



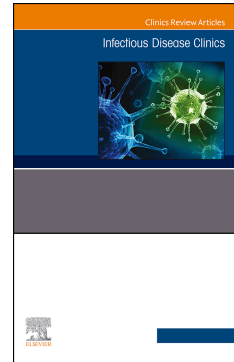
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PII: S0891-5520(22)00053-8

DOI: <https://doi.org/10.1016/j.idc.2022.07.002>

Reference: IDC 1140

To appear in: *INFECTIOUS DISEASE CLINICS OF NORTH AMERICA*

Please cite this article as: Athale J, Gallagher J, Busch LM, Management of Severe and Critical COVID-19 Infection with Immunotherapies, *INFECTIOUS DISEASE CLINICS OF NORTH AMERICA* (2022), doi: <https://doi.org/10.1016/j.idc.2022.07.002>.

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## **Management of Severe and Critical COVID-19 Infection with Immunotherapies**

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**Keywords:** Severe COVID-19 Infection, Critical COVID-19 Infection, immunotherapy

## Introduction

Early in the COVID-19 pandemic, clinicians and researchers sought to rapidly repurpose available candidate therapies for SARS-CoV-2 infection pending the development of directed antivirals and novel vaccines. Slowly, anecdotal case series and single-arm observational trials gave way to randomized control trials (RCTs) as the global research community mobilized to design, implement, and analyze studies in the midst of unprecedented pressure on healthcare systems. Despite early controversy surrounding the Emergency Use Authorization (EUA) and politicization of hydroxychloroquine therapy, progress soon followed in the form of remdesivir and dexamethasone, which became standard of care following EUA by the Food and Drug Administration (FDA) in May 2020(1) and release of the RECOVERY trial results in June 2020(2). Propelled by the dramatic impact on mortality conferred by the nonspecific immunosuppression of steroids, earnest investigation into directed immunomodulation soon followed, with modest mortality benefit demonstrated with these agents and an on-going need for larger studies.

A full discussion of steroid therapy in COVID-19 is beyond the scope of this article, but the initial practice-changing studies bear mention given their impact on the standard of care and interpretation of subsequent immunotherapy trials. RECOVERY was the first therapeutic trial to improve mortality in COVID-19. Dexamethasone treatment was associated with a 27% reduction in mortality (RR 0.83, 95% CI [0.75, 0.93]) from severe COVID-19 disease, quickly changing the standard of care for hospitalized patients globally(2). Notably, however, subsequent studies have not demonstrated such dramatic mortality benefit, and clinical practice has evolved to include a variety of different steroid regimens despite comparatively

smaller trial sizes and modest outcomes. There were three trials evaluating corticosteroid use in critically-ill COVID-19 patients which had to stop enrollment following release of RECOVERY data: REMAP-CAP, CoDEX, and CAPE COVID. The results from REMAP-CAP (n=403; endpoint: number of days alive and free of organ support at Day 21) suggested that hydrocortisone therapy had a high probability of benefit, though due to early stoppage they were unable to confirm this nor define an optimal regimen(3). CoDEX reported an increase in the number of ventilator-free days at Day 28 with dexamethasone vs control (6.6 vs 4.0d, p=0.04), though no benefit in mortality (56.3% vs 61.5%, p=0.83)(4). CAPE COVID reported no difference in their endpoint of treatment failure (composite death or ongoing respiratory support mechanical ventilation [MV] or high flow nasal cannula [HFNC]) at Day 21 (42.1% vs 50.7%, p=0.29) in patients randomized to hydrocortisone vs placebo (5). A concurrently published prospective meta-analysis from the World Health Organization (WHO) of seven RCTs examining corticosteroid administration in 1703 critically ill patients reported results favoring steroids for improved mortality, with a summary OR 0.66 (95% CI [0.53, 0.82])(6). A 2021 Cochrane systematic review included 11 available RCTs testing steroid use in hospitalized COVID-19 patients with summary findings of probable reduction in all-cause mortality (9 RCTs, 7930 subjects; RR 0.89, 95% CI [0.8, 1.0]). Unfortunately, due to inability to adjust for the impact of early deaths and wide intertrial heterogeneity, they were unable to provide further analysis regarding new initiation of mechanical ventilation, serious adverse events, or comparison of different steroid regimens(7). With the loss of equipoise for placebo-controlled steroid trials in the wake of RECOVERY, the clinical focus shifted to type of steroid and dosing regimen. Many providers and institutions protocolized the RECOVERY dexamethasone regimen, while others

looked to the broader ARDS literature, such as the DEXA ARDS trial(8), for alternative dosing regimens. While the landscape of steroid treatment in severe COVID-19 infection continues to evolve, investigation into targeted immunomodulatory therapies has grown rapidly. The agents with the most data and clinical experience to date are baricitinib and tocilizumab. We will focus on available data for treatment of severe COVID-19 infection, with specific attention to critical illness. This population represents a particular challenge with regard to directed therapeutics for many reasons: the high rate of mortality, dependence on life support measures, increased risk of secondary infections, complications of critical illness (e.g., gastrointestinal bleeding, limb ischemia, neuromuscular weakness), unique pharmacokinetic considerations, and high incidence of concurrent organ dysfunctions (e.g., renal failure, liver injury, coagulopathy, cardiac dysfunction). Furthermore, prolonged critical illness is itself associated with dysregulation and suppression of the immune system(9-11), and understanding how potential immunomodulatory therapies perform in this complex milieu is essential to maximize medical therapies in this vulnerable population, without predisposing to undo risk of infectious complications.

### **Immunomodulation for COVID-19**

The goal of immunotherapy for infectious diseases is to facilitate the functions of immune cells that are essential for microbial clearance while curbing potentially damaging aspects of host inflammation which can exacerbate organ injury. Infection with SARS-CoV-2 begins with binding of the viral spike glycoprotein to the angiotensin-converting enzyme-2 (ACE2) receptor on the respiratory epithelial cells, entry into which is facilitated by the host

transmembrane protease serine 2 (TMPRSS2). Recognition by immune cell pattern-recognition receptors spurs on the host response, largely governed by interleukin (IL)-1 and IL-6 signaling(12). Infections result in a wide spectrum of disease, from asymptomatic to mild influenza-like illness to severe pneumonia with acute respiratory distress syndrome (ARDS), multisystem organ failure, and death. The T cell response in severe COVID-19 infection shows some similarities to the immune dysregulation observed in bacterial sepsis including circulating monocyte downregulation of HLA-DR expression and CD4+ and CD8+ T cell lymphopenia. Interestingly, while T cell production of type II interferons is reduced, the cells retain capacity to produce other inflammatory cytokines—one target for potential therapeutics. Several case series have sought to describe T cell phenotypic and functional changes associated with COVID-19 infection(13-15), although it should be noted that the landmark RCTs and adaptive trials published to date have included few or no immunologic endpoints, so we lack data directly linking immunophenotypes with therapeutic responses. Below we will discuss several classes of immunomodulatory agents currently in use or under investigation for severe COVID-19 disease, with specific attention to the applicability of these data to critical illness.

## **Anti-cytokine therapy**

### IL-6 Inhibition

The aggressive hyperinflammatory response known as cytokine storm (CS) is a well-described feature of severe COVID-19 disease. IL-6 plays an important role in viral immunity and is a key cytokine associated with CS (16). Initial reports of elevated IL-6 levels associated with adverse outcomes coupled with the finding that critically ill COVID-19 patients had

significantly higher levels of IL-6 compared to patients with moderate disease spawned early investigations targeting this pathway to mitigate adverse effects (17-19). There are two classes of anti-IL-6 agents that are currently approved by the FDA, the IL-6 receptor monoclonal antibodies (IL-6ra) tocilizumab and sarilumab, and the IL-6 monoclonal antibody, siltuximab. The IL-6ra agents have the most robust data for the treatment of COVID-19 disease, while no data is available for siltuximab at the time of this review. Data from three large studies (RECOVERY, REMAP-CAP, and COVACTA) were published in early 2021 with conflicting results regarding efficacy, and with notable differences in study design and adjunct therapies (20) (21) (22). Both RECOVERY and REMAP-CAP demonstrated improved clinical outcomes associated with tocilizumab, while COVACTA found no difference in 28-day mortality when compared to placebo. The RECOVERY study enrolled all hospitalized patients with COVID-19 disease and elevated CRP, regardless of severity, with almost half (~45%) of patients requiring either no or low-flow supplemental oxygen. Investigators reported that tocilizumab compared to usual care alone significantly improved 28-day mortality, 31% vs 35% (RR 0.85, 95% CI 0.76-0.94,  $p=0.0028$ ). Tocilizumab was also associated with a greater probability of hospital discharge at day 28 and a lower risk of new initiation of mechanical ventilation or death(20). The REMAP-CAP study specifically enrolled critically ill patients with COVID-19 disease receiving either respiratory support (e.g., HFNC, noninvasive positive pressure ventilation [NIPPV], or MV) or cardiovascular support. Rather than mortality, however, the primary outcome of this study was number of respiratory or cardiovascular organ support free days at day 21. At the time of publication of the anti-IL-6 data in 2021, of the 2,274 patients enrolled in the Immunomodulatory Domain, 353 were assigned to the tocilizumab group, 48 to sarilumab, and



402 to standard of care (control). Patients in the tocilizumab and sarilumab arms had a greater median number of organ support-free days, 10 (IQR -1 to 15) and 11 (IQR 0 to 16), respectively, compared to 0 days in the control arm (IQR -1 to 15). Tocilizumab and sarilumab were also both associated with a significantly lower in-hospital mortality, 28% and 22%, respectively, compared to the control arm (36%)(21). These data are supported in the preprint edition of the complete REMAP-CAP Immunotherapy Domain RCT, which is pending peer review at the time of this manuscript preparation(23). Lastly, the COVACTA study enrolled hospitalized patients with severe COVID-19 disease with approximately two-thirds admitted to the ICU with high oxygen requirements (HFNC or greater). However, it is notable that the mortality in both groups was fairly low at 19%, despite the apparent high acuity of the population. This study found no difference in their primary outcome of clinical status improvement as measured by seven-point ordinal scale (OS) or secondary endpoint of mortality. One major difference between the RECOVERY and REMAP-CAP studies compared to COVACTA was the use of steroids in addition to IL-6ra or usual care(22). Fewer than 30% of patients in either arm of the COVACTA study received corticosteroids—just 19.4% in the tocilizumab arm vs 28.5% in the control arm. In contrast, greater than 80% of patients in RECOVERY and 90% of patients in REMAP-CAP received steroids. Furthermore, a meta-analysis which included all three studies found a signal towards improved survival in patients receiving steroids in addition to IL-6ras in a subgroup analysis (24). Thus, the current NIH treatment guidelines state that IL-6ras should only be given in combination with steroid treatment(25).

While the current literature suggests a benefit with the use of IL-6ras in patients with COVID-19 disease when used with steroids, it is important to note that most studies included

patients with moderate-severe disease, and several studies excluded patients who were mechanically ventilated at baseline. REMAP-CAP is the only study to have investigated IL-6ra therapy specifically in critically ill patients with COVID-19 and even then only 30% of patients in the tocilizumab arm, 17% in the sarilumab arm, and 30% in the control arm required mechanical ventilation at baseline(21). Consequently, the highest acuity COVID-19 patients remain underrepresented, and it is difficult to draw firm conclusions regarding the benefit of IL-6ras in this subgroup of critically ill patients.

### IL-1 inhibition

Although the IL-1 antagonists anakinra and canakinumab hold FDA approval for moderate-to-severe rheumatoid arthritis, they are often used in other acute conditions identified clinically by cytokine storm or capillary leak such as CAR-T cell associated cytokine release syndrome (CRS) and macrophage activation syndrome (MAS). These agents have not been submitted to the FDA for EUA in COVID-19 disease at the time of this writing, nor are they recommended by the NIH Treatment Guidelines Panel due to limited demonstrable efficacy in several trials. A brief summary of the data from the REMAP-CAP(23), SAVE-MORE(26), CORIMUNO-ANA-1(27), and CAN-COVID(28) is included below.

Of the 2,274 participants in REMAP-CAP randomized into the Immunodulatory Domain, 365 were assigned to receive anakinra and 406 assigned to the control arm. Of the available trials, this is the only one to specifically enroll critically ill subjects. Thirty-seven percent of the patients assigned to anakinra were receiving invasive MV at baseline, compared with 32% for the other arms. The median number of organ support-free days was similar between the

groups (0 days [IQR 1 to 15 days] vs 1 days [IQR -1 to 15 days]; aOR 0.99 (95% CrI 0.74,1.35, 46.6% posterior probability of superiority to control). Mortality was also similar at 60% vs 63% (43.6% posterior probability of superiority to control). The SAVE-MORE trial randomized 594 patients hospitalized with moderate or severe COVID-19 pneumonia, using a plasma soluble urokinase plasminogen receptor (suPAR) level greater than or equal to 6ng/ml as an inclusion criterion in order to identify patients most likely to benefit from therapy (as determined by the preceding phase 2 SAVE study(29)). Unfortunately, patients receiving noninvasive or invasive mechanical ventilation were excluded from the study. Subjects in the anakinra group demonstrated a lower odds of progression of disease based on the WHO-Clinical Progression Scale (CPS), as well as favorable secondary endpoints including absolute decrease in sequential organ failure assessment (SOFA) score from baseline to Day 7, median time to hospital discharge, median duration of ICU stay, and lower 28-day mortality (3.2% vs 6.9%; HR 0.45 [95% CI 0.21, 0.98,] p=0.045). Unfortunately, the suPAR assay is not widely available, limiting incorporation and further evaluation of these findings.

The CORIMUNO-ANA-1 randomized 116 subjects with severe COVID-19 requiring greater than three liters per minute supplemental oxygen to either anakinra or standard of care. Of note, patients requiring HFNC oxygen, MV, or ICU admission were excluded. There was no difference between the groups in the two co-primary endpoints of proportion of patients who died or required noninvasive or invasive mechanical ventilation at Day 4 and proportion of patients who survived without the use of noninvasive or invasive MV (including HFNC) at Day 14. Of note, there were more serious adverse events in the treatment group (46% vs 38%), including an increased incidence of fungal infections in the anakinra group (18.6% vs 7.3%).

CAN-COVID randomized 454 patients with severe COVID-19 that were hypoxemic but not requiring mechanical ventilation to receive either canakinumab or placebo. There was no difference in the primary endpoint of proportion of patients who survived without MV from Days 3-29 (88.8% vs 85.7%,  $p=0.29$ ). Of note, mortality was low in both groups (4.9% vs 7.7%, OR 0.67 [95% CI 0.30, 1.50]). The results are confounded by an imbalance in administration of both steroids and tocilizumab between the treatment and placebo groups (41% vs 32%, and 2.2% vs 8.8%, respectively).

Some smaller series and cohort studies have examined critically ill patients(30-32), providing some potential insights for further consideration by clinicians, but the results are significantly limited by small numbers and variable methodologies.

### **JAK Inhibition**

As discussed above, the rationale for immunomodulation in COVID-19 relies on inhibition of cytokines that result in inflammatory organ injury (33). Thus, it is not surprising that rather than targeting individual cytokines, the attention turned to blocking the Janus Tyrosine Kinase (JAK) and Signal Transducers and Activators of Transcription (STAT) pathway (34). The JAK-STAT pathway is a pivotal cell signaling pathway that leads to downstream activation of several cytokines and subsequent immune proliferation and adaptation. Several drugs target the JAK-STAT pathway, and most of the studies in COVID-19 have focused on baricitinib (JAK 1/2 inhibitor) and ruxolitinib (JAK 1/2 inhibitor). The main difference between the two being that baricitinib is not metabolized via cytochrome P450 and is renally cleared (35). A third JAK3 inhibitor, tofacitinib, has also been assessed in smaller studies, along with additional JAK-STAT inhibitors.

The largest among the JAK inhibitor studies, the Adaptive COVID-19 Treatment Trial 2 (ACTT-2), assessed the role of baricitinib and remdesivir when compared to remdesivir alone (36). The trial was a multicenter international randomized double-blind placebo-controlled trial of 1033 hospitalized patients with a primary outcome of time to recovery on an eight-point OS. The study included about 30% of patients in each group who were receiving either NIPPV, HFNC, MV, or extracorporeal membrane oxygenation (ECMO) support. Across the board, the study demonstrated a benefit of the combination treatment when compared to remdesivir alone. Importantly, while the rates of glucocorticoid and dexamethasone use after enrollment were not significantly different between the two groups, they were relatively low in both groups—as per the intent of the study. This is particularly noteworthy for dexamethasone, which was used in just 6% and 7% of the investigational and control groups, respectively. This is vastly different than the subsequent adopted practice in which dexamethasone treatment became standard of care and baricitinib was often added after further review and assessment. The ACTT authors acknowledge that there is no head-to-head trial of steroids vs baricitinib, but do not postulate about the effect of real-world application of the concurrent use of steroids and baricitinib. Interestingly, the study did find that the patients who had received steroids had a higher incidence of infections (25.1% vs. 5.5% in patients not receiving steroids)(37).

Following ACTT-2, the COV-BARRIER trial studied patients receiving steroids (79.3% of the total patients) with the addition of baricitinib. The trial included a lower acuity population (only a quarter of patients in each group at the time of enrollment were on HFNC or NIPPV) and found no significant reduction in disease progression (primary outcome) but noted an overall reduced mortality in hospitalized patients (38). Regarding tofacitinib, a smaller study in Brazil

randomized 289 inpatients (less than 20% in the ICU) to receive tofacitinib (89.3% of the patients were also on steroids) and noted a decrease in the incidence of their primary outcome of respiratory failure or death (RR 0.63; 95% CI 0.41 to 0.97;  $p=0.04$ )(39).

A couple of smaller meta-analyses have assessed the role of JAK-STAT inhibitors and COVID-19. In one of the larger analyses (6 cohort studies and 5 clinical trials, for a total of 2367 patients), ruxolitinib and baricitinib led to a decreased use of mechanical ventilation, and possible trend toward decreased ICU admission and ARDS. The overall relative risk of death was 0.42 [95% CI 0.30, 0.59];  $p<0.001$ (40). Based on these studies, the NIH guidelines recommend steroids and a JAK-STAT inhibitor in hospitalized COVID-19 patients requiring oxygen. There has always been concern about the combined immunosuppressive effects resulting in infectious complications, but few studies have systematically examined this complication.

### **Other agents under investigation**

#### Granulocyte macrophage colony stimulating factor (GM-CSF) inhibition

The OSCAR(41) and LIVE-AIR(42) trials have reported results for investigation of anti-GM-CSF therapy with otilimab and lenzilumab, respectively, for severe COVID-19 infection. OSCAR was a large phase II trial ( $n=793$ ) of hospitalized patients with new onset severe COVID-19 infection requiring HFNC, NIPPV or invasive MV. It should be noted that patients with additional organ support needs including high dose vasopressor, dialysis, or ECMO were excluded. The primary endpoint was proportion of subjects alive and free of respiratory failure at Day 28, while secondary endpoints included all-cause mortality at Day 60. 52% of subjects were in the ICU without invasive MV and 22% required MV. 71% of subjects in the otilimab arm

vs 67% of controls met the primary endpoint at Day 28, adjusted mean difference 5.3% (95% CI -0.8, 11.4,  $p=0.09$ ). There was no difference in mortality between the groups. However, in a preplanned analysis, benefit of otilimab was observed for subjects >70 years old ( $n=180$ ): 65% vs 46% for primary endpoint (adjusted mean difference 19.1% [95% CI 5.2, 33.3],  $p=0.009$ ), 27% vs 41% mortality (adjusted mean difference 14.4% [95% CI 0.9, 27.9],  $p=0.04$ ). Despite the potential benefit for this vulnerable subgroup, GlaxoSmithKline ended the program for further development for this indication(43). LIVE-AIR, a phase III RCT, randomized 479 hospitalized COVID-19 patients not requiring MV to receive either lenzilumab or placebo in addition to standard of care. The primary endpoint was survival without MV at Day 28, with secondary endpoints including survival, proportion of MV, ECMO or death, and time to recovery. The population was of fairly high acuity, with 40% requiring HFNC or NIPPV. Lenzilumab improved ventilator-free survival, although there was no significant mortality difference 9.6% vs 13.9% (HR 1.38 [95% CI 0.81, 2.37],  $p=0.239$ )(42). Subsequently, the FDA declined the request for EUA for lenzilumab(44), though this may be revisited pending the anticipated results of ACTIV-5/Big Effect Trial (BET-B) (NCT04583969). ACTIV-5/BET-B, evaluating efficacy of remdesivir plus lenzilumab, is still pending at the time of preparation of this manuscript. Primary outcomes for this study include: occurrence of MV or death through Day 29 in subjects with baseline OS 5 or 6; OS score 7 (hospitalized on MV or ECMO) or 8 (death) in subjections with baseline OS 5 or 6 and CRP <150mg/L and age <85years. Mortality is included as one of many secondary endpoints in the study.

#### Tyrosine kinase inhibition

Imatinib, a Bruton's Tyrosine Kinase inhibitor, is proposed to provide benefit in the treatment of COVID-19 disease by direct viral inhibition, anti-inflammatory effect on cytokine and chemokine signaling, and mitigation of pulmonary capillary permeability(45-47) (48). The first reported trial of imatinib use in COVID-19 was the CounterCovid study, a randomized, double-blinded, placebo-controlled trial of hospitalized patients requiring oxygen supplementation (49). The primary outcome of this trial was time to discontinuation of mechanical ventilation and/or supplemental oxygen for more than 48 consecutive hours while alive at day 28. The investigators did not find any difference in time to discontinuation between the imatinib and placebo groups (HR 0.95 [95% CI 0.76, 1.20],  $p=0.69$ ). The 28-day mortality was quite low at 8% in the imatinib group and 14% in placebo group and the unadjusted HR for mortality was significant, however, it became non-significant after adjusting for imbalances in baseline characteristics. The number of patients that were admitted to the ICU was low with only roughly 20% and 18% in the imatinib and placebo groups, respectively. The rate of mechanical ventilation was similarly low at 15% and 14%, respectively. At the time of preparation for this manuscript, there are four trials investigating imatinib for the treatment of COVID-19 disease that are open and actively recruiting.

### **Immune products for viral elimination**

While convalescent plasma and monoclonal antibodies directed against SARS-CoV-2 are not immunomodulators strictly speaking, a brief discussion is warranted. These immune therapies are designed to provide a ready-made humoral immune response without the time and cellular machinery required for an endogenous response to infection or vaccination. While



this strategy may be beneficial in special populations, large scale trials have not demonstrated efficacy in hospitalized patients with severe disease.

Convalescent plasma failed to demonstrate improved 28-day mortality in a Cochrane review of seven RCTs including over 12,000 subjects, nor did it reduce new need for MV or promote liberation from ventilation(50). Similarly, benefit was not demonstrated in either RECOVERY(51) or REMAP-CAP(52) trials. The initial EUA issued August 23, 2020 for COVID-19 convalescent plasma for treatment of hospitalized patients was subsequently reissued on January 7, 2022 to limit use to plasma with high titers of anti-SARS-CoV-2 antibodies for the treatment of disease in patients with immunosuppressive disease or receiving immunosuppressive treatment in the inpatient or outpatient settings. At the time of preparation of this manuscript, the most recent update(55) states that data in this population remains limited and there remains a need for well-controlled randomized trials to determine demonstrable efficacy for this therapy. Access remains limited to administration under the EUA or investigational use (IND) pathways—both single patient and expanded access, and may be subject to further institutional protocols given the cost and availability of this product (53).

Monoclonal antibodies (mAbs) engineered to interact with one or more predefined viral target with high neutralizing activity have enjoyed success in the outpatient treatment of high-risk patients, but have not been available for use in hospitalized patients with severe disease. There have now been several products that have demonstrated efficacy in preventing progression to severe disease (eg, bamlanivumab(54), casirivimab and imdevimab(55), sotrovimab(56), and tixagevimab plus cilgavimab(57)), but a notable drawback to these agents is that they are susceptible to immune escape mutations, potentially rendering them ineffective

against subsequent SARS-CoV-2 variants(58). Of note, the FDA EUA documents for all currently authorized mAbs state that benefit has not been observed in hospitalized patients and that monoclonals may be associated with worse clinical outcomes when administered to hospitalized patients requiring HFNC or mechanical ventilation. This recommendation stems from a safety signal observed in the ACTIV-3 trial, resulting in early stoppage of enrollment and unblinding of data safety monitoring board (DSMB) data for FDA review. On day 5, there was evidence of worsened clinical outcomes, most notable in the subjects requiring high flow nasal cannula at baseline (maximum support allowed per inclusion criteria). Further, there was increased incidence of grade three and four adverse events and death in one of the treatment groups. Ultimately, the DSMB review determined that there was no statistically significant difference in adverse events, deaths, or worsened pulmonary outcomes, but there was no evidence of benefit and bamlanivimab did not meet criteria to advance in the platform trial and randomization did not resume(59).

An important question remains: is there a role for monoclonal antibody therapy for patients with severe or critical illness, and without an endogenous antibody response? Patients with immunosuppressing conditions (e.g., those receiving anti-CD20 therapy, hematologic malignancies, or history of solid organ or hematopoietic stem cell transplantation) are at exceedingly high risk of poor outcomes. Given the limited efficacy of the available direct antiviral agents, exogenous antibody administration may be a useful tool to enhance viral clearance. Conducting trials in this immunosuppressed population is particularly challenging.

**COVID-19 and critical illness: few answers, many questions**

Despite the staggering number of deaths attributed to COVID-19 since the start of the pandemic, we remain limited in strong, evidence-based treatment recommendations for our most critically ill patients. Indeed, even in moderate and moderately-severe disease for which more evidence is available, demonstrable and durable efficacy has been elusive. In a recent publication evaluating the fragility index of available RCTs for COVID-19, Itaya et al evaluated 36 treatment RCTs and found a fragility index (IQR) of just 2.5 (1-6) (60). In the absence of robust data, clinicians must be prudent and realistic about their ability to extrapolate trial data to specific subgroups of patients, including those with severe and critical disease. Very few trials have been designed and powered specifically for the critically ill, a population which has been historically difficult to study(61, 62). Throughout the current pandemic, interpretation and extrapolation of data in critical illness has been particularly challenging due to variability in trial design, rapidly evolving standards of care, and the impact of surging caseloads on depleted healthcare systems.

An interesting facet of this era of unprecedented investigation is the preponderance of phase III RCTs for COVID therapeutics utilizing OS-based clinical endpoints in lieu of more traditional “hard endpoints” such as mortality. For example, the OS developed by the NIH investigators early in the pandemic for the ACTT studies (NCT 04280705), influenced the design of many subsequent trials. When specifically considering the critical care population, however, interpretation of OS measurements can be challenging. The NIH eight-point scale provides much more granularity on the lower end of the OS, and assigns equal weight to clinical changes with vastly different implications. This is counterintuitive to our understanding of critically ill patients, in whom prognosis is dramatically impacted by sequential organ dysfunction(63). That

all mechanically ventilated and ECMO patients receive the same score draws false equivalence between distinct phenotypes of patients, such as those with modest ventilator requirements, severe ARDS, need for renal replacement, liver failure, coagulopathy, or mechanical circulatory support. While the numeric distance for these patients to reach a recovery endpoint on the OS is the same, the clinical trajectory and risk of death is vastly different. Indeed, as one considers the myriad clinical challenges these subjects face and how relatively underrepresented they are in the majority of the landmark therapeutic trials, it becomes increasingly difficult to say with certainty what degree of benefit these patients may see from the same therapy as patients with moderate disease severity. Several publications have addressed the complexities of endpoint selection in this setting, including competing factors of wide clinical spectrum of disease associated with SARS-CoV-2 infection, urgent need for rapid evaluation of therapies in the face of widespread morbidity and mortality, fluctuating standards of care over time, and impact of extrinsic factors such as surging caseloads on healthcare systems(64-66). There are benefits to non-mortality endpoints in the setting of a global pandemic, and time-to-event endpoints such as used in ACTT attempt to overcome the risk of missing treatment effects due to selection of an incorrect time point *a priori*. However, “time to recovery” may not capture the dynamic morbidity incurred or resources utilized over the course of a prolonged critical illness. Similarly, “time to recovery” is really time to first measured recovery endpoint and does not account for patients that developed subsequent complications, hospital readmission, or even death, all of which are frequent complications following critical illness(67, 68). Finally, the statistical handling of death in time to recovery analysis can also feel lacking when viewed from a clinical lens of a critical care provider, where mortality has been reported as high as 30-60%(66). In

ACTT, deaths are censored at the end of the study period and imputed as an “infinite time to recovery”. While this may be reasonable approach from a viewpoint of a statistician or trialist, there is clearly a huge clinical difference between a subject failing to meet a composite recovery endpoint and death. The statistical choices made by clinical trialists are understandably aligned with the public health objective to address the needs of the vast numbers of patients impacted by mild, moderate, and severe disease with fairly modest and manageable clinical needs. Whether the results from these trials are meaningful and applicable to those with critical illness, however, is less clear. The accompanying Figure 1 provides a side-by-side comparison of the currently available treatment recommendations for severe and critical COVID-19(25, 69, 70) with a qualitative visual representation of the data discussed in this review, designed to reflect the applicability of the published immunotherapy trial results to a critically ill population. As depicted, only two studies possessed all three study design components examined, and these trials were relatively small and demonstrated minimal treatment benefit. Critically ill patients are physiologically distinct, have different pharmacokinetic and pharmacodynamic considerations, and, for those who do not die quickly, often require prolonged hospital courses with resultant increased risk of nosocomial complications. While extrapolation of data and therapeutics from a moderately ill population to the critically ill is not uncommon, it is fraught and likely to be inadequate. Unfortunately, for many of the reasons above, dedicated trials in the critically ill are challenging to perform and interpret. Thus, clinicians are often left to rely on subgroup analyses, Phase 1/2 data, small case series, and clinical experience to refine treatment protocols for the critically ill. Unfortunately, these data streams were also subjected to the constraints of the pandemic. Due to the

immense clinical need, the rapidity with which investigations and regulatory review were occurring, and fluidity of trial designs during this period, immunologic endpoints and biomarker data were relatively de-valued in regulatory review in lieu of clinical endpoints. While this was necessary, we likely lost granular immunologic data which may have allowed us to identify important physiologic differences between patients with moderate and severe disease in general, and those with critical illness specifically. Incorporating detailed immunophenotyping of patients across the wide spectrum of severe disease alongside mortality and clinical outcome endpoints in large RCTs may allow us discriminate between groups of patients and direct immunomodulator therapy to patients who may benefit most.

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**FIGURE LEGEND****Figure 1. Comparison of treatment recommendations for severe and critical COVID-19**

**infection and the relevance of clinical trial evidence to the ICU population.** A) Algorithm of currently recommended treatment guidelines for severe and critical COVID-19 infection. B)

Visual representation of the applicability and generalizability of the results of the cited trials to

a critically ill population by comparing three aspects of study design with the magnitude of treatment effect observed in the trials. Treatment effect is a qualitative measure which includes

comparison across multiple types of reported results including odds ratios, hazard ratios,

survival analyses. The size of the circle corresponds to the size of the trial. Abbreviations: ACTT;

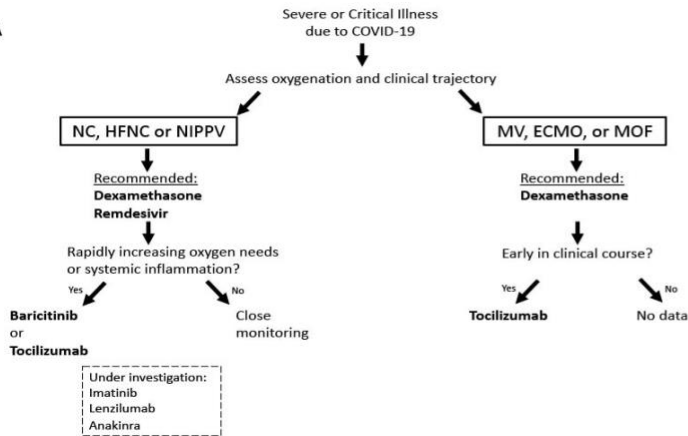
CDX = CODEX; CO AN = CORIMMUNO-ANA-1; COV BAR = COVID BARRIER; CN CO = CAN-COVID;

CP CO = CAPE COVID; CT CO = CounterCovid; CVTA = COVACTA; LA = LIVE AIR; OSC = OSCAR;

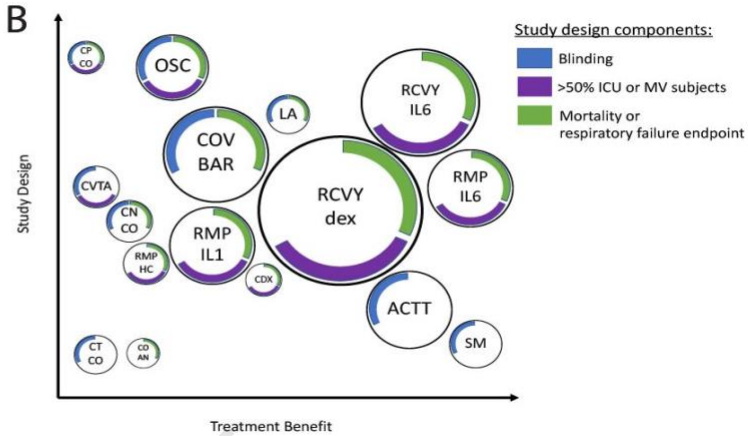
RCVY dex = RECOVERY dexamethasone; RCVY IL6 = RECOVERY tocilizumab; RMP IL1 = REMAP

CAP anakinra; RMP IL6 = REMAP CAP tocilizumab/sarilumab; SM = SAVE MORE.

A



B



**Figure. Comparison of treatment recommendations for severe and critical COVID-19 infection**

**and the relevance of clinical trial evidence to the ICU population. A)** Algorithm of currently

recommended treatment guidelines for severe and critical COVID-19 infection. B) Visual

representation of the applicability and generalizability of the results of the cited trials to a

critically ill population by comparing three aspects of study design with the magnitude of

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