INVITED REVIEW SERIES

COVID-19 FUNDAMENTAL REVIEWS

Contemporary narrative review of treatment options for COVID-19

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Abstract

The coronavirus disease 2019 (COVID-19) pandemic is ongoing and many drugs have been studied in clinical trials. From a pathophysiological perspective, anti-viral drugs may be more effective in the early stage while immunomodulators may be more effective in severe patients in later stages of infection. While drugs such as lopinavir-ritonavir, hydroxychloroquine and azithromycin have proved to be ineffective in randomized controlled trials, corticosteroids, neutralizing monoclonal antibodies, remdesivir, tocilizumab and baricitinib have been reported to benefit certain groups of patients with COVID-19. In this review, we will present the key clinical evidence and progress in promising COVID-19 therapeutics, as well as summarize the experience and lessons learned from the development of the current therapeutics.

KEYWORDS
baricitinib, convalescent plasma, corticosteroid, COVID-19, neutralizing monoclonal antibody, remdesivir, tocilizumab

INTRODUCTION

At the time of writing, it has been 1 year since the World Health Organization (WHO) announced coronavirus disease 2019 (COVID-19) to be a global pandemic in March 2020. From a pathophysiological perspective, there are two mechanisms in COVID-19, direct viral effect and dysregulated immune response.[1,2] Besides the respiratory tract, severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) was found in multiple other tissues and organs, such as heart and kidneys.[3,4] In the early or mild stage of the disease course, the direct viral effect dominates with viral load peaking about 1 week post symptom onset.[2,5] In the later or severe stage of the disease course, a dysfunctional immune response and hyperinflammation cause further organ

damage.[6,7] Based on this rationale, anti-viral drugs may be more effective in the early stage while immunomodulators may be more effective in severe patients in later stages of infection. Researchers have been trying to find effective treatment for the disease since the report of the first case. While drugs such as lopinavir-ritonavir, hydroxychloroquine and azithromycin have proved to be ineffective in randomized controlled trials (RCTs), corticosteroids, remdesivir, neutralizing monoclonal antibodies, Janus kinase (JAK) inhibitor baricitinib and IL-6 receptor antagonist tocilizumab have been reported to benefit certain groups of COVID-19 patients.[8-11] There are other drugs with potential benefits that are still under investigations.[8–11]

As of 28 March 2021, there have been more than 120 million confirmed COVID-19 cases.[12] Given the huge

number of cases and constant mutations of SARS-CoV-2, SARS-CoV-2 will probably continue to circulate in the future. Having an armamentarium of effective treatment including anti-viral and immunomodulatory drugs will allow us to treat critically ill COVID-19 patients even as many countries race to vaccinate their population and eventually SARS-CoV-2 may become less disruptive to societies when herd immunity is achieved in the medium term.

In this review, we will present the key clinical evidence and progress in promising COVID-19 therapeutics, as well as summarize the experience and lessons learned from the development of the therapeutics. A brief summary of the evidence on COVID-19 therapeutics is presented in Table 1.

ANTI-VIRAL THERAPIES

Remdesivir

Remdesivir is a broad-spectrum anti-RNA-virus nucleoside analogue, which inhibits virus replication by binding to viral RNA-dependent RNA polymerase.[13-16] Before COVID-19, remdesivir was previously tested in clinical trials of Ebola treatment and in laboratory studies for Middle East

respiratory syndrome coronavirus (MERS-CoV) as well as other coronaviruses, but the drug was not submitted for approval by the US Food and Drug Administration (FDA) for these indications.[17-22] Remdesivir showed potent anti-viral activity against SARS-CoV-2 in vitro and in vivo, and was thus considered as a promising repurposed drug at the beginning of the COVID-19 outbreak.[23-25] However, the results of the clinical trials for remdesivir varied.

The results of four RCTs comparing remdesivir with placebo/standard care have been reported.[26-29] All these trials recruited hospitalized patients and used an intravenous regimen of 200 mg remdesivir on the first day and 100 mg remdesivir on the following days (5-day and 10-day regimen vs. control in SIMPLE-2 trial; 10-day regimen in other trials). The first remdesivir trial ($n = 237$) enrolled severe patients and was underpowered because of rapid control of COVID-19 in China.[26] This study found no statistically significant clinical benefits in time to clinical improvement (defined as 2-point reduction on a 6-category ordinal scale; Table 2), 28-day mortality and other clinical outcomes. Nonetheless, in the subgroup analysis for patients admitted within 10 days post symptom onset, individuals treated by remdesivir had numerically faster clinical improvement. The SOLIDARITY trial, with 5475 patients randomized into

TABLE 1 Summary of clinical evidence and potential indications of the therapies discussed in this review

Drug	Evidence summary	Patients most likely to benefit
Remdesivir	A pooled analysis of low/very low certainty suggested remdesivir had no significant clinical benefits for hospitalized COVID-19 patients, such as in term of mortality and risk of mechanical ventilation The subgroup analysis of ACTT-1 trial provided signals that remdesivir may be more effective in accelerating clinical recovery for patients in earlier stage of disease requiring low-flow oxygen	Patients in the early stage of disease Patients who do not need supplementary oxygen Mild/moderate patients Patients on low-flow oxygen Patients on invasive mechanical ventilation are unlikely to benefit from remdesivir
Neutralizing monoclonal antibody	Phase II data suggested efficacy in reducing viral load Phase III data suggested efficacy in reducing risk of hospitalization and death	Outpatients in early stage of disease, especially at high risk of disease progression
Convalescent plasma	RCTs and meta-analysis of RCTs suggested no effects in severe/critically ill patients A single RCT suggested effects in preventing disease progression for older patients within 72 h of symptom onset	High-risk patients in the early stage of disease
Corticosteroid	RCTs and meta-analysis of RCTs suggested effects in reducing mortality in severe patients Subgroup analysis of the RECOVERY trial suggested no clinical benefit in patients who did not need oxygen	Hospitalized severe patients who need oxygen or ventilatory support
Tocilizumab	Meta-analysis of RCTs suggested efficacy in reducing mortality, risk of invasive mechanical ventilation	Hospitalized patients who need oxygen with evidence of systemic inflammation, or within 24 h of receiving ventilation in addition to corticosteroids
Baricitinib	ACTT-2 trial suggested benefits in time to recovery but not in mortality COV-BARRIER trial failed its primary composite endpoint but found benefits in mortality Meta-analysis of the two trials suggested potential benefits in 28-day mortality and risk of invasive mechanical ventilation	Hospitalized COVID-19 patients requiring oxygen therapy, especially patients receiving non-invasive ventilation or high-flow oxygen therapy

Abbreviations: COVID-19, coronavirus disease 2019; RCT, randomized controlled trial.

remdesivir arm and its control, recruited hospitalized COVID-19 patients with a full spectrum of disease severity (about 24%, 67% and 9% of patients receiving no oxygen, supplementary oxygen and mechanical ventilation, respectively).[27] The SOLIDARITY trial found no significant clinical benefits in mortality, initiation of mechanical ventilation and length of hospital stay, regardless of age and respiratory support at trial entry; information on time from disease onset was unavailable in the SOLIDARITY trial.[27]

The other two trials, ACTT-1 trial ($n = 1062$) and SIMPLE-2 trial ($n = 596$), reached the prespecified primary endpoints and had positive results.[28,29] Most of the enrolled patients ($n = 957$, 90.1%) in ACTT-1 trial had severe disease.[28] In ACTT-1 trial, clinical recovery was defined by meeting the criteria of score 1, 2 or 3 on the National Institute of Allergy and Infectious Diseases (NIAID) 8-category ordinal scale (Table 2).[28] In ACTT-1 trial, patients receiving remdesivir had a 5-day shorter median time to clinical recovery (rate ratio 1.29 [95% CI 1.12–1.49]), and lower 14-day mortality (hazard ratio 0.55 [95% CI 0.36–0.83]). However, there was no difference in 28-day mortality (hazard ratio 0.73 [95% CI 0.52–1.03]). In a subgroup analysis for the primary outcome—time to clinical recovery—the rate ratio was the largest among patients receiving low-flow oxygen (score 5 on the 8-category ordinal scale) at randomization (rate ratio 1.45 [95% CI 1.18–1.79]), but there was no statistically significant improvement for patients not requiring oxygen as well as patients receiving non-invasive ventilation or high-flow oxygen (scores 4 and 6 on the 8-category

ordinal scale, respectively). In subgroup analysis, the 28-day mortality was significantly reduced for the low-flow oxygen group (hazard ratio 0.30 [95% CI 0.14–0.64]). Besides, patients randomized within 10 days of symptom onset showed more significant improvement in time to clinical recovery (rate ratio 1.37 [95% CI 1.14–1.64]) than those randomized beyond 10 days after symptom onset (rate ratio 1.20 [95% CI 0.94–1.52]). In other secondary outcomes, remdesivir use was significantly associated with faster time to 1-point and 2-points improvement on the ordinal scale, and shorter length of hospitalization. In addition, remdesivir use was significantly associated with shorter time on oxygen, reduced progression to non-invasive mechanical ventilation or high-flow oxygen and reduced progression to mechanical ventilation.

The SIMPLE-2 trial recruited moderately ill hospitalized COVID-19 patients, who had pneumonia and peripheral oxygen saturation (SpO_2) >94% on room air.[29] About 84% of the recruited patients did not require oxygen therapy at baseline. For the primary outcome—the distribution of clinical status on day 11 assessed by a 7-category ordinal scale (Table 2)—the 5-day remdesivir group had significantly better distribution of clinical status than the standard care group (OR 1.65 [95% CI 1.09–2.48]), while no statistically significant difference was observed between the 10-day remdesivir group and the control group. However, there was no significant difference in Kaplan–Meier estimates of the very low 28-day mortality in these groups (5-day remdesivir group: 1% [95% CI 0.0%–2.6%], $p = 0.43$ vs. standard care

TABLE 2 Frequently used ordinal scales for RCTs mentioned in the main text

	6-category[26,72]	7-category[29]	NIAID 8-category[28,133,134]
1	Discharged or having reached discharge criteria	Death	Not hospitalized and no limitations of activities
2	Hospitalization but not requiring oxygen therapy	Hospitalized, receiving invasive mechanical ventilation or ECMO	Not hospitalized, with limitation of activities, home oxygen requirement or both
3	Hospitalization, requiring oxygen therapy (but not requiring high-flow or non-invasive ventilation)	Hospitalized, receiving non-invasive ventilation or high-flow oxygen devices	Hospitalized, not requiring supplemental oxygen and no longer requiring ongoing medical care (used if hospitalization was extended for infection control or other nonmedical reasons)
4	Hospitalization, requiring non-invasive ventilation or high-flow oxygen therapy	Hospitalized, requiring low-flow supplemental oxygen	Hospitalized, not requiring supplemental oxygen but requiring ongoing medical care
5	Hospitalization, requiring ECMO or invasive mechanical ventilation	Hospitalized, not requiring supplemental oxygen but receiving ongoing medical care	Hospitalized, requiring any supplemental oxygen
6	Death	Hospitalized, requiring neither supplemental oxygen nor ongoing medical care	Hospitalized, requiring non-invasive ventilation or use of high-flow oxygen devices
7	—	Not hospitalized	Hospitalized, receiving invasive mechanical ventilation or ECMO
8	—	—	Death
Examples	Wang et al.,[26] Li et al.[72]	SIMPLE-2[29]	ACTT-1,[28] ACTT-2,[133] COV-BARRIER[134]

Abbreviations: ECMO, extracorporeal membrane oxygenation; NIAID, National Institute of Allergy and Infectious Diseases; RCT, randomized controlled trial.

group; 10-day remdesivir group: 2% [95% CI 0.0%–3.6%], $p = 0.72$ vs. standard care group; standard care group: 2% [95% CI 0.1%–4.1%]). Remdesivir also did not confer significant clinical benefits in other outcomes such as time to recovery and time to discontinuation of oxygen support. An additional trial (SIMPLE-1 trial) comparing 5- and 10-day remdesivir without placebo/standard control group found no significant difference in clinical effects in these two regimens for severe COVID-19 patients not requiring mechanical ventilation.[30]

The difference in the results of these RCTs may stem from factors such as sample size, definitions of disease severity, enrolment criteria, locations where the trials were conducted, different protocols of standard care and definitions of the outcomes. Mortality is an outcome less likely to be influenced by designs of RCTs. Though a positive signal was indicated in the subgroup analysis of ACTT-1 trial, compared with placebo/standard care, none of the previously mentioned trials found significant clinical benefits of remdesivir on overall 28-day mortality for hospitalized patients as a whole. The WHO living network meta-analysis pooling the results of these RCTs showed remdesivir had no significant clinical benefits on mortality, need for mechanical ventilation, duration of hospital stay and time to symptom resolution/clinical improvement.[8] Given the heterogeneity of the RCTs, the certainty of the evidence in most outcomes was rated low to very low. Informed by the living network meta-analysis and considering costs and resources, the WHO living drug treatment guideline conditionally suggested against using remdesivir for hospitalized COVID-19 patients, regardless of disease severity.[8,31] The WHO guideline panel highlighted the uncertainty of current evidence and emphasized the importance of further studies.[8,31] Some other guidelines, such as the Infectious Diseases Society of America (IDSA), the National Institutes of Health (NIH) and the American College of Physicians (ACP), recommended using remdesivir in certain groups of COVID-19 patients.[32–34] The difference may be due to varying perspectives of considering the evidence as well as methods for pooling the data. For example, the NIH guideline recommended using remdesivir in hospitalized COVID-19 patients requiring supplementary oxygen but not on mechanical ventilation.[34] The NIH guideline panel mainly considered the subgroup analysis of ACTT-1, which provided signals that remdesivir may be effective in accelerating clinical recovery and reducing mortality for patients in their earlier stage of disease requiring low-flow oxygen.[34]

Another factor that may influence the efficacy of remdesivir is the timing of using the drug. Among the four trials comparing remdesivir with placebo/standard care, three trials reported median time from symptom onset to randomization, ranging from 8 to 11 days.[26,28,29] In the SIMPLE-2 trial targeting moderately ill patients, the median time from symptom onset to the first dose of remdesivir was 8 days in two remdesivir groups and 9 days in the control group.[29] For anti-viral drugs, earlier use may contribute to better effects. The trial to evaluate the safety and efficacy of remdesivir in an outpatient setting for patients with COVID-19 within 7 days of symptom onset and who have at least one risk factor for disease progression is ongoing.[35] The trial may provide further evidence for the timing of drug use and population likely to benefit from remdesivir.

In conclusion, current RCTs of remdesivir focused on hospitalized patients with varying disease severity, and a pooled analysis of low/very low certainty suggested remdesivir had no significant clinical benefits for hospitalized COVID-19 patients in clinical outcomes. However, some individual studies provided positive signals among patients in the early disease stage requiring low-flow oxygen. The interpretation of the evidence may vary from different perspectives.

Neutralizing monoclonal antibodies

Neutralizing monoclonal antibodies are a class of immune molecules that can specifically recognize and bind to certain antigens.[36] Neutralizing monoclonal antibodies can be rapidly derived and massively produced, so they are considered as a promising candidate therapy against emerging infectious diseases and have been successfully used in Ebola.[18,37] Angiotensin-converting enzyme 2 (ACE2) is the receptor for SARS-CoV-2 and the binding affinity of SARS-CoV-2 to ACE2 is much higher than SARS-CoV.[38,39] SARS-CoV-2 neutralizing monoclonal antibodies mainly target the spike protein (S protein) of SARS-CoV-2, which prevents the recognition and binding between SARS-CoV-2 and human ACE2 receptor, and prevents viral cell entry.[37,40] Several neutralizing monoclonal antibodies were issued Emergency Use Authorization (EUA) by the US FDA, including bamlanivimab alone (revoked on 16 April 2021), bamlanivimab with etesevimab, and casirivimab with imdevimab.[41–43] The information of relevant RCTs is presented in Table 3.

Bamlanivimab and etesevimab bind to different but overlapping epitopes in SARS-CoV-2 receptor-binding domain (RBD).[43] The BLAZE-1 trial is a double-blind phase II/III RCT on the efficacy and safety of bamlanivimab monotherapy or combined with etesevimab for patients with mild to moderate COVID-19 in the outpatient setting.[41,44,45] In the phase II part ($n = 577$), eligible patients were recruited within 3 days of the first positive SARS-CoV-2 antigen or PCR test. Key exclusion criteria included (1) $SpO_2 \leq 93\%$ on room air or partial pressure of arterial oxygen/fraction of inspired oxygen (PaO_2/FiO_2) < 300 mm Hg or respiratory rate ≥ 30/min or heart rate ≥ 125 bpm or receiving mechanical ventilation and (2) having positive SARS-CoV-2 serology test results. The patients were randomized into three bamlanivimab monotherapy groups of different doses (700, 2800 and 7000 mg), a bamlanivimab (2800 mg) and etesevimab (2800 mg) combination therapy group and a placebo group. Patients were first randomized into the bamlanivimab monotherapy groups or the placebo group (17 June 2020–21 August

TABLE 3 Characteristics of RCTs on the efficacy and safety of neutralizing monoclonal antibodies for COVID-19

RCT	Methods	Baseline characteristics	Primary outcome	Other important outcomes
BLAZE-1 Phase II[41,44,45] NCT04427501	**Double-blind placebo-controlled, phase II randomized trial** **Key inclusion criteria:** (1) Age ≥ 18 years (2) Have one or more mild or moderate COVID-19 symptoms: fever, cough, sore throat, malaise, headache, muscle pain, gastrointestinal symptoms or shortness of breath with exertion (3) Mild to moderate COVID-19 in outpatient setting (4) Within 3 days of the sample collection for first positive SARS-CoV-2 laboratory tests before the infusion **Key exclusion criteria:** (1) SpO$_2$ ≤ 93% on room air or PaO$_2$/FiO$_2$ < 300 mm Hg or respiratory rate ≥ 30/min or heart rate ≥ 125 bpm (2) Require mechanical ventilation or anticipated impending need for mechanical ventilation (3) having positive SARS-CoV-2 serology test results **Intervention and control:** (1) Three bamlanivimab monotherapy groups of different doses (700 mg [n = 101], 2800 mg [n = 107], 7000 mg [n = 101]) (2) A bamlanivimab (2800 mg) and etesevimab (2800 mg) combination therapy group (n = 112) (3) A placebo group (n = 156)	**Interim analysis:** **Female:** 171/309 (55.3%) versus 78/143 (54.5%) **Age (years):** 45 (18–86) versus 46 (18–77) *65 years or older:* 33/309 (10.7%) versus 20/143 (14.0%) **Having risk factors for severe COVID-19:** 215/309 (69.6%) versus 95/143 (66.4%) **Disease status:** *Mild:* 232/309 (75.1%) versus 113/143 (79.0%) *Moderate:* 77/309 (24.9%) versus 30/143 (21.0%) (data are bamlanivimab monotherapy groups [combined] vs. placebo) **Final analysis:** **Female:** 63/101 (62.4%) versus 51/107 (47.7%) versus 58/101 (57.4%) versus 58/112 (51.8%) versus 85/156 (54.5) **Age (years):** 39 (31–58) versus 45 (31–56) versus 46 (34–55) versus 44 (30–60) versus 46 (35–57) *65 years or older:* 11/101 (10.9%) versus 8/107 (7.5%) versus 14/101 (13.9%) versus 13/112 (11.6%) versus 23/156 (14.7%) **Having risk factors for severe COVID-19:** 74/101 (73.3%) versus 78/107 (72.9%) versus 63/101 (62.4%) versus 67/112 (59.8%) versus 105/156 (67.3%) **Disease status:** *Mild:* 83/101 (82.2%) versus 79/107 (73.8%) versus 70/101 (69.3%) versus 92/112 (82.1%) versus 125/156 (80.1%) *Moderate:* 18/101 (17.8%) versus 28/107 (26.2%) versus 31/101 (30.7%) versus 20/112 (17.9%) versus 31/156 (19.9%) (data are 700 mg bamlanivimab vs. 2800 mg bamlanivimab vs. 7000 mg bamlanivimab vs. 2800 mg bamlanivimab and 2800 mg etesevimab vs. placebo)	**Interim analysis:** (containing only three bamlanivimab monotherapy groups and placebo group) **The change from baseline in the viral load at day 11** The mean log change in 2800 mg bamlanivimab monotherapy group was significantly greater than the placebo group (difference −0.53 [95% CI −0.98 to −0.08]). The mean log change in 700 mg bamlanivimab monotherapy group (difference −0.20 [95% CI −0.66 to 0.25]) and 7000 mg bamlanivimab monotherapy group (difference 0.09 [95% CI −0.37 to 0.55]) was not significantly different from the placebo group **Final analysis:** (containing all the five groups) **The change from baseline in the viral load at day 11** The mean log change in 2800 mg bamlanivimab and 2800 mg etesevimab combination therapy group was significantly greater than the placebo group (difference −0.57 [95% CI −1.00 to −0.14]) The mean log change in 700 mg bamlanivimab monotherapy group (difference 0.09 [95% CI −0.35 to 0.52]), 2800 mg bamlanivimab monotherapy group (difference −0.27 [95% CI −0.71 to 0.16]) and 7000 mg bamlanivimab monotherapy group (difference 0.31 [95% CI −0.13 to 0.76]) was not significantly different from the placebo group	**Interim analysis:** The COVID-19-related hospitalization and emergency department visit was 1.6% (5/309) in the bamlanivimab group compared to 6.3% (9/143) in the placebo group: 700 mg bamlanivimab: 1/101 (1.0%); 2800 mg bamlanivimab: 2/107 (1.9%); 7000 mg bamlanivimab: 2/101 (2.0%); placebo: 9/143 (6.3%) **Final analysis:** The COVID-19-related hospitalization and emergency department visit were significantly lower in 2800 mg bamlanivimab and 2800 mg etesevimab combination therapy group (−4.9% [95% CI −8.9% to −0.8%]) and 700 mg bamlanivimab group (−4.8% [95% CI −8.9% to −0.6%]) Other groups versus placebo group: 2800 mg bamlanivimab: (−3.9% [95% CI −8.4% to 0.6%]); 7000 mg bamlanivimab: (−3.8% [95% CI −8.3% to 0.8%])

TABLE 3 (Continued)

RCT	Methods	Baseline characteristics	Primary outcome	Other important outcomes
BLAZE-1 Phase III[43,47,48] NCT04427501	**Double-blind placebo-controlled, phase III randomized trial** **Population:** Aged 12 and older, mild to moderate, *high risk* for progressing to severe COVID-19 and/or hospitalization **Intervention and control:** **The first cohort:** bamlanivimab 2800 mg and etesevimab 2800 mg ($n = 518$) versus placebo ($n = 517$) **The second cohort:** bamlanivimab 700 mg and etesevimab 1400 mg ($n = 511$) versus placebo ($n = 258$)	**The first cohort: Female:** 52% **Age (years):** 56 (median) *65 years or older:* 31% **Disease status:** *Mild:* 77% *Moderate:* 23% (no specific data in each group were presented in the FDA fact sheet or press release) **The second cohort:** No baseline data were presented in the press release	**The first cohort: The proportion of subjects with COVID-19-related hospitalization (defined as ≥24 h of acute care) or death by any cause by day 29:** Events occurred in 36/517 (7%) in placebo group, compared to 11/518 (2%) in bamlanivimab 2800 mg and etesevimab 2800 mg combination therapy group ($p < 0.001$) Ten deaths occurred in placebo group, compared to no death in 2800 mg bamlanivimab and 2800 mg etesevimab combination therapy group ($p < 0.001$) **The second cohort: The proportion of subjects with COVID-19-related hospitalization (defined as ≥ 24 h of acute care) or death by any cause by day 29** A significant decrease in the risk of hospitalization or death (0.78% vs. 5.8%, $p < 0.0001$)	Key secondary outcomes (no specific data were presented): Change from baseline to day 7 in SARS-CoV-2 viral load Persistently high SARS-CoV-2 viral load on day 7 Time to sustained symptom resolution COVID-related hospitalization, emergency department visit or death from any cause from baseline by day 29
ACTIV-3 Phase III[49] NCT04501978	**Double-blind placebo-controlled, phase III randomized trial** **Population:** Hospitalized COVID-19 patients, without end-organ failure and within 12 days of symptom onset **Intervention and control:** Bamlanivimab (7000 mg) ($n = 163$) versus placebo group ($n = 151$) in 1:1 ratio	**Female:** 66/163 (40%) versus 71/151 (47%) **Age (years):** 63 (50–72) versus 59 (48–71) **BMI (kg/m²):** ≥30: 81/163 (50%) versus 83/151 (55%) ≥40: 20/163 (12%) versus 22/151 (15%) **Oxygen requirement:** *No supplementary oxygen:* 44/163 (27%) versus 42/151 (28%) *Supplementary oxygen (<4 L/min):* 60/163 (37%) versus 57/151 (38%) *Supplementary oxygen (≥4 L/min):* 29/163 (18%) versus 34/151 (23%) *Non-invasive ventilation or high-flow device:* 30/163 (18%) versus 18/151 (12%) (data are 7000 mg bamlanivimab monotherapy group vs. placebo)	**A sustained recovery during a 90-day period and two ordinal outcomes that are measured at day 5** No significant benefits were found in these outcomes The rate ratio for a sustained recovery (until 26 October 2020) was 1.06 (95% CI 0.77–1.47) The OR for pulmonary ordinal outcome at day 5 was 0.85 (95% CI 0.56–1.29) The OR for pulmonary plus ordinal outcome at day 5 was 0.87 (95% CI 0.57–1.31)	Discharge from hospital (until 26 October 2020) Rate ratio 0.97 (95% CI 0.78–1.20)

TABLE 3 (Continued)

RCT	Methods	Baseline characteristics	Primary outcome	Other important outcomes
Casirivimab plus imdevimab Phase I/II[42,52] NCT04425629	**Double-blind placebo-controlled, phase I/II randomized trial** **Population:** Mild to moderate COVID-19 patients in outpatient setting with symptom onset ≤7 days **Intervention and control:** 2400 mg casirivimab plus imdevimab (n = 266) versus 8000 mg casirivimab plus imdevimab (n = 267) versus placebo (n = 266) in 1:1:1 ratio	**Female:** 53% **Age (years):** 42 (median) *65 years or older:* 7% (no specific data in each group were presented in the FDA fact sheet or press release)	**The time-weighted average change in viral load from baseline (day 1) through day 7** The difference (combined casirivimab plus imdevimab dose groups vs placebo group) was −0.36 $\log_{10}$ copies/mL ($p < 0.0001$). The largest effects were observed in patients with high viral load (−0.78 $\log_{10}$ copies/mL) and who were seronegative (−0.69 $\log_{10}$ copies/mL) at baseline	**The percentage of patients with at least one COVID-19-related medically attended visit through day 29** 2.8% for combined casirivimab plus imdevimab dose groups versus 6.5% for placebo
Casirivimab plus imdevimab Phase III[42,53,54] NCT04425629	**Double-blind placebo-control, phase III randomized trial** **Population:** Mild to moderate COVID-19 patients in outpatient setting with symptom onset ≤7 days Criteria for mFAS: patients aged 18 years and older, at *high risk* (≥1 risk factor) of severe COVID-19 (all population n = 4567; mFAS n = 4180) **Intervention and control:** Part 1: 1200 mg casirivimab plus imdevimab (n = 736) versus placebo (n = 748) Part 2: 2400 mg casirivimab plus imdevimab (n = 1355) versus placebo (n = 1341)	**Female:** 2400 mg versus placebo: 51.6% versus 52.8%; 1200 mg versus placebo: 50.5% versus 52.9% **Age (years):** 2400 mg versus placebo: 50 (39–60) versus 50 (37–58) 1200 mg versus placebo: 48.5 (37–57.5) versus 48 (35–57) **Median days of symptoms prior to baseline:** 2400 mg versus placebo: 3 (2–5) versus 3 (2–5) days 1200 mg versus placebo: 3 (2–4) versus 3 (2–5) days	**Proportion of patients with ≥1 COVID-19-related hospitalization or all-cause death through day 29 (in mFAS)** 2400 mg versus placebo: 18/1355 (1.3%) versus 62/1341 (4.6%), 71.3% (95% CI 51.7%–82.9%) reduction, $p < 0.0001$ 1200 mg versus placebo: 7/736 (1.0%) versus 24/748 (3.2%), 70.4% (95% CI 31.6%–87.1%) reduction, $p = 0.0024$	**Time to COVID-19 symptoms resolution** 2400 mg versus placebo: median 10 versus 14 days, 4 days reduction, $p < 0.0001$ 1200 mg versus placebo: median 10 versus 14 days, 4 days reduction, $p < 0.0001$

Note: Data are in n/N (%), median (IQR) or effect size (95% CI). The phase III data of BLAZE-1, as well as the final analysis phase II data and phase III data of casirivimab plus imdevimab were obtained from the FDA fact sheet and press release, so the data were incomplete and might be subjected to changes in later updates of these documents or in formal publications of the studies.

Abbreviations: COVID-19, coronavirus disease 2019; FDA, Food and Drug Administration; mFAS, modified Full Analysis Set; PaO_2/FiO_2, partial pressure of arterial oxygen/fraction of inspired oxygen; RCT, randomized controlled trial; SARS-CoV-2, severe acute respiratory syndrome coronavirus 2; SpO_2, peripheral oxygen saturation.

2020), and were then randomized into the bamlanivimab and etesevimab combination group or the placebo group (22 August 2020–3 September 2020). The interim analysis of the phase II part, which contained only the three bamlanivimab monotherapy groups and placebo group, showed that 2800 mg bamlanivimab monotherapy was associated with significantly accelerated decline of viral load in nasopharyngeal swab at day 11 (difference in mean log change −0.53 [95% CI −0.98 to −0.08]).[45] The COVID-19-related hospitalization and emergency department visit was 1.6% (5/309) in the pooled bamlanivimab group (1.0% in 700 mg group, 1.9% in 2800 mg group and 2.0% in 700 mg group) versus 6.3% (9/143) in the placebo group. For patients at high risk of disease progression, the hospitalization rate was 4.2% (pooled bamlanivimab group) versus 14.6% (placebo group). However, in the final analysis of the phase II part, which contained all five groups, only the bamlanivimab and etesevimab combination therapy group was associated with significant accelerated viral load decline compared with the placebo group (difference in mean log change −0.57 [95% CI −1.00 to −0.14]). The COVID-19-related hospitalization and emergency department visit were significantly lower in the combination therapy group (−4.9% [95% CI −8.9% to −0.8%]) and 700 mg bamlanivimab monotherapy group (−4.8% [95% CI −8.9% to −0.6%]), but not in the 2800 mg bamlanivimab monotherapy group.[44] The reason why the significant clinical benefits of 2800 mg bamlanivimab monotherapy in accelerating viral load decline in the interim analysis were not confirmed in the final analysis may include the incomplete follow-up of the placebo group in the interim analysis, as well as a higher number of placebo group patients in the final analysis.[46]

The phase III data of the BLAZE-1 trial was presented in a press release and FDA fact sheet, which has not been peer-reviewed.[43,47,48] The phase III part of BLAZE-1 trial enrolled mild to moderate COVID-19 patients at high risk of disease progression, defined as having high BMI, older age or underlying diseases, in the outpatient setting.[43,47,48] In the first cohort, patients were randomized to receive 2800 mg bamlanivimab and 2800 mg etesevimab combination therapy (n = 518) or placebo (n = 517).[43,47] The trial met its primary endpoint as the combination therapy resulted in about 70% reduction in COVID-19-related hospitalization (≥24 h of acute care) or all-cause death by day 29 (2% vs. 7%, p < 0.001). Besides, the combination therapy also resulted in significantly faster viral load decline. The second cohort of phase III BLAZE-1 trial enrolled 769 patients with the same eligibility criteria to receive 700 mg bamlanivimab and 1400 mg etesevimab combination therapy or placebo in a 2:1 ratio.[48] There was also a significant decrease in the risk of hospitalization or death (0.78% vs. 5.8%, p < 0.0001).[48] The virological and pharmacodynamic/pharmacokinetic data in the BLAZE-4 trial, an ongoing phase II trial exploring the effects of different doses of monoclonal antibody combination therapy, also showed similar effects of 700 mg bamlanivimab/1400 mg etesevimab and 2800 mg

bamlanivimab/2800 mg etesevimab.[43,47] In contrast, the ACTIV-3 trial is a double-blind RCT enrolling hospitalized COVID-19 patients within 12 days of symptom onset.[49] The patients were randomized into the 7000 mg bamlanivimab group or placebo group. The trial did not find favourable effects of bamlanivimab in terms of pulmonary ordinal outcomes at day 5, time to sustained recovery and hospital discharge.

Casirivimab plus imdevimab is an antibody cocktail therapy that binds to different sites in SARS-CoV-2 S protein.[50,51] A phase I/II double-blind RCT enrolled mild to moderate high-risk COVID-19 patients in 1:1:1 ratio to receive 2400 mg casirivimab plus imdevimab (1200 mg casirivimab and 1200 mg imdevimab, n = 266), 8000 mg casirivimab plus imdevimab (4000 mg casirivimab and 4000 mg imdevimab, n = 267) or placebo (n = 266) in the outpatient setting.[42,52] Compared with placebo, the pooled antibody therapy resulted in a significantly faster viral load decline in nasopharyngeal swab. The largest benefits were observed in seronegative patients or patients with a high viral load at baseline.[42,52] Lower proportion of medically attended visits was also observed in the pooled antibody therapy group (2.8% vs. 6.5%), and greater benefits were observed among patients with high risk for disease progression (3% vs. 9%). Besides, the efficacy and safety of 2400 and 8000 mg dose were similar in the phase II trial. A phase III trial enrolling more than 4000 participants found that, for high-risk COVID-19 outpatients, both 1200 mg casirivimab plus imdevimab (600 mg casirivimab and 600 mg imdevimab, 1.0% vs. 3.2%, p = 0.0024) and 2400 mg dose (1200 mg casirivimab and 1200 mg imdevimab, 1.3% vs. 4.6%, p < 0.0001) significantly reduced COVID-19-related hospitalization or death (composite outcome).[53,54]

There were several characteristics of the neutralizing monoclonal antibody trials. Current trials target outpatients within short duration of symptom onset, especially those with high risk of disease progression. The phase II trials were dose-ranging and explored the best dosing for phase III trials. The phase II trials mainly explored anti-viral effects (e.g., change in upper respiratory tract viral load) and might set secondary outcomes related to hospitalization/medical visits. As anti-viral effects do not necessarily translate into clinically important benefits (hospitalization, death, etc.), large-scale phase III trials are needed to validate the clinical benefits in reducing hospitalization and/or death. Phase III trials and the subgroup analyses of phase II trials found larger clinical benefits in high-risk mild/moderate COVID-19 patients. Current data did not find clinical benefits of monoclonal antibodies in hospitalized patients. Therefore, the neutralizing monoclonal antibodies were only approved for EUA in mild to moderate COVID-19 patients at high risk of disease progression.[41–43] The EUA in these neutralizing monoclonal antibodies did not include hospitalized patients or patients requiring oxygen therapy for COVID-19.[41–43]

Dosing is an important factor in neutralizing monoclonal antibodies. For safety and economic considerations, the best

dose should be the lowest effective dose. For example, the EUA dose for bamlanivimab and etesevimab combination therapy was 700 mg bamlanivimab and 1400 mg etesevimab. At the time when EUA was issued, there were only phase III data for 2800/2800 mg combination, and FDA considered the data from in vitro and pharmacokinetic/pharmacodynamic studies, as well as the phase II data in BLAZE-4 trial.[43] The results of the second phase III cohort in BLAZE-1 trial validated the similarity of the two doses.[48]

Another important issue is SARS-CoV-2 variants. The neutralizing antibody escape of some SARS-CoV-2 variants may occur under selective pressure of neutralizing monoclonal antibody therapies.[55,56] Moreover, neutralizing monoclonal antibody therapies may have reduced effects on some naturally existing SARS-CoV-2 variants.[57] For example, while B.1.1.7 variant normally did not influence antibody neutralizing ability, B.1.351 and P.1 variants were partially resistant to casirivimab and completely resistant to bamlanivimab in vitro.[41,57–59] In light of the markedly increasing spread of SARS-CoV-2 variants potentially resistant to bamlanivimab, the US government has halted distribution of bamlanivimab monotherapy on 24 March 2021, and the US FDA retracted the EUA of bamlanivimab monotherapy on 16 April 2021.[60,61] The combination use of two or more potent monoclonal antibodies targeting non-competing sites on SARS-CoV-2 may reduce the possibility of virus resistance and mutational escape.[50,56,62] Bamlanivimab and etesevimab had a reduced neutralizing ability for B.1.351 and P.1 variants, and remained active against B.1.1.7, B.1.427/B.1.429 and B.1.526 variants.[43] Casirivimab plus imdevimab combination therapy retained neutralization ability on the above-mentioned variants.[42] It is worth noting that the neutralizing effects of monoclonal antibodies on mutant strains are from in vitro studies, and it is still unclear how the changes of in vitro neutralizing activity will influence therapeutic effects in clinical settings.

Current data suggested the efficacy of several neutralizing monoclonal antibody therapies for reducing viral load and preventing hospitalization and/or death among outpatients at high risk of disease progression. However, it should be noted that much of the data have not been peer reviewed. Besides, given the rapid rise of SARS-CoV-2 mutants, neutralizing antibody monotherapy may induce further mutational escape. As SARS-CoV-2 variants are ever changing, it is important to monitor the variant types and their resistance to antibody therapies. Future research should focus on the development of combination antibody therapies.

Convalescent plasma

Convalescent plasma from recovered COVID-19 patients is postulated to have neutralizing antibodies and provide passive immunity.[63] Convalescent plasma was used in previous outbreak of other emerging infectious diseases, such as influenza, Ebola, SARS and MERS.[64,65] Given the theoretical effects, rapid availability and previous experience in

treatment of other infectious diseases, convalescent plasma has been used to treat COVID-19 since the beginning of the outbreak. There have been numerous observational studies as well as 10 RCTs[66–75] comparing the effects and safety of convalescent plasma and placebo/standard care.

The observational studies on convalescent plasma provided positive signals. In a prospective cohort study including 136 severe/critically ill COVID-19 patients treated by convalescent plasma and 251 matched controls, convalescent plasma treatment was associated with significantly reduced 28-day mortality for patients receiving the treatment within 72 h of hospital admission and with high-titer anti-RBD antibody in convalescent plasma.[76] However, the analysis restricted to patients receiving convalescent plasma after 72 h did not show significant mortality benefits.[76] A meta-analysis of 12 observational studies found statistically significant benefit in mortality (OR 0.66 [95% CI 0.50–0.86], $p = 0.002$), and consistent benefits in severe (OR 0.63 [95% CI 0.40–1.00], $p = 0.049$) and critically ill subgroups (OR 0.24 [95% CI 0.06–0.92], $p = 0.037$).[77] However, the results of RCTs have not found consistent mortality benefits. The first published RCT enrolled 103 severe/critically ill COVID-19 patients and found no clinical benefits in 28-day mortality, time to clinical improvement (defined by discharge or 2-point reduction on a 6-category ordinal scale; Table 2) and time from randomization to discharge.[72] A meta-analysis of 10 RCTs on convalescent plasma did not find significant clinical benefits in mortality (risk ratio 1.02 [95% CI 0.92–1.12]), length of hospital stay, need for mechanical ventilation and other clinically important outcomes.[78]

Besides the inherent defects of observational studies, such as poorer control of confounders, there are some other factors which may explain the negative results of RCTs, including the titers of antibodies in the convalescent plasma, the baseline antibody level in recruited patients and the patients' disease severity and stage.[71] Patients were less likely to benefit from convalescent plasma if they received convalescent plasma of low-titer antibodies, already developed antibody, were severe and in later stages of the disease when dysregulated immune response dominated. With sufficient sample size ($n = 11,558$) and strict quality control of convalescent plasma, the RECOVERY trial partially clarified the issue.[71] In the trial, convalescent plasma was not associated with lower 28-day mortality (rate ratio 1.00 [95% CI 0.93–1.07]), higher proportion of patients discharge within 28 days (rate ratio 0.99 [95% CI 0.94–1.03]) and lower risk of disease progression defined by a composite outcome of receiving invasive mechanical ventilation or death (risk ratio 0.99 [95% CI 0.93–1.05]). In the trial, all donors had high anti-spike IgG levels and the convalescent plasma was prepared in a uniform process, which ensured the quality and antibody titer of the plasma. Besides, the prespecified subgroup analysis on baseline SARS-CoV-2 IgG level (seropositive/seronegative) showed that, among seronegative patients, there was no significant mortality benefit (rate ratio 0.96 [95% CI 0.85–1.07]), or benefit in proportion of discharge

within 28 days (rate ratio 1.08 [95% CI 0.99–1.18]), but there were significant benefits in risk of disease progression (risk ratio 0.90 [95% CI 0.83–0.98]). However, there was a 10% difference in the proportion of patients with missing antibody test result between the convalescent plasma (12%) and control groups (22%). Also, seropositive patients tended to be younger, as well as have fewer women, longer time from symptom onset to randomization and higher level of respiratory support at baseline. Therefore, the subgroup analysis can only be considered as a positive signal but not definitive.

As for the influence of disease stage and severity on convalescent plasma, the prespecified subgroup analysis in the RECOVERY trial on different levels of respiratory support at baseline did not find statistically significant benefits in any subgroups, but a trend was observed that patients receiving lower level of respiratory support at baseline tended to have numerically better point estimates of the outcomes.[71] The post hoc subgroup analysis on the time from symptom onset to randomization did not find any statistically significant benefits in the subgroups, but patients randomized within 4 days of symptom onset had a numerically lower point estimate of rate ratio in mortality (rate ratio 0.91 [95% CI 0.77–1.07]). One of the potential reasons why no statistically significant clinical benefits were found in the milder subgroup may be that the patients were still comparatively severe in the RECOVERY trial. The subgroup of patients who did not require oxygen at baseline still had a 28-day mortality of 13% (convalescent plasma group) versus 15% (control group). Besides, the subgroup of patients who were within 4 days since symptom onset at baseline had a 28-day mortality of 29% versus 31%. By contrast, an RCT enrolling 160 mild older (mean age: 76.4 years in convalescent plasma group and 77.9 years in placebo group) patients within 72 h of symptom onset found that high-titer convalescent plasma could prevent the development of severe disease.[73] In this RCT, the overall mortality of participants was as low as 3.75%. Therefore, patients with shorter time of disease onset were more likely to benefit from convalescent plasma.

Similar to neutralizing monoclonal antibody therapy, the effects of convalescent plasma may be reduced in SARS-CoV-2 variants. The convalescent plasma from patients infected with original SARS-CoV-2 strains showed modest or no reduction of neutralizing ability for B.1.1.7 variant in two in vitro experiments.[79,80] However, B.1.351 showed marked resistance to convalescent plasma of early strains.[80,81] The clinical data of convalescent plasma for SARS-CoV-2 variants were scarce. As B.1.1.7 variant began to rapidly spread in the UK during December, the RECOVERY trial did an exploratory subgroup analysis, which divided patients by enrolment before or after 1 December 2020, and did not find difference in mortality in any of the subgroups.[71] However, not all patients received sequencing to identify SARS-CoV-2 variant type in the study, so further clinical data were needed.[71] As the production of convalescent plasma was dynamic, the plasma from patients infected with SARS-CoV-2 variants will be obtained as the variants

spread. It may be rational to monitor the types of SARS-CoV-2 variants of plasma donor to optimize the use of convalescent plasma. However, given the limited resources of sequencing, the surveillance may not be feasible for all donors. A specific strategy, such as random sampling, should be identified by the convalescent plasma production teams.

Current data suggest that the patients who are likely to benefit from convalescent plasma therapy are those who are in a very early stage of disease and have mild/moderate disease. As most previous RCTs enrolled severe/critical patients, or did not have enough sample size, further exploration in the above-mentioned population should be conducted. The rescue therapy of convalescent plasma for severe/critically ill is unlikely to bring clinical benefits. As the wide use of convalescent plasma is related to both the welfare of donors and recipients, the optimal indications and impact of SARS-CoV-2 variants should be carefully considered in RCTs and clinical use.[63]

IMMUNOMODULATORY THERAPIES

Systemic corticosteroid

Corticosteroids are a class of potent anti-inflammatory drugs widely used in clinical practice for various diseases.[82] Several meta-analyses of RCTs supported corticosteroids for patients with severe community-acquired pneumonia.[83–85] In SARS and MERS outbreak, the use of corticosteroids was frequent. There was no RCT evidence for SARS and MERS, and observational studies provided conflicting results.[86–88] Corticosteroids may curb the overwhelming inflammation in severe COVID-19 patients but may also induce immunosuppression and further aggravate the infection. Besides, the long-term and high-dose use of corticosteroids may bring adverse events such as avascular necrosis and hyperglycaemia.[89] Physicians tended to use corticosteroids for the most severe patients, often complicated with acute respiratory distress syndrome (ARDS) and/or sepsis.[90,91]

Whether corticosteroids should be used for COVID-19 have been heatedly discussed since the beginning of the outbreak.[89,92] The RECOVERY trial shed light on the question.[93] The RECOVERY trial randomized hospitalized patients to receive 6 mg dexamethasone for 10 days or until hospital discharge plus standard care ($n = 2104$) or standard care alone ($n = 4321$).[93] Dexamethasone was associated with 17% reduction of 28-day mortality (rate ratio 0.83 [95% CI 0.75–0.93]). For patients not receiving invasive mechanical ventilation at baseline, dexamethasone reduced the risk of invasive mechanical ventilation by 21% (risk ratio 0.79 [95% CI 0.64–0.97]). Subgroup analysis showed that the efficacy of dexamethasone on mortality was different among patients receiving invasive mechanical ventilation (rate ratio 0.64 [95% CI 0.51–0.81]), receiving supplementary oxygen (rate ratio 0.82 [95% CI 0.72–0.94]) or receiving no oxygen (rate ratio 1.19 [95% CI 0.92–1.55]). Hospitalized

patients not requiring oxygen did not benefit from corticosteroid therapy. The clinical benefits of corticosteroids shown in the RECOVERY trial were further validated by a meta-analysis including seven RCTs, which suggested corticosteroid treatment resulted in a marked reduction of 28-day mortality for critically ill patients (OR 0.66 [95% CI 0.53–0.82]).[94] Besides, no significant safety issues were identified in the meta-analysis. Low-dose, short-term corticosteroids are recommended for severe/critically ill patients with COVID-19, except those with contraindications.[31,33,34,95]

There are several unanswered questions for corticosteroid therapy in COVID-19. The optimal timing for initiating corticosteroid therapy is unclear. The direct virus injury dominates at the beginning of the infection while immune injury occurs later. There is no definite cut-off between the two stages, and the best timing to initiate corticosteroids needs further exploration. In RECOVERY subgroup analysis, the mortality benefit was evident in patients receiving corticosteroids >7 days from symptom onset, which was not shown for those ≤7 days of symptom onset.[93] While the dose and duration in the RECOVERY trial are used as a reference for current treatment regimen, lower doses and shorter duration can be studied. Detailed and long-term side effects were not studied in the RECOVERY trial. Current RCTs did not report enough data on secondary infections. For severe COVID-19 patients in the intensive care unit (ICU), bacterial co-infections are not uncommon.[96,97] Corticosteroids may increase the risk of secondary infections.

The therapeutic role of corticosteroid in severe COVID-19 patients, especially those who are mechanically ventilated, is conclusive. Further data on optimal timing, dosage and duration, type of corticosteroids and long-term side effects are needed. As it may not be ethical to conduct further RCTs about corticosteroids at this stage, these questions may be answered by large-scale observational studies.

Tocilizumab

IL-6 is a proinflammatory cytokine elevated in many severe diseases such as ARDS and sepsis.[98] Elevated IL-6 level was associated with severe COVID-19 and mortality, and some prognostic models of COVID-19 included IL-6 as a biomarker.[99–101] Based on the rationale, IL-6 blockade has been a popular target for repurposed COVID-19 drugs. Tocilizumab is a recombinant humanized monoclonal IL-6 receptor antagonist previously used in rheumatoid arthritis and cytokine release syndrome induced by chimeric antigen receptor (CAR) T-cell therapy.[102,103]

The efficacy and safety of tocilizumab in COVID-19 were investigated in many observational studies and RCTs, with varying results. The main characteristics and key findings of the 10 RCTs on tocilizumab are presented in Table 4.[11,104–112] While observational studies on tocilizumab provided positive signals in decreasing mortality and preventing disease progression, only one of the five RCTs with results reported in 2020 met the primary endpoints

and the meta-analysis of these five trials found no clinical benefits in mortality (Table 4).[113] Two RCTs reported in 2021, the REMAP-CAP and RECOVERY trials, had larger sample size and found decreased mortality and lower risk of invasive mechanical ventilation among patients receiving tocilizumab.[11,109]

There are several potential reasons contributing to the discrepancies in the results of these RCTs: (1) Study population: While most enrolled patients in these trials were hospitalized adults with severe COVID-19 needing oxygen therapy, the details of eligibility criteria varied. In some trials, the participants were required not to be on invasive mechanical ventilation before randomization and some trials set threshold of inflammatory biomarkers at baseline. Although most participants in these trials had severe COVID-19, there was huge disparity in actual disease severity, as reflected by the mortality of control groups, ranging from ∼5% to ∼30%. The participants in REMAP-CAP and RECOVERY trials were the most severe. Although most patients in the two trials received corticosteroids as standard care, the mortality was still high at about 30%.[11,109] (2) Standard care, especially the role of corticosteroids: As the understanding of COVID-19 is evolving rapidly, the standard care in the trials has been changing with time. Corticosteroids are confirmed to be an effective treatment for severe COVID-19 patients needing oxygen therapy by RECOVERY trial and meta-analyses.[8,93,94] The proportion of patients receiving corticosteroids as standard care ranged from <10% to >80%. The proportion of corticosteroids use is especially high in trials enrolling patients after June 2020. Besides, more than 80% participants received corticosteroids treatment in all the 3 RCTs which met the prespecified primary outcomes (EMPACTA trial, REMAP-CAP trial and RECOVERY trial).[11,108,109] A post hoc subgroup analysis of CORIMUNO trial found numerically higher clinical benefits for the combined endpoint of death or ventilatory support in patients receiving corticosteroids.[105] In the RECOVERY trial, tocilizumab did not show statistically significant benefits in mortality (rate ratio 1.16 [95% CI 0.91–1.48]), hospital discharge (rate ratio 0.98 [95% CI 0.79–1.22]) and risk for invasive mechanical ventilation or death (risk ratio 0.99 [95% CI 0.82–1.18]) in patients who did not receive corticosteroids.[11] The subgroup analysis suggested that the clinical benefits of tocilizumab were additional to corticosteroids. (3) Sample size: Several RCTs had sample size not exceeding 200 patients and may not have enough power to detect differences in outcomes.

The meta-analyses in the Australian guidelines for the clinical care of people with COVID-19 (version 39.0) included all the above-mentioned 10 RCTs.[114] It was found that tocilizumab probably lowered mortality (risk ratio 0.89 [95% CI 0.82–0.98]) and risk of receiving invasive mechanical ventilation (risk ratio 0.81 [95% CI 0.70–0.93]), as well as did not increase adverse events (risk ratio 1.06 [95% CI 0.86–1.30]) or serious adverse events (risk ratio 0.89 [95% CI 0.75–1.05]). It should be noted that the sample size in the safety outcomes was much lower than that of the other

TABLE 4   Characteristics of RCTs on the efficacy and safety of tocilizumab for COVID-19

RCT	Trial information	Population[a]	Intervention and control	Patients' baseline characteristics and corticosteroid use[b]	Primary outcome
COVACTA,[104] Rosas et al. NCT04320615 2020	Double-blind, placebo-controlled trial ($n = 452$; 2:1 ratio) Enrolment time 3 April 2020–28 May 2020 62 centers in nine countries	(1) Hospitalized adult (≥18 years) patients with severe COVID-19 pneumonia, confirmed by PCR of any body fluid and presented bilateral chest infiltrations on chest radiography or CT (2) $SpO_2 \le 93\%$ or $PaO_2/FiO_2 < 300$ mm Hg	Tocilizumab (8 mg/kg, up to 800 mg) + standard care versus placebo + standard care; a second dose of tocilizumab or placebo could be given 8–24 h after the first dose, if clinical signs or symptoms did not improve or worsened	Male: 205/294 (69.7%) versus 101/144 (70.1%) Age: 60.9 ± 14.6 versus 60.6 ± 13.7 IL-6: 88.1 (3.1–4020) versus 71.2 (3.1–2810) pg/ml CRP: 157.2 (1.1–446.6) versus 150.3 (1.6–499.6) mg/L Symptom onset to randomization: 12.1 ± 6.6 versus 11.4 ± 6.9 days Corticosteroid use: 57/294 (19.4%) versus 41/144 (28.5%) at baseline; 99/294 (33.7%) versus 75/144 (52.1%) during the trial	Clinical status at day 28 (7-category ordinal scale) Between-group difference −1.0 (95% CI −2.5 to 0.0), $p = 0.31$
CORIMUNO[105] Hermine et al. NCT04331808 2020	Open-label Bayesian trial ($n = 131$; 1:1 ratio) Enrolment time 31 March 2020–18 April 2020 Nine centers in France	(1) Hospitalized adult (≥18 years) patients with moderate or severe COVID-19 pneumonia (positive on PCR and/or typical chest CT presentations) (2) WHO 10-point CPS (WHO-CPS) score = 5 (3) Receiving at least 3 L/min oxygen but not receiving high-flow oxygen, non-invasive ventilation or invasive mechanical ventilation	Tocilizumab (8 mg/kg on day 1; an additional 400 mg dose might be given on day 3 if the oxygen requirement did not decrease by more than 50%) + standard care versus standard care	Male: 44/63 (69.8%) versus 44/67 (65.7%) Age: 64.0 (57.1–74.3) versus 63.3 (57.1–72.3) IL-6: — CRP: 119.5 (74.5–219.5) versus 127.0 (84.0–171.0) mg/L Symptom onset to randomization: 10 (7–13) versus 10 (8–13) days Corticosteroid use: 10/63 (15.9%) versus 12/67 (17.9%) at baseline; 19/63 (30.2%) versus 37/67 (55.2%) during the trial	(1) WHO-CPS > 5 at day 4: absolute risk difference −9.0% (95% CrI −23.3% to 5.5%) (2) Death or on high-flow oxygen, non-invasive ventilation, or invasive mechanical ventilation at day 14: cumulative incidence difference −12% (95% CI −28% to 4%)
RCT-TCZ-COVID-19[106] Salvarani et al. NCT04346355 2020	Open-label trial ($n = 126$; 1:1 ratio) Enrolment time 31 March 2020–11 June 2020 24 centers in Italy	(1) Hospitalized adult (≥18 years) patients with COVID-19 documented by radiological imaging and confirmed by PCR testing in a respiratory tract specimen (2) PaO_2/FiO_2 between 200 and 300 mm Hg (3) An inflammatory phenotype defined by a temperature > 38°C during the last 2 days and/or CRP ≥ 100 mg/L and/or CRP level increased to at least twice the the value on hospital admission (4) Not on non-invasive ventilation or invasive mechanical ventilation	Tocilizumab (a dose of 8 mg/kg up to a maximum of 800 mg within 8 h of randomization, followed by a second dose after 12 h) + standard care versus standard care	Male: 40/60 (66.7%) versus 37/66 (56.1%) Age: 61.5 (51.5–73.5) versus 60.0 (54.0–69.0); IL-6: 50.4 (28.3–93.2) versus 34.3 (19.0–59.3) pg/ml CRP: 105 (50–146) versus 65 (32–118) mg/L Symptom onset to randomization: 7.0 (4.0–11.0) versus 8.0 (6.0–11.0) days Corticosteroid use: 1/60 (1.7%) versus 4/63 (6.3%)	Clinical worsening within 14 days since randomization defined by the occurrence of one of the following events, whichever first: (1) Admission to ICU with invasive mechanical ventilation (2) Death from any cause (3) $PaO_2/FiO_2 < 150$ mm Hg Rate ratio 1.05 (95% CI 0.59–1.86), $p = 0.87$

(Continues)

TABLE 4 (Continued)

RCT	Trial information	Population[a]	Intervention and control	Patients' baseline characteristics and corticosteroid use[b]	Primary outcome
BACC Bay[107] Stone et al. NCT04356937 2020	Double-blind, placebo-controlled trial ($n = 243$; 2:1 ratio) Enrolment time 20 April 2020–15 June 2020 Seven centers in the United States	(1) Hospitalized adult (19–85 years) patients with COVID-19 confirmed by either nasopharyngeal swab PCR or serum IgM antibody assay (2) Hyperinflammatory states as defined by meeting any of the following laboratory criteria: CRP > 50 mg/L or ferritin >500 ng/ml or D-dimer >1000 ng/ml or LDH > 250 U/L (3) At least two of the following signs: fever (body temperature > 38°C) within 72 h before enrolment, pulmonary infiltrates, or a need for supplemental oxygen in order to maintain an SpO_2 higher than 92%; (4) Not receiving supplemental oxygen at a rate higher than 10 L/min	Tocilizumab (a dose of 8 mg/kg up to a maximum of 800 mg) + standard care versus placebo + standard care	Male: 96/161 (59.6%) versus 45/82 (54.9%) Age: 61.6 (46.4–69.7) versus 56.5 (44.7–67.8) IL-6: 23.6 (14.0–49.9) versus 25.4 (14.6–40.3) pg/ml CRP: 116.0 (67.1–190.6) versus 94.3 (58.4–142.0) mg/L Symptom onset to randomization: 9.0 (6.0–13.0) versus 10.0 (7.0–13.0) Corticosteroid use: 18/161 (11.2%) versus 5/81 (6.2%)	Intubation (or death, for patients who died before intubation) after administration of tocilizumab or placebo Day 28 Percentage of patients with the event of primary outcome: 10.6% [95% CI 6.7%–16.6%] versus 12.5% [95% CI 6.9%–22.0%] HR 0.83 (95% CI 0.38–1.81), $p = 0.64$
EMPACTA[108] Salama et al. NCT04372186 2020	Double-blind, placebo-controlled trial ($n = 388$; 2:1 ratio) Enrolment time: — Multiple centers in six countries	(1) Hospitalized adult (≥18 years) patients with COVID-19 pneumonia confirmed by PCR test and radiographic imaging (2) SpO_2 < 94% on ambient air (3) Not receiving continuous positive airway pressure, bilevel positive airway pressure or mechanical ventilation	Tocilizumab (one or two doses of 8 mg/kg up to a maximum of 800 mg per dose) + standard care versus placebo + standard care	Male: 150/249 (60.2%) versus 73/128 (57.0%) Age: 56.0 ± 14.3 versus 55.6 ± 14.9 IL-6: — CRP: 124.50 (2.5–2099.0) versus 143.40 (9.0–3776.0) mg/L Symptom onset to randomization: 8.0 (0.0–31.0) versus 8.0 (0.0–36.0) Corticosteroid use: 200/249 (80.3%) versus 112/128 (87.5%) (within 7 days prior to the first dose of study drug or during the study)	Mechanical ventilation (invasive mechanical ventilation or extracorporeal membrane oxygenation) or death by day 28 HR 0.56 (95% CI 0.33–0.97), $p = 0.04$
REMAP-CAP[109] Gordon et al. NCT02735707 2021[c]	Open-label trial ($n = 803$; tocilizumab $n = 353$, sarilumab $n = 48$, control $n = 402$) Enrolment time: 19 April 2020–19 November 2020 113 centers in six countries	(1) Critically ill adult (≥18 years) COVID-19 patients (clinically suspected or microbiologically confirmed) admitted to ICU (2) Receiving respiratory or cardiovascular organ support (3) Patients must be enrolled within 24 h after initiating above-mentioned organ support in the ICU	Tocilizumab (one dose of 8 mg/kg up to a maximum of 800 mg, a second dose can be given in 12–24 h after the first dose if the clinicians consider the clinical improvement insufficient) + standard care versus sarilumab (400 mg) + standard care versus standard care	Male: 261/353 (73.9%) versus 283/402 (70.4%) Age: 61.5 ± 12.5 versus 61.1 ± 12.8 IL-6: — CRP: 150 (85–221) versus 130 (71–208) mg/L Symptom onset to randomization: — Corticosteroid use: 252/272 (92.7%) versus 293/312 (93.9%) (for patients enrolled after 17 June 2020; about 80% of participants were enrolled after 17 June 2020)	The number of respiratory and cardiovascular organ support-free days up to day 21 10 (−1–16) versus 0 (−1–15) Adjusted OR (median) 1.64 (95% CrI 1.25–2.14)

(Continues)

TABLE 4 (Continued)

RCT	Trial information	Population[a]	Patients' baseline characteristics and corticosteroid use[b]	Intervention and control	Primary outcome
TOCIBRAS[110] Veiga et al. NCT04403685 2021	Open-label trial ($n = 129$; 1:1 ratio) Enrolment time 8 May 2020–17 July 2020 Nine centers in Brazil	(1) Hospitalized adult (≥18 years) patients with COVID-19 confirmed by PCR test (2) Symptom onset for more than 3 days (3) Severe or critical illness with radiographical evidence and receiving supplemental oxygen to keep $SpO_2 > 93\%$ or receiving mechanical ventilation for less than 24 h before randomization (4) Two or more of the following inflammatory tests: D-dimer >1000 ng/ml, CRP >50 mg/L, ferritin >300 µg/L or LDH > upper limit of normal	Male: 44/65 (67.7%) versus 44/64 (68.8%) Age: 57.4 ± 15.7 versus 57.5 ± 13.5 years IL-6: 192 ± 313 versus 208 ± 586 pg/ml CRP: 160 ± 104 versus 193 ± 283 mg/L Symptom onset to randomization: 10.0 ± 3.1 versus 9.5 ± 3.0 days Corticosteroid use: 45/65 (69.2%) versus 47/64 (73.4%) at baseline; 56/67 (83.6%) versus 55/62 (88.7%) in the first 15 days	Tocilizumab (a dose of 8 mg/kg up to a maximum of 800 mg) + standard care versus standard care	The original primary outcome was 'clinical status at 15 days evaluated with the use of a 7-level ordinal scale'. The assumption of proportional odds was not fulfilled, so the primary outcome was analysed as '(invasive) mechanical ventilation or death', as prespecified in the protocol OR 1.54 (95% CI 0.66–3.66)
RECOVERY[11] Horby et al. NCT04381936 2021	Open-label trial ($n = 4116$; 1:1 ratio) Enrolment time 23 April 2020– 24 January 2021 131 centers in the UK	(1) Hospitalized adult (≥18 years) patients (including pregnant women) with clinically suspected or laboratory-confirmed COVID-19 (2) Clinical evidence of progressive COVID-19 defined as hypoxia ($SpO_2 < 92\%$ on air or requiring oxygen therapy) and CRP ≥ 75 mg/L	Male: 1337/2022 (66.1%) versus 1437/2094 (68.6%) Age: 63.3 ± 13.7 versus 63.9 ± 13.6 years IL-6: — CRP: 143 (107–203) versus 144 (106–205) mg/L Symptom onset to randomization: 9 (7–13) versus 10 (7–14) Corticosteroid use: 1664/2022 (82.3%) versus 1721/2094 (82.2%)	Tocilizumab (weight > 90 kg: 800 mg, weight > 65 and ≤90 kg: 600 mg, weight > 40 and ≤65 kg: 400 mg, weight ≤ 40 kg: 8 mg/kg) + standard care versus standard care	28-day mortality: rate ratio 0.85 (95% CI 0.76– 0.94)
COVINTOC[111] Soin et al. CTRI/2020/05/025369 2021	Open-label trial ($n = 180$; 1:1 ratio) Enrolment time 30 May 2020– 31 August 2020 12 centers in India	(1) Hospitalized adult (≥18 years) patients with laboratory-confirmed COVID-19 (positive PCR test [respiratory, blood, urine, stool, other body fluid]) (2) Moderate to severe disease (moderate: respiratory rate 15–30/ min [revised to 24-30/min on 13 June 2020] and SpO_2 90%–94%; and severe: respiratory rate ≥ 30/min or $SpO_2 < 90\%$ in ambient air, or ARDS or septic shock)	Male: 76/91 (83.5%) versus 76/88 (86.4%) Age: 56 (47–63) versus 54 (43–63) years IL-6: 115.5 ± 245.6 versus 85.2 ± 232.2 pg/ml CRP: 110.7 ± 107.2 versus 88.1 ± 81.1 mg/L Symptom onset to randomization: — Corticosteroid use: 83/91 (91.2%) versus 80/88 (90.9%)	Tocilizumab (one dose of 6 mg/kg up to a maximum of 480 mg; a second dose of 6 mg/kg [maximum 480 mg/kg] could be given if clinical symptoms worsened or did not show improvement within 12 h to 7 days after the first dose) + standard care versus standard care	The proportion of patients with progression of COVID-19 (from moderate to severe or from severe to death) up to day 14 8/91 (8.8%) versus 11/88 (12.5%) Difference −3.7% (95% CI −18.2% to 11.2%) $p = 0.42$

(Continues)

TABLE 4 (Continued)

RCT	Trial information	Population[a]	Patients' baseline characteristics and corticosteroid use[b]	Intervention and control	Primary outcome
Wang et al.[112] ChiCTR2000029765 2021	Open-label trial (n = 65; 1:1 ratio) Enrolment time 13 February 2020–13 March 2020 Six centers in China	(1) Hospitalized adult (18–85 years) patients with PCR-confirmed COVID-19 (2) Elevated plasma IL-6 levels (3) Moderate to severe disease (moderate: fever or other respiratory symptoms, bilateral pulmonary infiltrations on radiographical testing; and severe is defined as meeting any of the criteria: a. respiratory rate ≥ 30/min; b. SpO2 ≤ 93% on room air; c. PaO2/FiO2 ≤ 300 mm Hg)	Male: 18/34 (52.9%) versus 15/31 (48.4%) Age: 63.5 (58–71) versus 63 (54–69) years IL-6: 26.03 (12.76–58.04) versus 24.35 (9.895–85.325) pg/ml CRP: 9.95 (3.3–23.6) versus 6.28 (1.15–33.7) mg/L Symptom onset to randomization: 20 (9–29) versus 24 (19–33) Corticosteroid use: 5/34 (14.7%) versus 2/31 (6.5%)	Tocilizumab (the first dose was 400 mg; a second dose might be given if the patient remained to have fever in 24 h following the first dose) + standard care versus standard care	Cure rate, defined by (1) normal temperature for 7 days, (2) two consecutively negative SARS-CoV-2 PCR tests, (3) CT demonstrating chest infiltrations improved more than 50% 32/34 (94.12%) versus 27/31 (87.10%) Rate difference 95% CI: −7.19% to 21.23% (no point estimate was reported)

Abbreviations: ARDS, acute respiratory distress syndrome; COVID-19, coronavirus disease 2019; CPS, Clinical Progression Scale; CrI, credible interval; CRP, C-reactive protein; CT, computed tomography; HR, hazard ratio; ICU, intensive care unit; LDH, lactate dehydrogenase; PaO2/FiO2, partial pressure of arterial oxygen/fraction of inspired oxygen; RCT, randomized controlled trial; SARS-CoV-2, severe acute respiratory syndrome coronavirus 2; SpO2, peripheral oxygen saturation; WHO, World Health Organization.
[a]Inclusion criteria and important exclusion criteria related to oxygen requiring status.
[b]Data are presented in the form of n/N (%), mean ± SD or median (IQR), and the comparisons were tocilizumab group versus control group. The unit of data was converted when necessary (e.g., CRP in mg/dl was converted to mg/L).
[c]In REMAP-CAP trial, only the outcomes in the tocilizumab group and the control group were presented in the table. Data of tocilizumab and sarilumab were not combined.

outcomes, as some of the largest trials (e.g., RECOVERY trial) did not provide sufficient safety data. As the efficacy of anti-viral drugs (e.g., remdesivir and neutralizing monoclonal antibodies) in severe COVID-19 patients was not yet determined, the use of double immunosuppressants should be carefully considered to reduce the risk of serious infections and prolonged viral replication.

The eligibility criteria of the RECOVERY and REMAP-CAP trials provided clues that tocilizumab may work best in hospitalized patients requiring oxygen, with evidence of systemic inflammation, or within 24 h of receiving mechanical ventilation.[11,109] Current guidelines recommend use of tocilizumab in such populations.[33,34,95,114] Dosing is another question. Although most RCTs adopted 8 mg/kg with maximum of 800 mg dose, the use of second dose varied across these studies. Some studies used only a single dose while some studies relied on physicians' judgement on the need for a second dose. The optimal number of doses and the criteria of giving more than one dose are still not determined. Another question is whether the benefit of tocilizumab can be extended to other IL-6 receptor antagonists. Current RCT data are mainly on tocilizumab while data on sarilumab and other IL-6 receptor antagonists are limited and not supportive.[115] Individual patient-level data meta-analysis of these trials may provide further insights on suitable patients and optimal treatment protocol. A WHO collaborating group which includes principal investigators of many tocilizumab RCTs has initiated such a meta-analysis project.[116] The prospective meta-analysis project set a variety of pre-specified subgroup analyses, such as baseline factors (e.g., age, sex, race and disease severity), dose of therapy and use of corticosteroids.

Baricitinib

The JAKs are a class of non-receptor, intracellular tyrosine kinases, which serves as downstream linkers in the signal cascades of various cytokines.[117–121] JAKs bind to the cytoplasmic domains of type I and type II cytokine receptors and activate signal transducers and activators of transcription (STATs) to transfer extracellular signals.[117–122] In humans, JAK family is found to consist of JAK1, JAK2, JAK3 and tyrosine kinase 2 (TYK2).[117–122] Many cytokines related to COVID-19 immune pathogenesis, such as IL-2, IL-6 and interferon-γ, activated JAK–STAT pathway and participated in immune responses.[121–123] Theoretically, for severe hospitalized COVID-19 patients' immune dysregulation, inhibiting JAK–STAT pathway with JAK inhibitors may curb the cytokine storm and produce clinical benefits.

Baricitinib is an oral JAK inhibitor targeting both JAK1 and JAK2, and used to treat rheumatoid arthritis.[118,124] For COVID-19 patients, baricitinib may prevent the overwhelming immune damage mediated by proinflammatory cytokines.[121] Besides, baricitinib may prevent the cell entry of SARS-CoV-2 by inhibiting AP2-associated protein kinase 1 (AAK1).[125–127] A pilot study enrolled 12 consecutive

moderately ill hospitalized COVID-19 patients to receive baricitinib (4 mg per day) in addition to lopinavir-ritonavir for 2 weeks.[128] A historical control group treated by lopinavir-ritonavir and hydroxychloroquine included the last 12 consecutive patients hospitalized before the date of patients treated by baricitinib.[128] In the study, baricitinib group showed significant improvement in outcomes such as fever, SpO_2, PaO_2/FiO_2, C-reactive protein (CRP), ICU admission and discharge rate. This study was among the first studies on the efficacy of baricitinib and showed positive results. However, due to the non-randomized design, small sample size and poor selection of controls, the results are not conclusive and can only be hypothesis-generating. A multicenter retrospective study comparing the effects of baricitinib plus lopinavir-ritonavir ($n = 113$) versus hydroxychloroquine plus lopinavir-ritonavir ($n = 78$) showed that the baricitinib group had lower ICU admission and mortality, as well as significant decline in CRP and IL-6.[129] A prospective cohort study enrolled moderate to severe COVID-19 patients and compared the effects of baricitinib plus corticosteroids ($n = 62$) versus corticosteroids alone ($n = 50$). The study showed that the baricitinib group had better improvement in respiratory function (measured by SpO_2/FiO_2) from hospital admission to discharge, as well as lower proportion of patients requiring supplementary oxygen at discharge and 1 month after discharge.[130] Several other studies also indicated potential clinical benefits of baricitinib in mitigating the hyperinflammatory status of COVID-19 patients.[123,131,132]

The results of two RCTs are available.[133,134] The ACTT-2 trial is a multicenter double-blind, placebo-controlled randomized trial conducted in 67 centers across eight countries.[133] In ACTT-2 trial, 1033 hospitalized patients were randomized to receive baricitinib plus remdesivir ($n = 515$) or placebo plus remdesivir ($n = 518$). The clinical status in ACTT-2 trial was measured by the NIAID 8-category ordinal scale used in ACTT-1 trial (Table 2). Patients with scores 4, 5, 6 and 7 at baseline accounted for 13.7%, 54.6%, 20.9% and 10.7% of total patients, respectively. The dosage of baricitinib was 4 mg per day for (2 mg per day for patients with estimated glomerular filtration rate < 60 ml/min/1.73 m²) 14 days or until discharge. The trial met its primary endpoint and observed significantly shorter time to recovery (defined by meeting the criteria of scores 1, 2 or 3 on the NIAID 8-category ordinal scale) in baricitinib group (median 7 vs. 8 days, rate ratio 1.16 [95% CI 1.01–1.32]). Prespecified subgroup analysis on baseline score on the 8-category ordinal scale showed that the greatest benefits were observed in patients requiring non-invasive ventilation or high-flow oxygen (i.e., score 6 on the ordinal scale) at baseline (median 10 vs. 18 days, rate ratio 1.51 [95% CI 1.10–2.08]). While no statistically significant benefits in time to recovery were observed in other subgroups (scores 4, 5 and 7), patients requiring low-flow oxygen (score 5) showed the best point estimate for primary outcome (rate ratio 1.17 [95% CI 0.98–1.39]). Besides, significantly higher odds of improvement in clinical status

(measured by NIAID 8-category ordinal scale) at day 15 were observed in baricitinib group (OR 1.3 [95% CI 1.0–1.6]). The largest effect was also observed among patients receiving non-invasive ventilation or high-flow oxygen at baseline. Numerically, lower 28-day mortality was observed in baricitinib group overall (5.1% vs. 7.8%, hazard ratio 0.65 [95% CI 0.39–1.09]) and more marked in low-flow and high-flow oxygen subgroups.

The COV-BARRIER was a multicenter double-blind, placebo-controlled randomized trial conducted in 101 centers across 12 countries.[134] The COV-BARRIER trial enrolled laboratory-confirmed, hospitalized COVID-19 patients with pneumonia and ≥1 elevated inflammatory marker (CRP, D-dimer, lactate dehydrogenase or ferritin).[134] The COV-BARRIER trial also used NIAID 8-category ordinal scale to assess the clinical status of patients (Table 2).[134] Initially, the trial enrolled patients score 4–6 in the ordinal scale at baseline, and excluded patients requiring invasive machinal ventilation (score 7 in the ordinal scale). In a protocol amendment during the trial, hospitalized patients not requiring oxygen therapy (score 4 in the ordinal scale) at baseline were excluded and the trial focused on patients requiring oxygen therapy (scores 5 and 6 in the ordinal scale) subsequently. Overall, enrolled patients ($n = 1525$) with scores 4, 5 and 6 in the ordinal scale at baseline were 12.3%, 63.4% and 24.4%, respectively. The primary outcome in the trial was the proportion of patients with disease progression defined by receiving non-invasive ventilation or high-flow oxygen, invasive mechanical ventilation or extracorporeal membrane oxygenation (ECMO) or death (i.e., score 6–8 on the ordinal scale). No statistically significant difference in the primary outcome was found between baricitinib and control groups (27.8% vs. 30.5%, OR 0.85 [95% CI 0.67–1.08]) and a secondary analysis focused on patients requiring oxygen (scoring 5 and 6) at baseline also found no significant difference (28.9% vs. 27.1%, OR 1.12 [95% CI 0.58–2.16]). The result was consistent across subgroups of baseline ordinal scale score and study regions. However, baricitinib group had a significantly lower 28-day mortality compared with control group (8.1% vs. 13.1%, hazard ratio 0.57 [95% CI 0.41–0.78]). While no statistically significant mortality benefits were found in patients with score 4 or 5 separately, the largest mortality benefits were shown in patients requiring non-invasive ventilation or high-flow oxygen (score 6) at baseline (17.5% vs. 29.4%, hazard ratio 0.52 [95% CI 0.33–0.80]). A secondary analysis focused on patients requiring oxygen (scoring 5 and 6) also found significant benefits in mortality (5.2% vs. 14.7%, hazard ratio 0.31 [95% CI 0.11–0.88]). Prespecified subgroup analysis on baseline concomitant drug use found significant mortality benefits in patients receiving corticosteroids, not receiving corticosteroids and not receiving remdesivir. For the subgroup of patients receiving remdesivir, a numerical mortality reduction was observed. The definition of time to recovery outcome in the COV-BARRIER trial was the same as the ACTT-2 trial, but no significant benefits were

observed (5.2% vs. 14.7%, rate ratio 1.11 [95% CI 0.99–1.24]).

In light of the benefits observed in the ACTT-2 trial, FDA issued EUA on baricitinib and remdesivir combination treatment for hospitalized patients requiring oxygen therapy.[135,136] However, knowledge gaps and clinical practice issues still exist. First, the exact benefits of baricitinib have not yet been well defined. The ACTT-2 trial found baricitinib was beneficial in time to recovery but not in mortality, while the COV-BARRIER trial reported the converse. Differences in study population, concomitant drugs and definitions of outcomes may contribute to the discrepancy in the results of ACTT-2 and COV-BARRIER trials. The primary outcome is the most important outcome selected for an RCT, and the sample size and power calculation are based on the primary outcome.[137] The analysis on secondary outcomes may have increased risk of false-negative as well as false-positive errors because of factors such as insufficient sample size and multiple comparisons.[137–140] As mortality was not the primary outcome in ACTT-2 trial, it was not powered to detect the difference in mortality. Besides, the clinical significance of time to recovery with absence of mortality benefits makes baricitinib less useful. In the COV-BARRIER trial, mortality was also not the primary endpoint. However, although the sample size of over 1500 patients was large and the authors used graphical testing procedure to control for type I error of multiple comparisons, as the trial failed to meet its primary endpoint, the confidence in the mortality benefits has been questioned.[137–140] Nevertheless, a meta-analysis of ACTT-2 and COV-BARRIER trials indicated potential benefits in 28-day mortality (risk ratio 0.63 [95% CI 0.48–0.81]) and risk of invasive mechanical ventilation (risk ratio 0.66 [95% CI 0.46–0.93]).[114] Later trials with larger sample size, such as the ongoing baricitinib arm of the RECOVERY trial, are expected to provide further information on the role of baricitinib.

The second question is the role of baricitinib in clinical practice. As corticosteroids are cheap and widely available, with mortality benefits for hospitalized patients requiring oxygen therapy, physicians may not choose other immune modulators unless corticosteroids are contraindicated. Besides, the ACTT-4 trial, a double-blind RCT comparing the effects of baricitinib and dexamethasone in a head-to-head comparison, was closed prematurely as interim analysis showed that there was unlikely to be statistically significant differences between the two groups in the primary outcome of progression to mechanical ventilation or death.[141] Therefore, similar to tocilizumab, baricitinib may more likely be considered as an addition to corticosteroids but not a replacement. Similar to REMAP-CAP and RECOVERY trials for tocilizumab, about 80% of patients in the COV-BARRIER trial received corticosteroids, which suggested its benefits may be additional to corticosteroids.[134]

Notably, in both trials, baricitinib showed the greatest benefit in patients requiring non-invasive ventilation or high-flow oxygen therapy, followed by patients requiring low-flow oxygen.[133,134] Similar to corticosteroids, baricitinib may not bring benefits for patients not requiring oxygen therapy, as these patients may not have severe inflammatory immune responses and use of immunomodulators may hamper virus clearance. The clinical benefits in patients requiring invasive mechanical ventilation were unclear. In the subgroup analysis of ACTT-2 primary outcome, baricitinib did not show significant benefits in patients requiring invasive mechanical ventilation (rate ratio 1.08 [95% CI 0.59–1.97]). In light of this result, the published cohort of COV-BARRIER trial did not enrol these patients. However, as the sample size of this subgroup in the ACTT-2 trial was only 111, further study may be needed.

Other JAK inhibitors such as ruxolitinib and tofacitinib may have a role in treating severe COVID-19 patients. For ruxolitinib, there was only one available pilot RCT with very small sample size ($n = 43$) on its efficacy for severe COVID-19 patients.[142] The trial did not find statistically significant difference between ruxolitinib and placebo groups in the primary outcome of time to clinical improvement as well as most secondary outcomes such as 28-day mortality and virus clearance time.[142] The most important finding in the trial was that patients in the ruxolitinib group had faster computed tomography improvement and recovery from lymphopenia.[142] No RCT data about tofacitinib are available. As current evidence about other JAK inhibitors is very limited and not adequately powered, it is questionable whether they can be interchangeable for baricitinib. Further RCTs are ongoing and expected to assess the efficacy of ruxolitinib and tofacitinib in the future.[143]

In summary, baricitinib may be effective in hospitalized COVID-19 patients requiring oxygen therapy, especially patients receiving non-invasive ventilation or high-flow oxygen therapy. However, given the mixed results of the two available RCTs, the exact benefits of baricitinib need to be confirmed by further studies.

LESSONS FROM COVID-19 THERAPEUTIC DRUG TRIALS

Within 1 year of the pandemic, many drugs have been studied. Therapeutic drug trials during the COVID-19 pandemic provided us with very valuable experience to better confront challenges of other possible emerging infectious diseases in the future.

A large number of clinical trials were registered and conducted, both for novel and repurposed drugs for COVID-19. However, the results of many seemingly promising drugs were unsatisfying. For example, hydroxychloroquine is an anti-malarial and anti-inflammatory drug. Although hydroxychloroquine was reported to have in vitro anti-viral effects on SARS-CoV-2,[144–146] RCTs and meta-analyses showed that hydroxychloroquine had no clinical benefits in reducing mortality, accelerating clinical improvement, lowering length of hospital stay, preventing SARS-CoV-2 infection and other important clinical outcomes, and may increase the incidence of adverse events.[8,9,147,148]

Before the conclusive results of RCTs were published, the off-label use of hydroxychloroquine was common for

treatment or prophylaxis during the early stage of the pandemic.[149–151] Similar phenomenon also existed for other drugs, which may be widely used before efficacy was confirmed. As in vitro anti-viral effects do not necessarily translate into clinical effects and off-label use of drugs may cause adverse events, it is necessary to interpret the results of cell culture and animal experiments as well as observational studies cautiously, and evaluate the efficacy and safety of candidate drugs with rigorously designed RCTs.[152] Large-scale off-label use of seemingly promising drugs may obscure the actual efficacy of the drugs and hamper the enrolment of RCTs.[152]

Large RCTs such as the RECOVERY and SOLIDARITY trials have provided valuable models for pandemic research in the future.[11,27,93] It is important to coordinate the research resources of affected regions to maximize sample sizes of RCTs. RCTs with small sample sizes can only provide signals but not conclusive information. They should be discouraged in favour of large collaborative multicenter RCTs. The eligibility criteria of the RCTs are also important. For example, the best timing of anti-viral drugs should be in the early stage of disease. However, the early RCTs of convalescent plasma focused on severe/critically ill patients, which may not reflect the actual therapeutic effects. Observational studies can provide valuable clues for the selection of eligible study populations of RCTs. In addition, the selection of outcome measures should reflect the likely clinical efficacy of the drug, as well as account for pathophysiology and disease stage/severity of the study population. For severe patients, the most important outcome is mortality. However, for patients with mild COVID-19, the risk of hospitalization and progression to severe disease may be equally important.[153] Especially for areas with limited medical resources, lowering hospitalization rate is of great public health significance.[153] For better comparison and synthesis of the results of different RCTs, researchers should consider including the outcomes in the core outcome sets for COVID-19.[154–156] The working group of the WHO recommended a minimal common outcome measure set for COVID-19 clinical research, including mortality, viral load and clinical course (progression and recovery).[154]

As the evidence of COVID-19 therapeutics is rapidly evolving, the importance of living meta-analysis has emerged. There are several big living network meta-analysis programmes with focus on different clinical outcomes.[8,157] However, given the heterogeneity of the RCTs (e.g., standard care, medical resources and eligibility criteria), the results of meta-analyses should be interpreted cautiously. Global collaboration among study groups and individual patient-level meta-analysis may help better interpret the study results, as it will be feasible to conduct subgroup analyses on disease severity and the effect of concomitant drugs.

In conclusion, after 1 year, current evidence indicates that neutralizing monoclonal antibodies can reduce the risk of hospitalization and disease progression in high-risk outpatients while corticosteroids provide mortality benefits in severe COVID-19 patients requiring oxygen therapy. Remdesivir improves clinical recovery and may reduce mortality if given early especially in patients on low-flow oxygen, while baricitinib improves recovery and may reduce mortality in patients on high-flow oxygen. Tocilizumab may provide additional benefits in critically ill mechanically ventilated patients on corticosteroids. For this and future pandemics, it is important to conduct RCTs with large sample sizes to test the efficacy and safety of potential therapeutic drugs. The eligibility criteria, primary and secondary outcomes should be carefully selected based on the pathophysiology of the infection and pharmacology of the potential therapeutic drugs to best assess clinical efficacy.

CONFLICT OF INTEREST
Dr David Chien Lye declared to be a member of Gilead global advisory panel on remdesivir 2020 (no honorarium accepted).

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