Guidelines

Japanese rapid/living recommendations on drug management for COVID-19: updated guidelines (September 2021)

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Background: The coronavirus disease 2019 (COVID-19) has spread worldwide since early 2020, and there are still no signs of resolution. The Japanese Clinical Practice Guidelines for the Management of Sepsis and Septic Shock (J-SSCG) 2020 Special Committee created the Japanese rapid/living recommendations on drug management for COVID-19 using the experience of creating the J-SSCG.

Methods: The Grades of Recommendation, Assessment, Development, and Evaluation (GRADE) approach was used to determine the certainty of the evidence and strength of the recommendations. The first edition of this guideline was released on September 9, 2020, and this document is the revised edition (version 4.0; released on September 9, 2021). Clinical questions (CQs) were set for the following seven drugs: favipiravir (CQ1), remdesivir (CQ2), corticosteroids (CQ4), tocilizumab (CQ5), anticoagulants (CQ7), baricitinib (CQ8), and casirivimab/imdevimab (CQ9). Two CQs (hydroxychloroquine [CQ3] and ciclesonide [CQ6]) were retrieved in this updated version.

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Recommendations: Favipiravir is not suggested for all patients with COVID-19 (GRADE 2C). Remdesivir is suggested for patients with moderate COVID-19 requiring supplemental oxygen/hospitalization (GRADE 2B). Corticosteroids are recommended for patients with moderate COVID-19 requiring supplemental oxygen/hospitalization (GRADE 1B) and for patients with severe COVID-19 requiring mechanical ventilation/intensive care (GRADE 1A); however, their administration is not recommended for patients with mild COVID-19 not requiring supplemental oxygen (GRADE 1B). Tocilizumab is suggested for patients with moderate COVID-19 requiring supplemental oxygen/hospitalization (GRADE 2B). Anticoagulant administration is recommended for patients with moderate COVID-19 requiring supplemental oxygen/hospitalization and patients with severe COVID-19 requiring mechanical ventilation/intensive care (good practice statement). Baricitinib is suggested for patients with moderate COVID-19 requiring supplemental oxygen/hospitalization (GRADE 2C). Casirivimab/imdevimab is recommended for patients with mild COVID-19 not requiring supplemental oxygen (GRADE 1B). We hope that these updated clinical practice guidelines will help medical professionals involved in the care of patients with COVID-19.

Key words: Coronavirus, evidence-based medicine, GRADE approach, practice guideline, SARS-CoV-2

BACKGROUND

THE CORONAVIRUS DISEASE 2019 (COVID-19), an infectious disease caused by the novel coronavirus severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) that developed at the end of 2019, has spread worldwide since the beginning of 2020, and there are still no signs of resolution. Although the severity and mortality for patients with COVID-19 are improving due to increasing vaccination rate, the number of infected patients remains high and a severe and fatal course among nonelderly has recently become a problem. The main pathological condition is severe respiratory failure triggered by pneumonia, but it also presents with coagulopathy and multiple organ failure, and the mechanism has not been fully elucidated.

Stringent policies have been implemented to control infectious diseases worldwide, such as lockdowns. Medical care to save the lives of patients with COVID-19 is being offered day and night in the medical field. Based on the intensity and urgency of the social impact, clinical evidence of various qualities is being published daily in preprint and top journals regarding various drug therapies. In the presence of evidence of varying quality, clinicians have limited time to shift through the reliable evidence needed for decision making.

Therefore, the Japanese Clinical Practice Guidelines for the Management of Sepsis and Septic Shock (J-SSCG) 2020 Special Committee, jointly organized by the Japanese Society of Intensive Care Medicine and the Japanese Association for Acute Medicine, made use of their experience to create the J-SSCG based on the Grades of Recommendation, Assessment, Development, and Evaluation (GRADE) system. We aimed to create an edition specializing in the COVID-19 drug management to provide the latest information on websites of both the societies and support evidence-based medical care. The first edition of this clinical practice guideline was released on September 9, 2020, and third edition was published in English.[1] This document is the revised 4.0 edition (released on September 9, 2021; Table 1, Fig. 1).

OVERVIEW AND BASIC PRINCIPLES OF THIS CLINICAL PRACTICE GUIDELINE

Purpose of the guideline

COVID-19 is a serious disease that affects all age groups. It is of great social significance to create reliable clinical practice guidelines to support clinical practice. A variety of clinical evidence exists in preprint servers. However, clinicians have limited time to identify high-quality information. This clinical practice guideline aims to support appropriate decision making in COVID-19 clinical practice.

Target patient population for the recommendations

The target population was adult patients with COVID-19. It covered all patients, including mildly ill patients who were undergoing medical treatment outside the medical institution (home and hotels), moderately ill patients who required supplemental oxygen or hospitalization, and severely ill patients who required intensive care management.

Participation of representatives of relevant expert groups and external evaluation by experts

A task force within the J-SSCG 2020 Special Committee was selected to work on this clinical practice guideline. All Task Force members were physicians who were familiar with the treatment of sepsis and COVID-19. One core working member (MA) was commissioned as an expert on the GRADE approach adopted in this clinical practice guideline.

Table 1. Clinical questions and recommendations†

CQ1	**Should favipiravir be administered to patients with COVID-19?**
Recommendation	• We suggest against favipiravir administration to all patients with COVID-19 (weak recommendation/low certainty of evidence: GRADE 2C).
CQ2	**Should remdesivir be administered to patients with COVID-19?**
Recommendation	• We have not made a clear recommendation on remdesivir administration to patients with mild COVID-19 who do not require oxygen supplemetation (no recommendation). • We suggest remdesivir administration to patients with moderate COVID-19 requiring oxygen supplementation/hospitalization (weak recommendation/moderate certainty of evidence: GRADE 2B). • We suggest against remdesivir administration to patients with severe COVID-19 requiring mechanical ventilation/intensive care (weak recommendation/moderate certainty of evidence: GRADE 2B).
CQ4-1	**Should corticosteroid be administered to patients with COVID-19?**
Recommendation	• We recommend against corticosteroid administration to patients with mild COVID-19 who do not require oxygen supplementation (strong recommendation/moderate certainty of evidence: GRADE 1B). • We recommend corticosteroid administration to patients with moderate COVID-19 requiring oxygen/hospitalization (strong recommendation/moderate certainty of evidence: GRADE 1B). • We recommend corticosteroid administration to patients with severe COVID-19 requiring mechanical ventilation/intensive care (strong recommendation/high certainty of evidence: GRADE 1A).
CQ4-2	**Should corticosteroid pulse therapy be administered to patients with moderate/severe COVID-19?**
Recommendation	• We have not made clear recommendations on corticosteroid pulse therapy to patients with moderate COVID-19 requiring oxygen administration/hospitalization, and those with severe COVID-19 requiring mechanical ventilation/intensive care (no recommendation).
CQ5	**Should tocilizumab be administered for patients with COVID-19?**
Recommendation	• We have not made a clear recommendation on tocilizumab administration to patients with mild COVID-19 who do not require oxygen supplementation (no recommendation). • We suggest tocilizumab administration to patients with moderate COVID-19 requiring oxygen supplementation/hospitalization (weak recommendation/moderate certainty of evidence: GRADE 2B). • We have not made a clear recommendation on tocilizumab administration to patients with severe COVID-19 requiring mechanical ventilation/intensive care (no recommendation).
CQ7	**Should anticoagulants be administered to patients with COVID-19?**
Recommendation	• We have not made a clear recommendation on anticoagulant administration to patients with mild COVID-19 who do not require oxygen supplementation (no recommendation) • We recommend anticoagulant administration to patients with moderate COVID-19 requiring oxygen administration/hospitalization and those with severe COVID-19 requiring mechanical ventilation/intensive care (good practice statement).
CQ8	**Should baricitinib be administered to patients with COVID-19?**
Recommendation	• We have not made a clear recommendation on baricitinib administration to patients with mild COVID-19 who do not require oxygen supplementation (no recommendation) • We suggest baricitinib administration to patients with moderate COVID-19 requiring oxygen supplementation/hospitalization (weak recommendation/low certainty of evidence: GRADE 2C) • We have not made a clear recommendation on baricitinib administration to patients with severe COVID-19 requiring mechanical ventilation/intensive care (no recommendation)
CQ9	**Should casirivimab/imdevimab be administered to patients with COVID-19?**
Recommendation	• We recommend casirivimab/imdevimab administration to patients with mild COVID-19 who do not require oxygen supplementation (strong recommendation/moderate certainty of evidence: GRADE 1B) • We have not made a clear recommendation on casirivimab/imdevimab administration to patients with moderate COVID-19 requiring oxygen supplementation/hospitalization and those with severe COVID-19 requiring mechanical ventilation/intensive care (no recommendation).

CQ, clinical question; COVID-19 coronavirus disease 2019; GRADE, Grades of Recommendation, Assessment, Development, and Evaluation.
†Two CQs (hydroxychloroquine [CQ3] and ciclesonide [CQ6]) were not updated in this updated version.

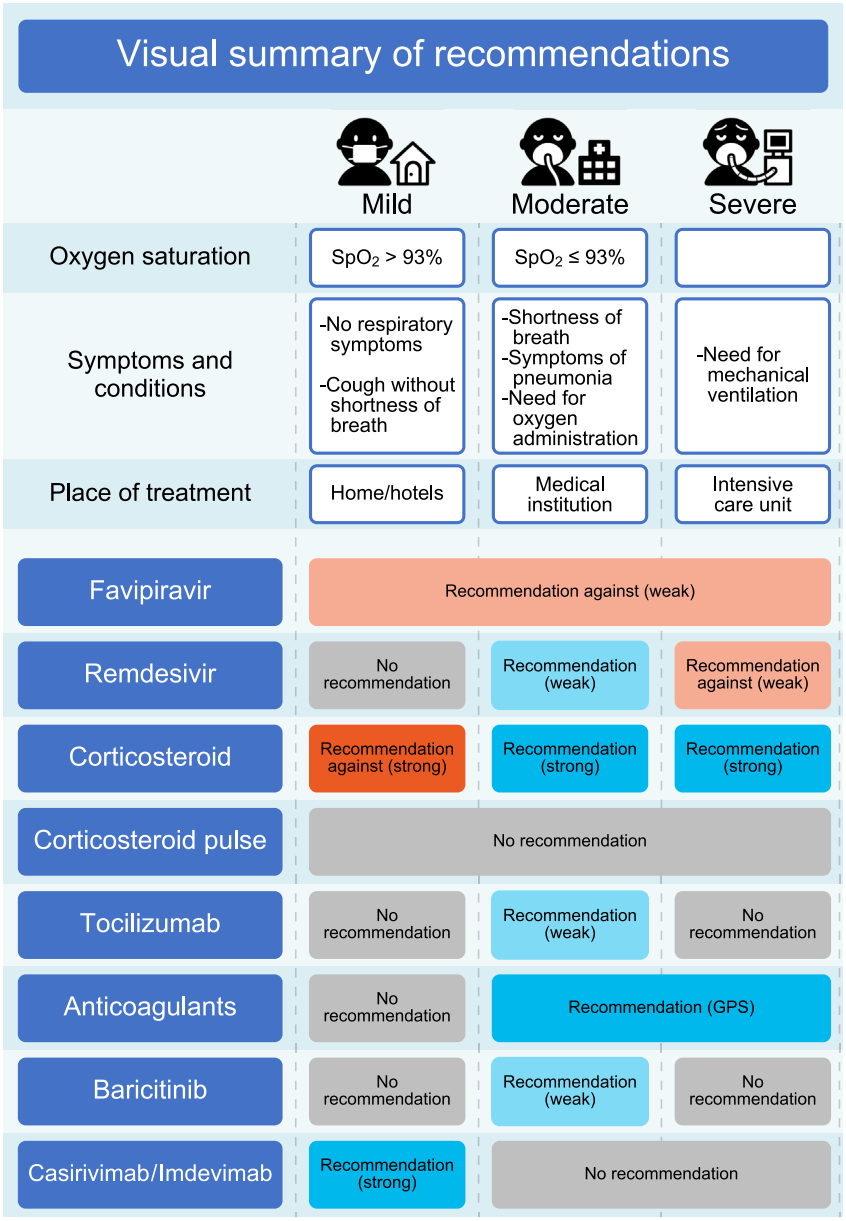

Fig. 1. A visual summary of recommendations. Recommendations for each medication are visually summarized. In each medication, recommendations were provided depending on the severity of COVID-19: mild, moderate, and severe. COVID-19, coronavirus disease 2019; GPS, good practice statement.

Devising ways to reflect the values and preferences of the target group (patients and the general public)

The number of people with COVID-19 was limited, and no qualitative research on the values and preferences of patients was conducted.

Users of this clinical practice guideline

This includes all medical professionals such as physicians, nurses, pharmacists, physiotherapists, clinical engineers, pharmacists, and registered dietitians who are engaged in or involved in COVID-19 medical care.

Dissemination of this clinical practice guideline

This clinical practice guideline will be published free of charge on the websites of the Japanese Society of Intensive Care Medicine and the Japanese Association for Acute Medicine. In addition, the latest version will be released on the Making GRADE the Irresistible Choice (MAGIC) app and will be provided in a form that is easy to use in clinical settings.

Funding

This clinical practice guideline was prepared with funding from the Japanese Society of Intensive Care Medicine and the Japanese Association for Acute Medicine. None of the members received any reward for the work.

Transparency in creating clinical practice guidelines

Audit committee members were appointed to conduct an internal peer review of various work processes in real time. The economic conflict of interest was applied and disclosed for 3 years from 2017, in accordance with the guidance on the criteria for participation in the formulation of clinical practice guidelines of the Japanese Association of Medical Sciences.

Revision schedules

Updates will be made accordingly as evidence is modified or added. The period for continuing revision will last until the COVID-19 epidemic period is over. The decision to end the revision will be made by the board of directors of both the academic societies.

METHOD OF PREPARING THIS CLINICAL PRACTICE GUIDELINE

THE JAPANESE RAPID/LIVING recommendations on drug management for COVID-19 were prepared in accordance with the GIN-McMaster guideline development checklist (extension of the Guideline Development Checklist for rapid guidelines),[2] and the GRADE approach was adopted to determine the strength and certainty of the evidence and recommendations.

Scope and clinical question planning

According to the current situation of COVID-19 medical care in Japan, the drug with a high clinical importance was selected as a clinical question (CQ) among the drug therapies available in clinical practice. The selection was decided by the consensus of the Task Force members. The agreement criteria were acceptance by two-third or more participating members, and the degree of disagreement was evaluated using the Rand/UCLA (University of California at Los Angeles) method.[3]

PICOT settings for recommendations

For a fully formulated comparative effectiveness systematic review topic as the base of recommendations, key questions in their final form concretely specify the patient populations, interventions, comparators, outcome measures of interest, timing (PICOT) to be addressed in the review.

Target patient population

The target population was adult patients with COVID-19. It covered all patients, including mildly ill patients who were undergoing medical treatment outside the medical institution (home and hotels), moderately ill patients who required supplemental oxygen or hospitalization, and severely ill patients who required intensive care management. The COVID-19 severity classification is defined as shown in Table 2 with reference to the Ministry of Health, Labor, and Welfare "Clinical Management of Patients with COVID-19."[4] As a general rule, recommendations were made according to severity and, if necessary, recommendations were presented for each target subgroup depending on the CQ.

Intervention treatment

The target drugs were selected as appropriate, taking into consideration the state of evidence collection and social conditions at that time, through discussions with and voting of the governing committee and task force.

Comparison

Only direct (head-to-head) comparison was included in this practice guideline: intervention treatment versus standard treatment (or conventional care, placebo treatment) of interest.

Outcome

The importance of outcomes was graded using a 1–9-point scale (9 being most patient important). Ultimately, we set three significant patient outcomes (i.e., rated scale of 7–9) for making recommendations: all-cause mortality, clinical improvement, and serious adverse events.

Table 2. COVID-19 severity classification in this guideline

Severity	Oxygen saturation	Clinical condition	Place of medical treatment
Mild	$SpO_2 > 93\%$	No respiratory symptoms Cough only, no shortness of breath	Need medical treatment outside the medical institution (home and hotels)
Moderate	$SpO_2 \leq 93\%$	Shortness of breath, symptoms of pneumonia Oxygen administration required	Need hospitalization at a medical institution
Severe		Need a mechanical ventilator	Need treatment in the intensive care unit

COVID-19, coronavirus disease 2019; SpO_2, saturated oxygen in arterial blood.

Time frame

As a general rule, the outcome was measured 28 days after the intervention, but depending on the evidence obtained, if there were no (or few) outcomes after 28 days, we also adopted those after 7 or 14 days.

GRADE-ADOLOPMENT for development of practical and trustworthy guideline

The "GRADE-ADOLOPMENT" approach to guideline production combines adoption, adaptation, and, as needed, *de novo* development of recommendations. The information sources of existing evidence synthesis that we used are the COVID-living NMA (https://covid-nma.com/living_data/index.php) and PubMed Central. We also included nonpeer–reviewed preprint server articles. Conference abstracts and press releases were not adopted. This version 4.0 is created based on the evidence obtained as of July 30, 2021.

Evaluation of the certainty of the body of evidence using GRADE

Definition and evaluation method for the certainty of the evidence

We assessed the certainty of evidence using the grading of recommendations assessment, development, and evaluation (GRADE) approach, and rated the certainty for each outcome as high (A), moderate (B), low (C), or very low (D) based on the following eight factors of GRADE: five factors that might lead to the rating down of the certainty of evidence (risk of bias [RoB], inconsistency, indirectness, imprecision, and publication bias), and three factors that might lead to the rating up (large effect, plausible confounding, and dose–response gradient). For individual studies and the overall evidence of RoB, Cochrane RoB 2.0[5] was used for randomized controlled trials (RCTs) and the risk of bias in nonrandomized studies of interventions (ROBINS-I) tool[6] for nonrandomized studies.

Calculation of net effect estimates for overall outcomes (net effect estimate)

The GRADE Working Group introduced the concept of certainty of net benefit to clarify and simplify methodology to report and assess the balance of benefits and harms in the context of fully contextualizing certainty of evidence across outcomes.[7] Specifically, it can be predicted that the three critical outcomes set in this guideline are not equally patient important. Therefore, to evaluate the balance between benefit and harm, the effects of these outcomes were integrated by taking into account the difference in importance (utility value), and the importance-adjusted net effect estimate was then calculated. The overall imprecision across outcomes was assessed based on the magnitude and confidence intervals of the calculated net effect estimates.

Formulation of recommendations and consensus building

The Panel Committee determined direction and strength of recommendation using the GRADE/DECIDE evidence-to-decision frameworks,[8] which includes four key criteria (certainty of evidence, balance of benefits and harms, patient values and preferences, cost/resource use), as well as acceptability and feasibility. According to GRADE/evidence-to-decision, the Panel graded the strength of recommendations as strong or conditional (for or against intervention of interest). However, if the overall certainty of evidence across the critical outcome was very low, it was decided to be no recommendation. The Panel Committee voted and reached a consensus using the Rand/UCLA appropriateness method.[3]

For the CQ that handled extremely common themes, and for which RCTs were theoretically impossible, we made recommendations using decision algorithm of good practice statement.[9]

Prompt disclosure of recommendations

For the rapid publication of recommendations, the MAGIC Authoring and Publication Platform (MAGIC-App) was utilized, designed by MAGIC that supports efficient guideline writing, dissemination, dynamic updating, and consultation decision making in the medical field.[10]

RECOMMENDATIONS AND THEIR RATIONALES

CQ1 Should favipiravir be administered to patients with COVID-19?

Recommendation

- We suggest against favipiravir administration to all patients with COVID-19 (weak recommendation/low certainty of evidence: GRADE 2C).

Background Favipiravir is an antiviral drug that was developed for the treatment of new or re-emerging influenza virus infections. Its effect on RNA virus is expected due to the selective inhibition of RNA polymerase by the triphosphorylated product converted *in vivo*. Although the drug is expected to be effective against COVID-19, its efficacy has not been determined, and it is likely to have a great clinical significance in planning CQs.

Recommendation rationale

■ Balance of benefits and harm.

In five RCTs[11–15] including 549 cases, point estimates were not expected to have a clinically meaningful effect on clinical improvement within 10–28 days (an increase of 33 per 1,000). Serious adverse events were unlikely to occur; however, the previously mentioned teratogenicity should be noted. The assessment of mortality outcomes was inadequate because the patients targeted for RCTs had predominantly mild symptoms (Fig. 2).

Based on the aforementioned statements on the balance between benefit and harm, it was determined that favipiravir administration was not beneficial for all patients with COVID-19.

■Certainty of evidence

The certainty of the evidence was judged to be "low" in terms of clinical improvement, all-cause mortality, and serious adverse events. Taking this direction into consideration, the overall certainty of the evidence was judged to be "low" for all patients with COVID-19.

CQ2 Should remdesivir be administered to patients with COVID-19?

Recommendation

- We have not made a clear recommendation on remdesivir administration to patients with mild COVID-19 who do not require oxygen (no recommendation)
- We suggest remdesivir administration to patients with moderate COVID-19 requiring oxygen/hospitalization (weak recommendation/moderate certainty of evidence: GRADE 2B)
- We suggest against remdesivir administration to patients with severe COVID-19 requiring mechanical ventilation/intensive care (weak recommendation/moderate certainty of evidence: GRADE 2B)

Background Remdesivir, developed as a therapeutic drug for Ebola hemorrhagic fever and Marburg virus infection, has been shown to have antiviral activity against single-stranded RNA viruses such as Middle East respiratory syndrome (MERS) virus, SARS virus, and SARS-CoV-2. It is a drug whose therapeutic target is RNA-dependent RNA polymerase, which is essential for the self-renewal of RNA viruses. In Japan, it was approved as a therapeutic drug for the novel coronavirus infection on May 7, 2020, under the "special approval system." It was officially approved in the United States on October 22, 2020. Therefore, it is considered to be of great clinical significance in planning CQs.

Recommendation rationale

■ Balance of benefits and harm.

There were four RCTs[16–19] with the adopted evidence. The effect on all-cause mortality in patients with mild COVID-19 is unclear (a decrease of 3 per 1,000). Small effects were expected for all-cause mortality (a decrease of 22 per 1,000) and clinical improvement (an increase of 68 per 1,000) in patients with moderate COVID-19. No effect was expected for all-cause mortality (an increase of 62 per 1,000) and clinical improvement (decrease of 20 per 1,000) in patients with severe COVID-19. There was no increase in the incidence of serious adverse events in patients with moderate and severe COVID-19 (a decrease of 61 per 1,000; Fig. 3).

For mild COVID-19, the range of estimated effects was wide and undecidable, and for moderate COVID-19, the benefit of remdesivir administration was determined to be greater. However, it was determined that the harm caused by the administration of remdesivir would be greater in patients with severe COVID-19.

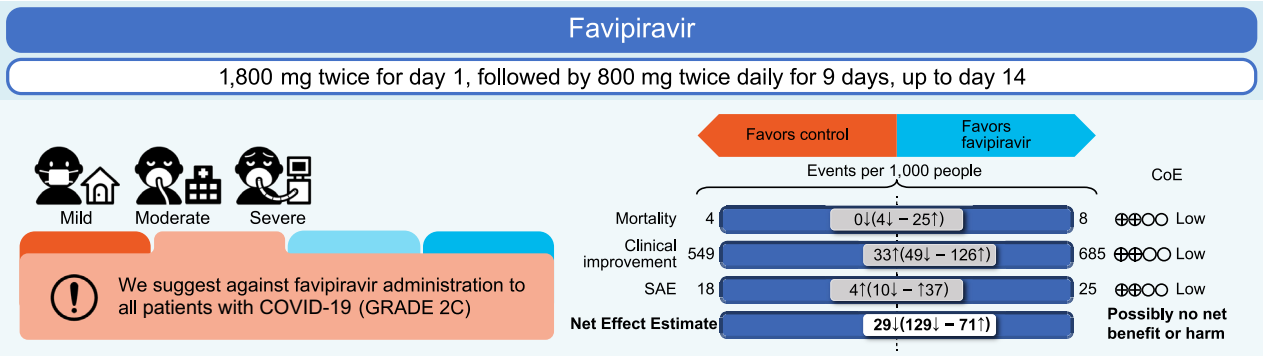

Fig. 2. Recommendations of favipiravir (CQ1). We suggest against favipiravir administration to all patients with COVID-19. Net effect estimates of favipiravir in all patients with COVID-19 were calculated with the effects of each outcome, in which the importance of mortality was considered to be three times higher than those of other outcomes. Overall imprecision across outcomes was assessed as "possibly no net benefit or harm", based on the magnitude of point estimate and 95% confidence intervals of the calculated net effect estimates. Abbreviations: CoE, certainty of evidence; COVID-19, coronavirus disease 2019; CQ, clinical question; GRADE, Grades of Recommendation, Assessment, Development, and Evaluation; SAE, severe adverse event.

■ Certainty of evidence

The certainty of evidence for each outcome ranged from "low" to "moderate." Analysis was performed according to the severity, and it was judged to be "low" for mild COVID-19, "moderate" for moderate COVID-19, and " moderate" for severe COVID-19.

■ Others (tolerability and feasibility).

On November 20, 2020, the World Health Organization made a conditional recommendation, but no severity classification was made. Although the recommended directions differ between moderate and severe, it is difficult to make a strict distinction between these two severities. However, recommendations may change due to the accumulation of evidence.

CQ4-1 Should corticosteroid be administered to patients with COVID-19?

Recommendation

- We recommend against corticosteroid administration to patients with mild COVID-19 who do not require oxygen supplementation (strong recommendation/moderate certainty of evidence: GRADE 1B)
- We recommend corticosteroid administration to patients with moderate COVID-19 requiring oxygen supplementation/hospitalization (strong recommendation/moderate certainty of evidence: GRADE 1B)
- We recommend corticosteroid administration to patients with severe COVID-19 requiring mechanical ventilation/intensive care (strong recommendation/high certainty of evidence: GRADE 1A)

Background Various types of corticosteroids have been used for the treatment of various diseases for a long time. It is speculated that the mechanism by which COVID-19 becomes severe is that organ damage occurs due to an excessive immune response to the host, such as viral pneumonia (H5N1 influenza, SARS, and H1N1 influenza) that were prevalent in the past. Corticosteroids are expected to attenuate immune responses. Therefore, CQ planning is considered to have a significant clinical significance.

Recommendation rationale

■ Balance of benefits and harm.

There were nine RCTs[20–27] with the adopted evidence. In the mild COVID-19 group, one RCT with 1,535 cases was adopted, and no effect was expected on all-cause mortality. No data were available for clinical improvement nor any serious adverse events. In the moderate COVID-19 group, four RCTs with 4,293 cases were adopted, and a moderate effect was expected in all-cause mortality and clinical improvement (a decrease of 156 per 1,000). No data were available for serious adverse events. In the severe COVID-19 group, seven RCTs with 2,047 cases were adopted, and it was expected to have a great effect on all-cause mortality and clinical improvement (a decrease of 279 per 1,000). There were a few serious adverse events (Fig. 4).

Therefore, regarding the balance of benefit and harm, it was judged that the benefit was superior in patients with moderate/severe COVID-19, and the harm was greater in patients with mild COVID-19.

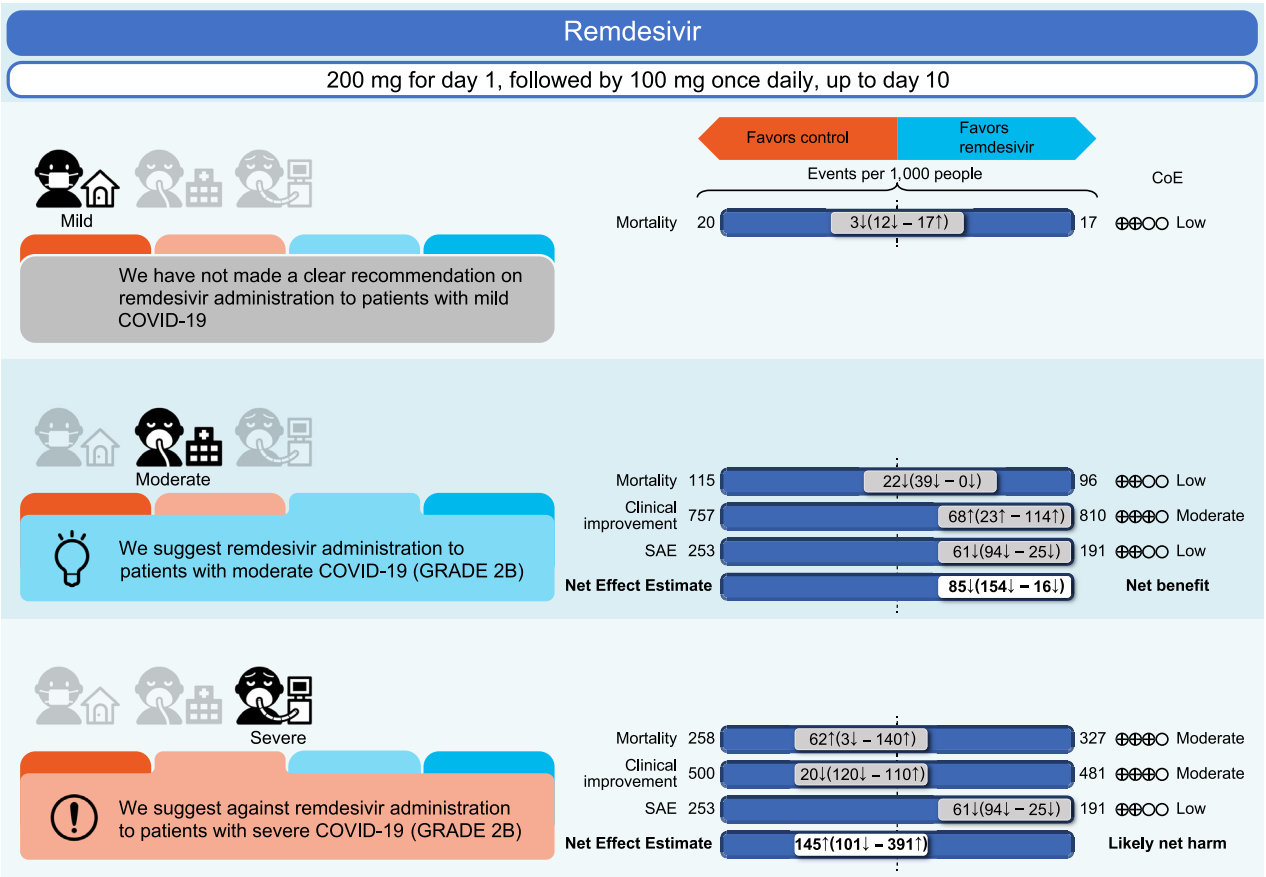

Fig. 3. Recommendations of remdesivir (CQ2). We have not made a clear recommendation on remdesivir administration to patients with mild COVID-19, suggest remdesivir administration to patients with moderate COVID-19, and suggest against remdesivir administration to patients with severe COVID-19. Net effect estimates of remdesivir in patients with moderate and severe COVID-19 were calculated with the effects of each outcome, in which the importance of mortality was considered as two times higher in moderate COVID-19 and three times higher in severe COVID-19, compared with those of other outcomes. Overall imprecisions across outcomes were assessed as "net benefit" in moderate COVID-19 and "likely net benefit" in severe COVID-19, based on the magnitude of point estimate and 95% confidence intervals of the calculated net effect estimates. CoE, certainty of evidence; COVID-19, coronavirus disease 2019; CQ, clinical question; GRADE, Grades of Recommendation, Assessment, Development, and Evaluation; SAE, severe adverse event.

■Certainty of evidence

Only one outcome was adopted for mild COVID-19, and the overall certainty of evidence was "moderate." It was rated as "moderate" in the moderate and "high" in the severe groups.

CQ4-2 Should corticosteroid pulse therapy be administered to patients with moderate/severe COVID-19?

Recommendation

- We have not made clear recommendations on corticosteroid pulse therapy for patients with moderate COVID-19 requiring oxygen administration/hospitalization and for those with severe COVID-19 requiring mechanical ventilation/intensive care (no recommendation).

Background Corticosteroid pulse therapy is a treatment method that has been investigated for its effectiveness in patients with viral pneumonia, such as SARS, and in patients with extremely severe respiratory failure, such as acute respiratory distress syndrome, for whom high-dose corticosteroids are administered. It is a treatment method that sets it apart from other corticosteroid therapies, and a new CQ was developed for patients with severe illness.

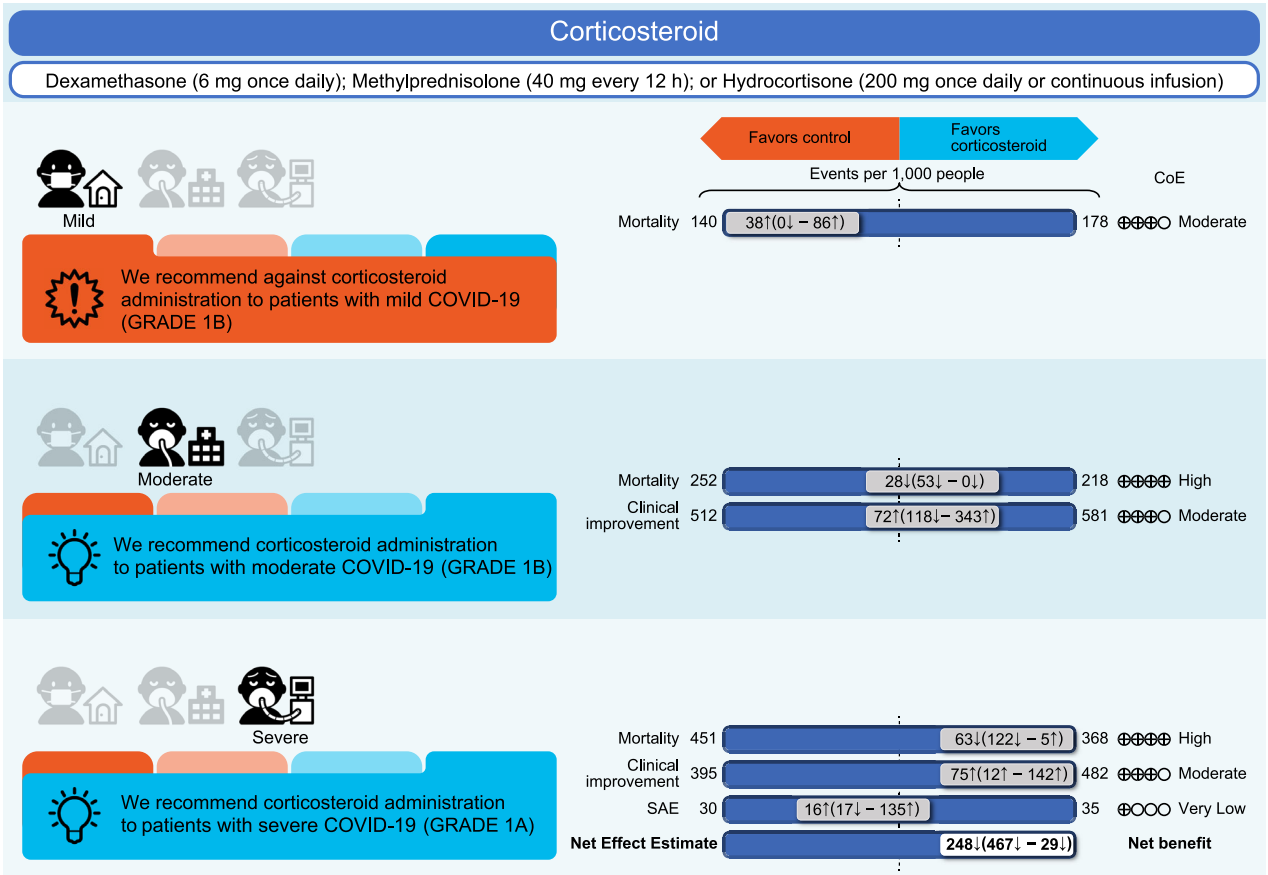

Fig. 4. Recommendations of corticosteroid (CQ4-1). We recommend against corticosteroid administration to patients with mild COVID-19 and recommend corticosteroid administration to patients with moderate and severe COVID-19. Net effect estimates of corticosteroid in patients with severe COVID-19 were calculated with the effects of each outcome, in which the importance of mortality was considered as three times higher than those of other outcomes. Overall imprecisions across outcomes were assessed as "net benefit," based on the magnitude of point estimate and 95% confidence intervals of the calculated net effect estimates. CoE, certainty of evidence; COVID-19, coronavirus disease 2019; CQ, clinical question; GRADE, Grades of Recommendation, Assessment, Development, and Evaluation; SAE, severe adverse event.

Recommendation rationale

■ Balance of benefits and harm.

We adopted one RCT for hospitalized patients.[28] This RCT determined that the target patients were admitted to the intensive care unit but were not ventilated. As such, it was classified as "moderate" in the classification of this guideline. However, approximately 75% received high-flow or high-concentration oxygen therapy and targeted the more severe group among patients with moderate COVID-19.

Sixty-two cases were adopted, and a large effect was expected in all-cause mortality at the time of discharge (a decrease of 369 per 1,000). No data were available for clinical improvement, and serious adverse events were expected to have a slight effect (13 per 1,000 reductions). However, the quality of the RCT was low, the dose of corticosteroids was different from the general dose in Japan, and the overall certainty of evidence was very low. As such, the balance of the effects was unclear.

■ Certainty of evidence

The overall certainty of evidence was set to "very low."

CQ5 Should tocilizumab be administered to patients with COVID-19?

Recommendation

- We have not made a clear recommendation on tocilizumab administration to patients with mild COVID-19 who do not require oxygen supplementation (no recommendation).

- We suggest tocilizumab administration to patients with moderate COVID-19 requiring oxygen supplementation/hospitalization (weak recommendation/moderate certainty of evidence: GRADE 2B)
- We have not made a clear recommendation on tocilizumab administration to patients with severe COVID-19 requiring mechanical ventilation/intensive care (no recommendation)

Background Increased production of inflammatory cytokines, including interleukin-6 (IL-6), has been reported to be associated with disease progression in patients with COVID-19. Tocilizumab, an IL-6 receptor antagonist, is expected to suppress the action of inflammatory cytokines in patients with COVID-19 and improve prognosis. As such, many clinical studies have been conducted; however, its effectiveness has not been clarified. This CQ was formulated because it is likely to have a great clinical significance as a candidate for COVID-19 therapeutic drugs.

Recommendation rationale

■ Balance of benefits and harm.

In 12 RCTs[29–40] with 7,543 cases of inpatients with severe/moderate COVID-19, tocilizumab for moderate COVID-19 was expected to decrease all-cause mortality by 30 per 1,000 and increase clinical improvement by 34 per 1,000 on day 28. The incidence of serious adverse events did not increase (a decrease of 21 per 1,000). For severe COVID-19, a decrease of 16 per 1,000 was expected for all-cause mortality at 28 days, and an increase of 24 per 1,000 for improvement of clinical symptoms. The incidence of serious adverse events did not increase (7 per 1,000 decrease; Fig. 5).

Based on the aforementioned statements, it was determined that the benefit of tocilizumab administration would outweigh harm in patients with moderate COVID-19. In critically ill patients, the certainty of evidence for the overall outcome was very low; therefore, we decided not to specify the recommendation. The balance between the benefits and harm of tocilizumab was undeterminable in patients with mild COVID-19.

■ Certainty of evidence

The certainty of evidence for each outcome was "moderate" in patients with moderate COVID-19 and "low" or "moderate" in patients with severe COVID-19. Considering the net effect estimate, the overall certainty of evidence was judged to be "moderate" for patients with moderate COVID-19 and "very low" for patients with severe COVID-19.

CQ7 Should anticoagulants be administered to patients with COVID-19?

Recommendation

- We have not made a clear recommendation on anticoagulant administration to patients with mild COVID-19 who do not require oxygen supplementation (no recommendation)
- We recommend anticoagulant administration to patients with moderate COVID-19 requiring oxygen administration/hospitalization and those with severe COVID-19 requiring mechanical ventilation/intensive care (good practice statement).

Background Coagulopathy due to angiopathy associated with viral infection is considered one of the pathological conditions of COVID-19. Along with the decrease in antithrombotic properties of the vascular endothelium, various coagulation factors take effect, and factors related to inflammation such as cytokine storms are intricately intertwined to form a thrombus. Prevention of thrombus formation in COVID-19 is expected to lead to improved patient prognosis, and anticoagulant administration to patients with COVID-19 is being considered.

Recommendation rationale

■ Implementation of anticoagulant therapy

Some RCTs related to anticoagulant administration in patients with COVID-19 have been reported. However, no RCT comparing the presence or absence of anticoagulant administration has been reported. In addition, overseas guidelines do not recommend the implementation of anticoagulant therapy. As far as these guidelines and the comparative control group in RCTs reported so far are concerned, the discussion is premised on administrating anticoagulants. As such, we decided that the implementation of anticoagulant therapy constituted a good practice statement.

■ Types of anticoagulant therapy

The types and doses of anticoagulants and the outcomes being considered vary in the RCTs reported so far. A further consideration is required for the grouping and outcome set to be examined in the meta-analysis when presenting recommendations. Therefore, in this version, recommendations on the type and dose of anticoagulant therapy considered have been deferred.

CQ8 Should baricitinib be administered to patients with COVID-19?

Recommendation

- We have not made a clear recommendation on baricitinib administration to patients with mild COVID-19 who do not require oxygen supplementation (no recommendation)

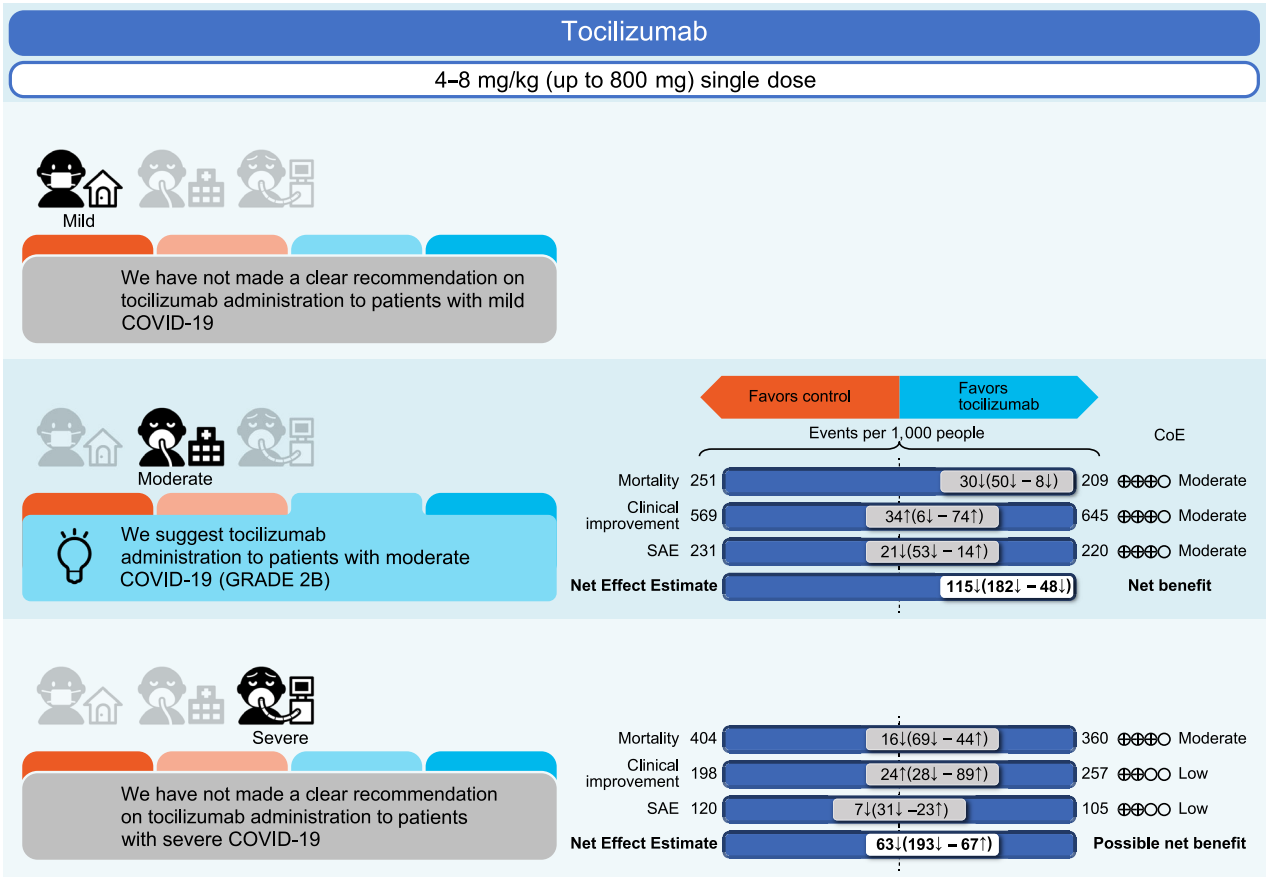

Fig. 5. Recommendations of tocilizumab (CQ5). We have not made a clear recommendation on tocilizumab administration to patients with mild and severe COVID-19 and suggest tocilizumab administration to patients with moderate COVID-19. Net effect estimates of tocilizumab in patients with moderate and severe COVID-19 were calculated with the effects of each outcome, in which the importance of mortality was considered as two times higher than those of other outcomes. Overall imprecisions across outcomes were assessed as "net benefit" in moderate COVID-19 and "possible net benefit" in severe COVID-19, based on the magnitude of point estimate and 95% confidence intervals of the calculated net effect estimates. CoE, certainty of evidence; COVID-19, coronavirus disease 2019; CQ, clinical question; GRADE, Grades of Recommendation, Assessment, Development, and Evaluation; SAE, severe adverse event.

- We suggest baricitinib administration to patients with moderate COVID-19 requiring oxygen supplementation/hospitalization (weak recommendation/low certainty of evidence: GRADE 2C)
- We have not made a clear recommendation on baricitinib administration to patients with severe COVID-19 requiring mechanical ventilation/intensive care (no recommendation)

Background The aggravation of COVID-19 has been attributed to an excessive immune response. Baricitinib is an orally available, selective inhibitor of Janus kinases 1 and 2. Baricitinib suppresses the excessive immune response by suppressing the intracellular signal pathway of cytokines. In Japan, it was approved for use in combination with remdesivir for cases requiring supplemental oxygen on April 23, 2021. The efficacy of baricitinib has not been determined and is considered to have great clinical significance in planning CQ.

Recommendation rationale

■ Balance of benefit and harm

In two RCTs[41,42] with 2,558 cases of patients with severe/moderate COVID-19, baricitinib for moderate COVID-19 was expected to decrease all-cause mortality by 42 per 1,000 and increase clinical improvement by 24 per 1,000. The incidence of serious adverse events did not increase (a decrease by 40 per 1,000). The net effect estimates were 190 fewer per 1,000 (95% confidence interval 272 fewer to 108 fewer) when the weighted importance of mortality outcomes

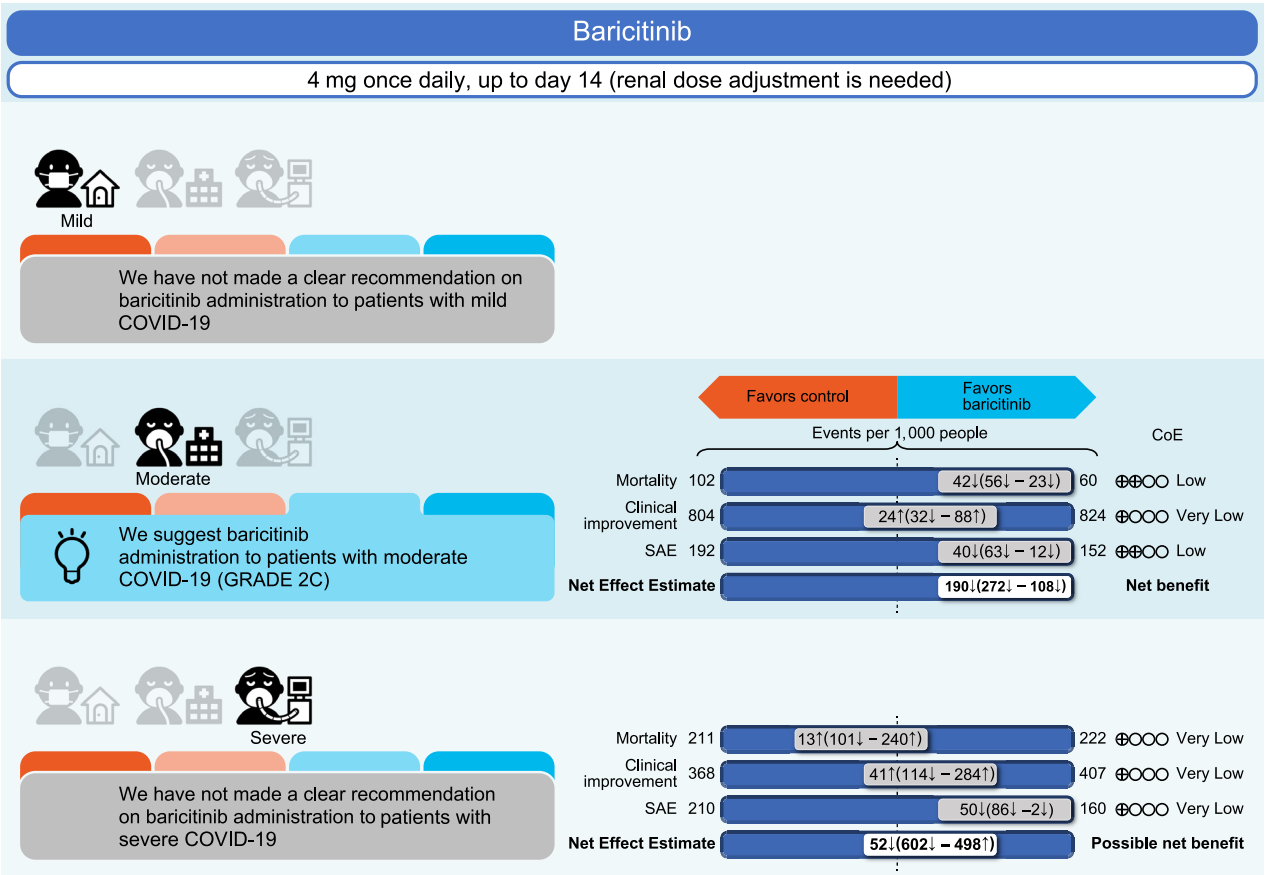

Fig. 6. Recommendations of baricitinib (CQ8). We suggest baricitinib administration to patients with moderate COVID-19 and have not made a clear recommendation on baricitinib administration to patients with mild and severe COVID-19. Net effect estimates of baricitinib in patients with moderate and severe COVID-19 were calculated with the effects of each outcome, in which the importance of mortality was considered as three times higher than those of other outcomes. Overall imprecisions across outcomes were assessed as "net benefit" in moderate COVID-19 and "possible net benefit" in severe COVID-19, based on the magnitude of point estimate and 95% confidence intervals of the calculated net effect estimates. CoE, certainty of evidence; COVID-19, coronavirus disease 2019; CQ, clinical question; GRADE, Grades of Recommendation, Assessment, Development, and Evaluation; SAE, severe adverse event.

was tripled over other outcomes and the directionality was the same as when it was not weighted. Therefore, we believed that the benefits outweighed the harm. For severe COVID-19, the balance between benefit and harm was undeterminable (Fig. 6).

- Certainty of evidence

The certainty of evidence at each outcome was "low" or "very low" in moderate and "very low" in severe cases. Considering the net effect estimate, the overall certainty of the evidence was determined as "low" in the moderate and "very low" in the severe group.

- Others (tolerability, feasibility)

Baricitinib received approval in Japan for the treatment of COVID-19 in combination with remdesivir. The efficacy of the combined use of the three drugs (baricitinib, remdesivir, and steroid) has not been fully evaluated.

Q9 Should casirivimab/imdevimab be administered to patients with COVID-19?

Recommendation

- We recommend casirivimab/imdevimab administration to patients with mild COVID-19 who do not require oxygen (strong recommendation/moderate certainty of evidence: GRADE 1B)
- We have not made a clear recommendation on casirivimab/imdevimab administration to patients with moderate COVID-19 requiring oxygen/hospitalization and those

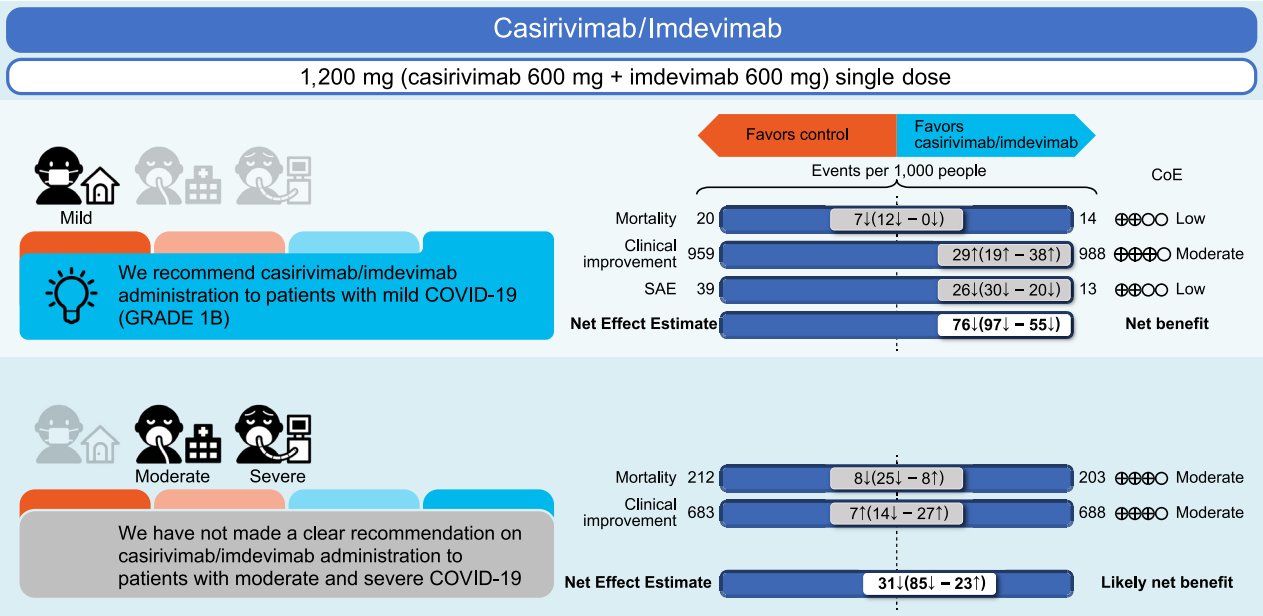

Fig. 7. Recommendations of casirivimab/imdevimab (CQ9). We recommend casirivimab/imdevimab administration to patients with mild COVID-19 and have not made a clear recommendation on casirivimab/imdevimab administration to patients with moderate and severe COVID-19. Net effect estimates of casirivimab/imdevimab in all patients with COVID-19 were calculated with the effects of each outcome, in which the importance of mortality was considered as three times higher than those of other outcomes. Overall imprecisions across outcomes were assessed as "net benefit" in mild COVID-19 and "likely net benefit" in moderate and severe COVID-19, based on the magnitude of point estimate and 95% confidence intervals of the calculated net effect estimates. CoE, certainty of evidence; COVID-19, coronavirus disease 2019; CQ, clinical question; GRADE, Grades of Recommendation, Assessment, Development, and Evaluation; SAE, severe adverse event.

with severe COVID-19 requiring mechanical ventilation/intensive care (no recommendation).

Background Steroids, remdesivir, and baricitinib were determined by clinical trials to be effective. These are all treatments for at least moderate-to-severe diseases that require supplemental oxygen. Casilibimab/imdebimab, an antibody cocktail therapy, was approved in Japan on July 19, 2021, as a drug considered to have an effect in patients with mild COVID-19. However, its effectiveness has not been established, and it was determined that it has a great clinical significance in planning CQ.

Recommendation rationale

■ Balance of benefit and harm

In 5,135 cases of patients with mild COVID-19 in three RCTs,[43–45] all-cause mortality was expected to decrease by 7 per 1,000; clinical improvement was expected to increase by 29 per 1,000; and serious adverse events were expected to decrease by 26 per 1,000. In all outcomes, the intervention group was shown to have benefits. By contrast, in 9,144 cases of moderate/severe patients in one RCT, all-cause mortality was expected to decrease by 8 per 1,000 and clinical improvement was expected to increase by 7 per 1,000, but there were no available data to assess serious adverse events (Fig. 7).

Based on these conclusions, the benefits outweighed harm in patients with mild COVID-19, whereas it was indeterminate in patients with moderate/severe COVID-19.

■ Certainty of evidence

The certainty of evidence in all-cause mortality, clinical improvement, and serious adverse events was "low," "moderate," "low" in patients with mild COVID-19, respectively, and "moderate," "moderate," and no data in patients with moderate/severe COVID-19, respectively. Taking that direction of effectiveness into account, the overall certainty of evidence was determined to be "moderate" for patients with mild COVID-19 and "low" for patients with moderate/severe COVID-19.

RECOMMENDATIONS THAT STOPPED THE UPDATES

IT HAS BEEN 2 years since COVID-19 emerged. Some drugs that were initially expected to be effective against

COVID-19 have been denied, and several other novel drugs have been developed. Considering these clinical situations about COVID-19, the Panel decided to stop the updates of two CQs (hydroxychloroquine [CQ3] and ciclesonide [CQ6]) in this updated version. The unupdated recommendations are as follows[1]:

CQ3 Should hydroxychloroquine be administered to patients with COVID-19? (Last updated on July 11, 2021)

Recommendation

- We recommend against hydroxychloroquine administration to all patients with COVID-19 (strong recommendation/moderate certainty of evidence: GRADE 1B).

CQ6 Should ciclesonide be administered by inhalation to patients with COVID-19? (Last updated on January 27, 2021)

Recommendation

- We have not made a clear recommendation on ciclesonide inhalation to all patients with COVID-19 (no recommendation).

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DISCLOSURE

APPROVAL OF THE research protocol with approval No. and committee Name: N/A.

Informed Consent: N/A.

Registry and the Registration No. of the study/trial: N/A.

Animal Studies: N/A.

Conflict of Interest: The Japanese Society of Intensive Care Medicine and the Japanese Association for Acute Medicine submitted this COI disclosure jointly, based on the same policy issued by the Japanese Association of Medical Sciences. In accordance with these guidelines, organizations are only required to disclose COI that relates to associated companies or for-profit organizations as financial COI. We asked all members to submit their financial and academic COI for the past 3 years (2017, 2018, and 2019), in accordance with the current policy, shown in the Supporting information.

REFERENCES

1 Yamakawa K, Yamamoto R, Ishimaru G *et al*. Japanese Rapid/Living recommendations on drug management for COVID-19. Acute Med. Surg. 2021; 8: e664.
2 Morgan RL, Florez I, Falavigna M *et al*. Development of rapid guidelines: 3. GIN-McMaster Guideline Development Checklist extension for rapid recommendations. Health Res. Policy Syst. 2018; 16: 63.
3 Fitch K, Bernstein SJ, Aguilar MD *et al*. The Rand/UCLA Appropriateness Method User's Manual. Santa Monica, CA: RAND Corporation, 2001.
4 The Ministry of Health, Labor, and Welfare in Japan. Clinical Management of Patients with COVID-19: A Guide for Front-line Healthcare Workers.
5 Sterne JAC, Savović J, Page MJ *et al*. RoB 2: a revised tool for assessing risk of bias in randomised trials. BMJ 2019; 366: l4898.
6 Sterne JA, Hernán MA, Reeves BC *et al*. ROBINS-I: a tool for assessing risk of bias in non-randomised studies of interventions. BMJ 2016; 355: i4919.
7 Alper BS, Oettgen P, Kunnamo I *et al*. Defining certainty of net benefit: a GRADE concept paper. BMJ Open 2019; 9: e027445.
8 Alonso-Coello P, Oxman AD, Moberg J *et al*. GRADE Evidence to Decision (EtD) frameworks: a systematic and transparent approach to making well informed healthcare choices. 2: Clinical practice guidelines. BMJ 2016; 353: i20.
9 Guyatt GH, Alonso-Coello P, Schünemann HJ *et al*. Guideline panels should seldom make good practice statements: guidance from the GRADE Working Group. J. Clin. Epidemiol. 2016; 80: 3–7.
10 MAGIC – MAGIC (Making Grade the Irresistible Choice). New Trustworthy Guidelines, Evidence Summaries and Decision Aids That We can All Use and Share [homepage on the internet]. Magicevidence.org2021 [cited 6 Sept 2021]. Available from: https://magicevidence.org/
11 Lou Y, Liu L, Qiu Y *et al*. Clinical outcomes and plasma concentrations of baloxavir marboxil and favipiravir in COVID-19 patients: an exploratory randomized, controlled trial. Eur. J. Pharm. Sci. 2021; 157: 105631.
12 Ivashchenko AA, Dmitriev KA, Vostokova NV *et al*. AVIFAVIR for treatment of patients with moderate COVID-19: interim results of a Phase II/III multicenter randomized clinical trial. Clin. Infect. Dis. 2021; 73: 531–534.
13 Balykova L, Грановская МВ, Заславская КЯ *et al*. Новые возможности направленной противовирусной терапии COVID-19: результаты многоцентрового клинического

исследования эффективности и безопасности применения препарата Арепливир. Infektsionnye bolezn 2020; 9: 16–29.
14 Ruzhentsova T, Chukhliaev P, Khavkina D *et al*. Phase 3 Trial of Coronavir (Favipiravir) in Patients with Mild to Moderate COVID-19. Available at SSRN: https://ssrn.com/abstract=3696907 or https://doi.org/10.2139/ssrn.3696907
15 Udwadia ZF, Singh P, Barkate H *et al*. Efficacy and safety of favipiravir, an oral RNA-dependent RNA polymerase inhibitor, in mild-to-moderate COVID-19: A randomized, comparative, open-label, multicenter, phase 3 clinical trial. Int. J. Infect. Dis. 2020; 103: 62–71.
16 Beigel JH, Tomashek KM, Dodd LE *et al*. Remdesivir for the treatment of covid-19 - final report. N. Engl. J. Med. 2020; 383: 1813–1826.
17 Wang Y, Zhang D, Du G *et al*. Remdesivir in adults with severe COVID-19: a randomised, double-blind, placebo-controlled, multicentre trial. Lancet 2020; 395: 1569–1578.
18 Spinner CD, Gottlieb RL, Criner GJ *et al*. Effect of remdesivir vs standard care on clinical status at 11 days in patients with moderate COVID-19: a randomized clinical trial. JAMA 2020; 324: 1048–1057.
19 WHO Solidarity trial consortium, Pan H, Pet R, *et al*. Repurposed antiviral drugs for COVID-19 interium WHO SOLIDARITY trial results. N. Eng. J. Med. 2021; 384: 497–511.
20 Horby P, Lim WS, Emberson JR *et al*. Dexamethasone in hospitalized patients with covid-19. N. Eng. J. Med. 2021; 384: 693–704.
21 Tomazini BM, Maia IS, Cavalcanti AB *et al*. Effect of dexamethasone on days alive and ventilator-free in patients with moderate or severe acute respiratory distress syndrome and COVID-19: the CoDEX randomized clinical trial. JAMA 2020; 324: 1307–1316.
22 Angus DC, Derde L, Al-Beidh F *et al*. Effect of hydrocortisone on mortality and organ support in patients with severe COVID-19: the REMAP-CAP COVID-19 corticosteroid domain randomized clinical trial. JAMA 2020; 324: 1317–1329.
23 Dequin PF, Heming N, Meziani F *et al*. Effect of hydrocortisone on 21-day mortality or respiratory support among critically ill patients with COVID-19: a randomized clinical trial. JAMA 2020; 324: 1298–1306.
24 Jeronimo CMP, Farias MEL, Val FFA *et al*. Methylprednisolone as adjunctive therapy for patients hospitalized with COVID-19 (metcovid): a randomised, double-blind, phase IIb, placebo-controlled trial. Clin. Infect. Dis. 2021; 72: e373–e381.
25 Chen CP, Lin YC, Chen TC *et al*. A Multicenter, randomized, open-label, controlled trial to evaluate the efficacy and tolerability of hydroxychloroquine and a retrospective study in adult patients with mild to moderate Coronavirus disease 2019 (COVID-19). PLoS One 2020; 15: e0242763.
26 Tang X, Feng YM, Ni JX *et al*. Early use of corticosteroid may prolong SARSCoV-2 shedding in non-intensive care unit patients with COVID-19 pneumonia: a multicenter, single-blind, randomized control trial. Respiration. Int. Rev. Thoracic Dis. 2021; 100: 116–126.
27 Jamaati H, Hashemian SM, Farzanegan B *et al*. No clinical benefit of high dose corticosteroid administration in patients with COVID-19: A preliminary report of a randomized clinical trial. Eur. J. Pharmacol. 2021; 897: 173947.
28 Edalatifard M, Akhtari M, Salehi M *et al*. Intravenous methylprednisolone pulse as a treatment for hospitalised severe COVID-19 patients: results from a randomized controlled clinical trial. Eur. Respir. J. 2020; 56: 2002808.
29 Rosas I, Bräu N, Waters M *et al*. Tocilizumab in hospitalized patients with COVID-19 pneumonia. N. Engl. J. Med. 2021; 384: 1503–1516.
30 Wang D, Fu B, Peng Z *et al*. Tocilizumab ameliorates the hypoxia in COVID-19 moderate patients with bilateral pulmonary lesions: a randomized, controlled, openlabel, multicenter trial. Front. Med. 2021; 15: 486–494.
31 Stone JH, Frigault MJ, Serling-Boyd NJ *et al*. Efficacy of tocilizumab in patients hospitalized with Covid-19. N. Engl. J. Med. 2020; 383: 2333–2344.
32 Hermine O, Mariette X, Tharaux PL *et al*. Effect of tocilizumab vs usual care in adults hospitalized with COVID-19 and moderate or severe pneumonia: a randomized clinical trial. JAMA Intern. Med. 2021; 181: 32–40.
33 Salvarani C, Dolci G, Massari M *et al*. Effect of tocilizumab vs standard care on clinical worsening in patients hospitalized with COVID-19 pneumonia: a randomized clinical trial. JAMA Intern. Med. 2021; 181: 24–31.
34 Salama C, Han J, Yau L *et al*. Tocilizumab in patients hospitalized with covid-19 pneumonia. N. Engl. J. Med. 2021; 384: 20–30.
35 Veiga VC, Prats JAGG, Farias DLC, Coalition covid-19 Brazil VI Investigators. Effect of tocilizumab on clinical outcomes at 15 days in patients with severe or critical coronavirus disease 2019: randomised controlled trial. BMJ 2021; 372: n84.
36 REMAP-CAP Investigators, Gordon AC, Mouncey PR *et al*. Interleukin-6 receptor antagonists in critically ill patients with covid-19. N. Engl. J. Med. 2021; 22: 1491–1502.
37 RECOVERY Collaborative Group, Horby PW, Pessoa-Amorim G, Peto Leon *et al*. Tocilizumab in patients admitted to hospital with COVID-19 (RECOVERY): preliminary results of a randomised, controlled, open-label, platform trial. Lancet 2021; 397: 1637–1645.
38 Soin AS, Kumar K, Choudhary NS *et al*. Tocilizumab plus standard care versus standard care in patients in India with moderate to severe COVID-19-associated cytokine release syndrome (COVINTOC): an open-label, multicentre, randomised, controlled, phase 3 trial. Lancet Respir. Med. 2021; 9: 511–521.
39 Rutgers A, Westerweel P, van der Holt B *et al*. Timely Administration of Tocilizumab Improves Survival of Hospitalized COVID-19 Patients. Available at SSRN: https://ssrn.com/abstract=3834311 or https://doi.org/10.2139/ssrn.3834311

40 Talaschian M, Akhtari M, Mahmoudi M *et al*. Tocilizumab failed to reduce mortality in severe COVID-19 patients: results from a randomized controlled clinical trial. Res. Square 2021. https://doi.org/10.21203/rs.3.rs-463921/v1
41 Kalil AC, Patterson TF, Mehta AK *et al*. Baricitinib plus remdesivir for hospitalized adults with Covid-19. N. Engl. J. Med. 2021; 384: 795–807.
42 Vincent C, Athimalaipet V, Stephanie *et al*. Baricitinib plus standard of care for hospitalized adults with COVID-19. medRxiv. 2021.04.30.21255934.
43 Horby P, Mafham M, Peto L *et al*. Casirivimab and imdevimab in patients admitted to hospital with COVID-19 (RECOVERY): a randomised, controlled, open-label, platform trial. medRxiv. 2021.06.15.21258542.
44 Weinreich D, Sivapalasingam S, Norton T *et al*. REGN-COV2, a neutralizing antibody cocktail, in outpatients with Covid-19. N. Engl. J. Med. 2021; 384: 238–251.
45 O'Brien MP, Forleo-Neto E, Sarkar N *et al*. Subcutaneous REGEN-COV antibody combination in early SARS-CoV-2 infection. medRxiv. 2021.06.14.21258569.