlanivimab alone or bamlanivimab/etesevimab to treat COVID-19, with the exception of appropriately supervised randomized clinical trials.

Table 7. Classification of severity of illness referred by National Institutes of Health

Severity of illness	Definition
1. Asymptomatic	Individuals who test positive for SARS-CoV-2 using a virologic test (*i.e.*, a nucleic acid amplification test or an antigen test), but who have no symptoms that are consistent with COVID-19.
2. Mild	Individuals who have any of the various signs and symptoms of COVID-19 (*e.g.*, fever, cough, sore throat, malaise, headache, muscle pain, nausea, vomiting, diarrhea, loss of taste and smell) but who do not have shortness of breath, dyspnea, or abnormal chest imaging.
3. Moderate	Individuals who show evidence of lower respiratory disease during clinical assessment or imaging and who have saturation of oxygen (SpO_2) ≥94% on room air at sea level.
4. Severe	Individuals who have SpO_2 <94% on room air at sea level, a ratio of arterial partial pressure of oxygen to fraction of inspired oxygen (PaO_2/FiO_2) <300 mmHg, respiratory frequency >30 breaths per minute, or lung infiltrates >50%.
5. Critical	Individuals who have respiratory failure, septic shock, and/or multiple organ dysfunction.

Source: NIH. Clinical Spectrum of SARS-CoV-2 Infection. Available at: https://www.covid19treatmentguidelines.nih.gov/overview/clinical-spectrum/[11].
COVID-19, coronavirus disease 2019.

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5. Other considerations

- On January 13, 2021, the results of a phase 2 clinical trial of 327 patients from the United States of America (USA), Spain, Romania, and Korea treated with regdanvimab - a COVID-19 neutralizing antibody product developed by Celltrion in Korea - were reported at the Pharmaceutical Society of Korea Academic Conference. Following the COVID-19 Treatment/Vaccine Verification Advisory Committee meeting and Central Pharmacist Review Committee meeting in January 2021, the Ministry of Food and Drug Safety of Korea conditionally approved the administration of regdanvimab in high-risk patients with mild COVID-19 over the age of 60 with underlying diseases and patients with moderate COVID-19 over the age of 18 on February 5, 2021, subject to submission of phase 3 clinical trial results.
- On March 26, 2021, the European Medicines Agency announced that regdanvimab could be used to treat adults at high risk of severe COVID-19 who did not require adjuvant oxygen therapy [12].
- As SARS-CoV-2 variants are observed worldwide, we must collect additional clinical data on the effects of each anti-SARS-CoV-2 monoclonal antibody product against variants. Careful selection of appropriate antibody products should be based on the spread of variants.

6. Description of individual supporting documents

Bamlanivimab and etesevimab are monoclonal antibodies that neutralize spike proteins, which are purified from the serum of two patients who recovered from COVID-19 in the USA and China. In a phase 2 clinical study (BLAZE-1) of 452 mild and patients with moderate COVID-19 who did not require inpatient treatment at 41 medical institutions in the USA, the effects of bamlanivimab (309 patients) were compared to that of placebo (143 patients). Treatment groups received 700 mg (n = 101), 2,800 mg (n = 107), and 7,000 mg (n = 101) of bamlanivimab. Among these groups, the 2,800 mg group showed the greatest decrease in viral load compared to the placebo group. Approximately a 3.4-fold decrease in the average log virus load was observed on the 11th day compared to the placebo group. On the 29th day, the rates of hospitalization or emergency room visits related to COVID-19 were 1.6% and 6.3% in the bamlanivimab and placebo groups, respectively. The rate of hospitalization or emergency room visits in high-risk patients was 2.9% in the bamlanivimab group, compared to 10.1% in the placebo group. Additionally, symptom scores improved on the second day of bamlanivimab treatment compared to 6th day of placebo administration [5]. Based on these findings, on November 9, 2020, the U.S. FDA authorized emergency use of bamlanivimab in patients with mild and moderate COVID-19 at high risk of developing severe COVID-19. When bamlanivimab/etesevimab combination therapy was compared to placebo, the between-group difference in viral load on the 11th day was -0.57 (95% CI: -1.0 - -0.14; $P = 0.01$) in the combination therapy group, significantly reduced compared to the monotherapy group. Compared to the placebo group, the combination treatment group showed significantly reduced hospitalization rate and emergency room visits (-4.9%, 95% CI: -8.9 - -0.8; $P = 0.049$) [4]. However, bamlanivimab monotherapy was ineffective in patients with severe COVID-19 in a phase 3 clinical trial, and the study was discontinued early on October 26, 2020. Based on additional combination therapy findings, the U.S. FDA authorized emergency use of bamlanivimab /etesevimab combination therapy on February 9, 2021. In the new phase 3 BLAZE-1 study, combination therapy of bamlanivimab 700 mg and etesevimab 1400 mg was administered. A total of 769 patients with moderate COVID-19 with a high risk of developing severe COVID-19 were assigned to the treatment (n = 511) and control (n = 258) groups. The combination therapy of bamlanivimab 700 mg and etesevimab 1,400 mg lowered hospitalization and mortality secondary to COVID-19 by 87% compared to placebo [13].

According to the results of an interim analysis of the phase 1/2 clinical trial of 269 patients with mild COVID-19 who did not require inpatient treatment, the least-squares mean difference in the time-weighted average change in viral load of the REGN-COV2 group was 0.41 $\log_{10}$ copies/mL compared to the placebo group. In comparison, a decrease of 0.56 $\log_{10}$ copies/mL was observed in COVID-19 antibody-negative group. Moreover, in patients with a viral load of 10^7 copies/mL or more, the mean decrease in viral load at day 7 was approximately 2 logs greater in those receiving REGN-COV2 than those receiving placebo. More than one hospital visit was observed in 6% and 3% of the placebo and REGN-COV2 groups, respectively. In COVID-19 antibody-negative patients, 15% of the placebo group and 3% of REGN-COV2 visited the hospital more than once. As of November 21, 2020, the U.S. FDA authorized emergency use of REGN-COV2 in patients with mild and moderate COVID-19 at high risk of developing severe COVID-19. On April 16, 2021, the U.S. FDA canceled authorization for emergency use of bamlanivimab monotherapy.

In patients at high risk from COVID-19, REGN-COV2 showed 100% efficacy in preventing symptomatic infection (0/186) compared to placebo (8/223). Additionally, REGN-COV2 reduced all infections, including asymptomatic infections, by 50% (10/185) compared to placebo (23/223). All COVID-10 infections in the REGN-COV2 group were asymptomatic. The highest viral concentration of the REGN-COV2 group was lower than that of the placebo group, and the virus excretion period was also reduced in the REGN-COV2 group compared to the placebo group [14].

On January 13, 2021, the phase 2 clinical trial of 327 patients from the USA, Spain, Romania, and Korea treated with regdanvimab (CT-P59), a COVID-19 neutralizing antibody product developed by Celltrion in Korea, was reported. The incidence of severe COVID-19 cases requiring inpatient treatment was reduced by 54% among all COVID-19 patients and 68% among patients with moderate COVID-19 older than age 50. Furthermore, the time for clinical recovery was 5.4 days CT-P59 groups, which was reduced by 3.4 days compared to 8.8 days in the placebo group (95% CI: 5.35 [3.97 – 6.78] to 8.77 [6.72 - 11.73], log-rank $P = 0.0097$) [15].

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SUPPLEMENTARY MATERIAL

Korean version.

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