Choosing immunomodulating therapies for the treatment of COVID-19

Recommendations based on placebo-controlled trial evidence

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Systematic review

Choosing immunomodulating therapies for the treatment of COVID-19: recommendations based on placebo-controlled trial evidence

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ABSTRACT

Background: Immunomodulatory therapy has been extensively studied in randomized clinical trials for the treatment of patients hospitalized for COVID-19 with inconsistent findings. Guideline committees, reviewing the same clinical trial data, have generated different recommendations for immunomodulatory therapy.
Objectives: We hypothesize that trial design differences, specifically whether the study utilized an open-label or placebo-controlled design, accounted for the inconsistent mortality effects reported in clinical trials of immunomodulator therapies for COVID-19.
Sources: We reviewed COVID-19 treatment guidelines (World Health Organization [WHO], Infectious Diseases Society of America [IDSA] and The National Institutes of Health [NIH]) and identified the meta-analyses associated with glucocorticoids, IL-6 inhibitors, JAK kinase inhibitors, and complement C5a inhibitors that were available to the guideline authors at the time recommendations were either made or updated.
Content: We identified a meta-analysis for each of the immunomodulator classes that are included in current COVID-19 treatment guidelines: glucocorticoids [WHO Rapid Evidence Appraisal for COVID-19 Therapies (REACT) Working Group; Shankar-Hari M, Vale CL, Godolphin PJ, Fisher D, Higgins JPT, et al. Association between administration of IL-6 antagonists and mortality among patients hospitalized for COVID-19: A meta-analysis. JAMA. 2021;326:499–518] (cited 419), IL-6 antagonists [WHO Rapid Evidence Appraisal for COVID-19 Therapies (REACT) Working Group; Shankar-Hari M, Vale CL, Godolphin PJ, Fisher D, Higgins JPT, et al. Association between administration of IL-6 antagonists and mortality among patients hospitalized for COVID-19: A meta-analysis. JAMA. 2021;326:499–518] (cited 419), JAK inhibitors [Kramer A, Prinz C, Fichtner F, Fischer AL, Thieme V, Grundeis F, et al. Janus kinase inhibitors for the treatment of COVID-19. Cochrane Database Syst Rev. 2022;6:CD015209] (cited 34), and complement C5a inhibitors [Tsai CL, Lai CC, Chen CY, Lee HS. The efficacy and safety of complement C5a inhibitors for patients with severe COVID-19: A systematic review and meta-analysis. Expert Rev Anti Infect Ther. 2023;21:77–86] (cited 1). Using the same randomized clinical trials, we evaluated the four meta-analyses accounting for trial design: placebo-controlled or open-label. Glucocorticoids (Risk Ratio [RR] 0.91 [95% CI, 0.49–1.69]), IL-6 inhibitors sarilumab (RR 1.17 [95% CI, 0.96–01.43]), and tocilizumab (RR 0.95 [95% CI, 0.76–1.19]) did not reduce mortality in placebo-controlled trials, whereas baricitinib did confer a large survival benefit (RR 0.65 [95% CI, 0.52–0.81]). The complement C5a inhibitor, vilobelimab, also reduced mortality in a single placebo-controlled trial (RR 0.76 [95% CI, 0.57–1.0]).
Implications: Placebo-controlled trial evidence indicates that baricitinib should be the first choice immunomodulator for patients hospitalized for COVID-19 who require any form of oxygen support—low- or high-flow oxygen, non-invasive or invasive ventilation. Vilobelimab warrants study in a

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large placebo-controlled trial. Treatment guidelines for future pandemics should prioritize the results of placebo-controlled trials. **Daniel A. Sweeney, Clin Microbiol Infect 2024;30:611**

Introduction

The use of immunomodulation—to enhance, maintain, or dampen the host immune response to an infection—has been of great interest to clinicians and physician-scientists for decades, although successful treatment regimens have been few. In the case of pneumonia, efforts to modulate the immune response have focused on reducing inflammation with the best example being the combination of adjunctive glucocorticoids with trimethoprim/sulfamethoxazole to treat patients with acquired immunodeficiency syndrome and *Pneumocystis pneumonia* [1]. Immunomodulation including glucocorticoid therapy for the treatment of other types of pneumonia has not been consistently successful and in some cases, possibly harmful [2,3]. The SARS-CoV-2 pandemic rekindled the enthusiasm for immunomodulatory therapies for the treatment of pneumonia. After the results of the open-label RECOVERY trial, glucocorticoids therapy became the standard of care for hospitalized patients with COVID-19 who required oxygen therapy [4]. Subsequently, other immunomodulators (IL-6 pathway inhibitors, Janus kinase [JAK] inhibitors, and complement C5a inhibitors) were studied using either open-label or placebo-control designs yielding inconsistent results, leaving clinicians (and guideline authors) with numerous treatment options to offer hospitalized patients with COVID-19 albeit with uncertainty as to which therapy or therapies are best for their patients. We hypothesized that trial design, and in particular, the use of open-label or placebo-controlled designs, may account for these disparate results. To account for differences in patient populations and supportive care, and in hospital resource allocation across the multiple studies conducted in many different countries, a random-effects meta-analysis was employed. The aim of this review is to re-analyse the data supporting each of these modulators and guideline recommendations, and ultimately provide the reader with clear recommendations for how to choose immunomodulation therapy for hospitalized patients with COVID-19.

Methods

In addition to performing a narrative review, we re-analysed published meta-analyses addressing the three major classes of immunomodulatory therapies tested for the treatment of hospitalized patients with COVID-19. Studies were chosen based on whether they directly informed major guidelines. In the case of glucocorticoid therapy, we found the meta-analysis that was conducted by WHO and referenced by both the NIH and IDSA guidelines [5] (cited 1724). There was one meta-analyses of IL-6 antagonists that was also conducted by WHO and referenced by the IDSA guidelines [6] (cited 419). None of the major guidelines referenced a meta-analysis addressing JAK inhibitor therapy and so we gave priority to the Cochrane library meta-analysis of JAK inhibitor therapy for COVID-19 [7] (cited 40). For the complement C5a inhibitor, vilobelimab, which is discussed by one major guideline (NIH), a PubMed search identified only one meta-analysis addressing this therapeutic class for the treatment of COVID-19 [8] (cited 2). Using the same randomized controlled clinical trials (RCTs) included in these studies, we replicated the four meta-analyses (Cochrane RevMan Web [https://revman.cochrane.org/info]) above and tested our hypothesis by accounting for the original trial design: placebo-controlled and open-label. The mortality data were extracted directly from each of the four meta-analyses, but also confirmed by reviewing all of the individual trials included in these meta-analyses. The effect size was measured using risk ratio and the analyses employed the random-effects model to account for the standard of care variability among trials, hospital sites, and countries.

Glucocorticoids

On 22 June 2020, the RECOVERY trial published its preliminary results concluding that oral dexamethasone therapy (6 mg daily for 10 days or until discharge—whichever occurred first) resulted in a 3% absolute mortality benefit for patients hospitalized with COVID-19 (22.9% vs. 25.7% for treatment vs. usual care; rate ratio 0.83; 95% CI, 0.74–0.93), although there was concern for the risk of harm in individuals not requiring oxygen (mortality of 17.8% vs. 14.0% for treatment vs. usual care; rate ratio 1.19; 95% CI, 0.92–1.55) [9]. The greatest mortality reduction was noted among patients receiving mechanical ventilation (29.3% vs. 41.4% for treatment vs. usual care; rate ratio 0.64; 95% CI, 0.51–0.81). Dexamethasone was heralded as the first treatment to reduce the risk of mortality in patients with COVID-19 and was quickly adopted as the standard of care for hospitalized patients who required supportive oxygen.

Despite the size of the RECOVERY trial ($n = 11\,303$), there were several reasons to question the study conclusions. The high heterogeneity of supportive care among the 176 hospital sites could have created a performance bias in favour or against experimental therapies, and this bias could not have been prevented by randomization alone because it occurs after the randomization procedure. A total of 43% of the recruited patients ultimately did not undergo randomization and trial enrolment: 18% were excluded because dexamethasone was not available, or the attending physician considered the patient not suitable to receive the drug; 25% were randomized to receive dexamethasone or other drugs of the RECOVERY trial. A total of 11% of patients did not have laboratory-confirmed SARS-CoV-2 infection at time of enrolment. No reliable data on monitoring safety (adverse events and superinfections) or long-term outcomes were collected. There were also no data reported that were specific to immunosuppressed patients. Most concerning, the mortality rate of the usual care group was unexpectedly very high at day 28 (41.4% in ventilated patients, 26.2% in patients on oxygen, and 14% in patients without oxygen). These rates are several folds higher than the control groups of other RCTs conducted at that time in settings with similar resources, raising critical questions both about the quality of usual care and whether these results are externally valid [10,11].

The results of the RECOVERY study are better understood when considered alongside all the RCTs that assessed the impact of glucocorticoids for the treatment of COVID-19 including trials that employed a placebo-controlled design. A WHO-led meta-analysis of RCTs conducted during the pandemic concluded that glucocorticoids were associated with a mortality reduction; however, the RECOVERY trial was heavily weighted in this study. Moreover, this meta-analysis favoured the use of a fixed-effect model that assumes that the treatment effect was identical ('fixed') among all hospital sites of all trials from all different countries, which does not represent the real-world experience. Because these trials enrolled patients at different stages of the disease course and received highly

variable supportive care across more than 25 countries with very heterogeneous hospital resource availability, the assumption that the treatment effect would be identical is neither likely nor realistic, and therefore a random-effects model is the most appropriate approach. When this analysis is performed using a random-effects model, there is no significant mortality benefit associated with glucocorticoid therapy (RR 0.86 [95% CI, 0.73–1.01]) (Fig. 1). And when this meta-analysis is further analysed by accounting for study design, the open-label trials showed a survival benefit (RR 0.83 [95% CI, 0.71–0.96]); however, no benefit was detected among the placebo-controlled trials (RR 0.91 [95% CI, 0.49–1.69]).

IL-6 pathway inhibitors

IL-6 has been identified as a plausible immunotherapy target for patients with COVID-19 because elevated levels of this proinflammatory cytokine are found in patients with SARS-CoV-2 infections, although it should be noted that IL-6 levels in severe COVID-19 disease are approximately 10–40 fold less than what has been observed in acute respiratory distress syndrome trials performed before the pandemic [12,13]. Guidelines broadly recommend the use of IL-6 pathway inhibitors tocilizumab or sarilumab for most patients hospitalized for COVID-19 who require some form of oxygen support. Per NIH guidelines, the minimum criteria for IL-6 pathway inhibitor therapy is a rapidly increasing supplemental oxygen need, whereas other guidelines recommend starting IL-6 pathway inhibitors if the patient's oxygen saturation on room air is <90% (WHO Guidelines) or <94% (IDSA Guidelines) [14–16]. Within this therapeutic class, tocilizumab (8 mg/kg not to exceed 800 mg single IV dose; a second dose could be considered depending on the patient's clinical course)—more so than sarilumab—is the most commonly recommended IL-6 pathway inhibitor for the treatment of COVID-19. Despite these broad recommendations for the use of tocilizumab, there are important aspects of the individual supporting studies and the subsequent statistical meta-analysis of these studies that weakens the conclusion that tocilizumab is beneficial for the treatment of patients with COVID-19.

The two trials (both open-label design) that led these guideline committees to update their recommendations to include the use of tocilizumab therapy were the REMAP-CAP and RECOVERY studies [17,18]. The REMAP-CAP trial specifically enrolled patients treated in the intensive care unit (multi-centre, 366 randomized to receive tocilizumab, 48 to sarilumab, and 412 to standard of care) and the secondary endpoint showed a reduction in hospital mortality associated with IL-6 pathway inhibitor therapy (28.0% for tocilizumab, 22.2% for sarilumab compared with 35.8% for patients receiving standard of care). However, these results were not robust because the fragility index for tocilizumab and mortality benefit was only 2. The results of the open-label RECOVERY study most influenced these guideline committees because this is the single largest open-label trial (4116 participants) evaluating tocilizumab for the treatment of COVID-19 and it showed a 28-day mortality benefit of IL-6 pathway inhibition compared with usual care (31% for tocilizumab and 35% for usual care). However, the actual effect of tocilizumab in the RECOVERY trial is difficult to parse from the effect of corticosteroid therapy that was also administered in 82% of the participants. Indeed, the RECOVERY trial authors note an interaction between glucocorticoid and tocilizumab treatment and mortality, which indicates that the effect of tocilizumab was present only when given together with glucocorticoids. In fact, the I^2 value associated with this analysis was 86% suggesting that 86% of the heterogeneity regarding the tocilizumab mortality effect was because of glucocorticoids and not because of chance. Most worrisome, the mortality risk ratio for tocilizumab therapy in the absence of concomitant corticosteroid therapy changed toward harm (RR 1.16 [95% CI, 0.91–1.48]).

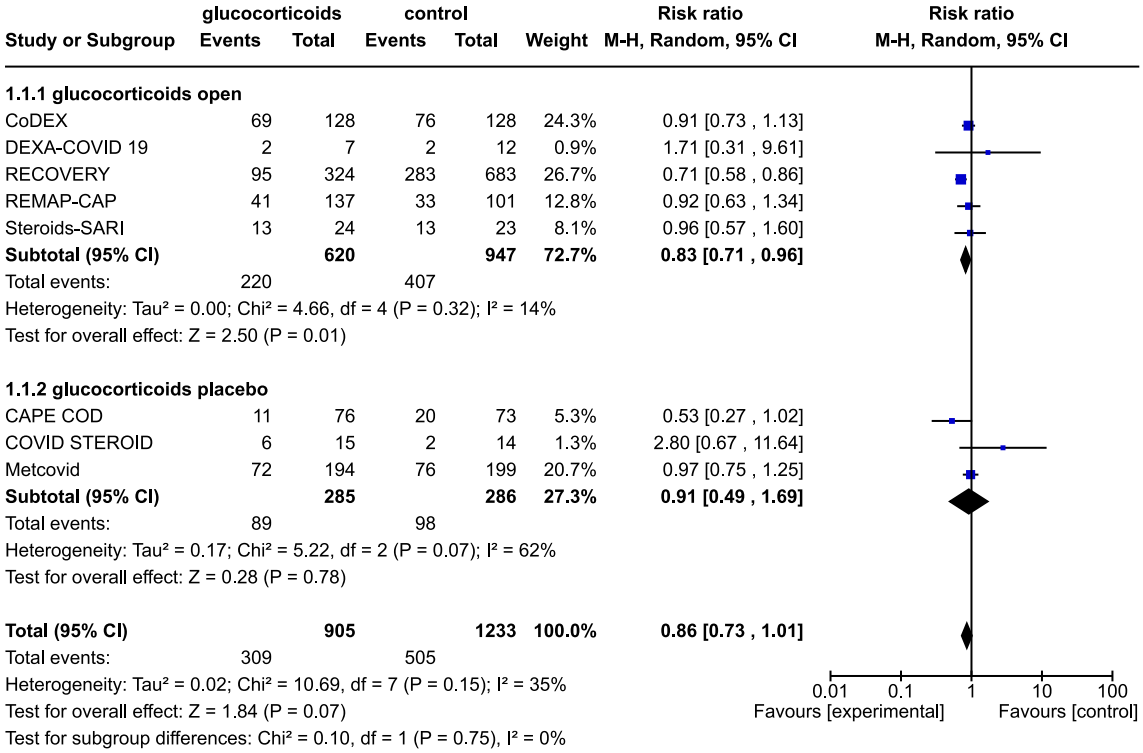

Fig. 1. Forest plot of RCTs testing the effect of glucocorticoid treatment on mortality of patients hospitalized for COVID-19. The trials are subdivided into open-label ("open") and placebo-controlled ("placebo") groups.

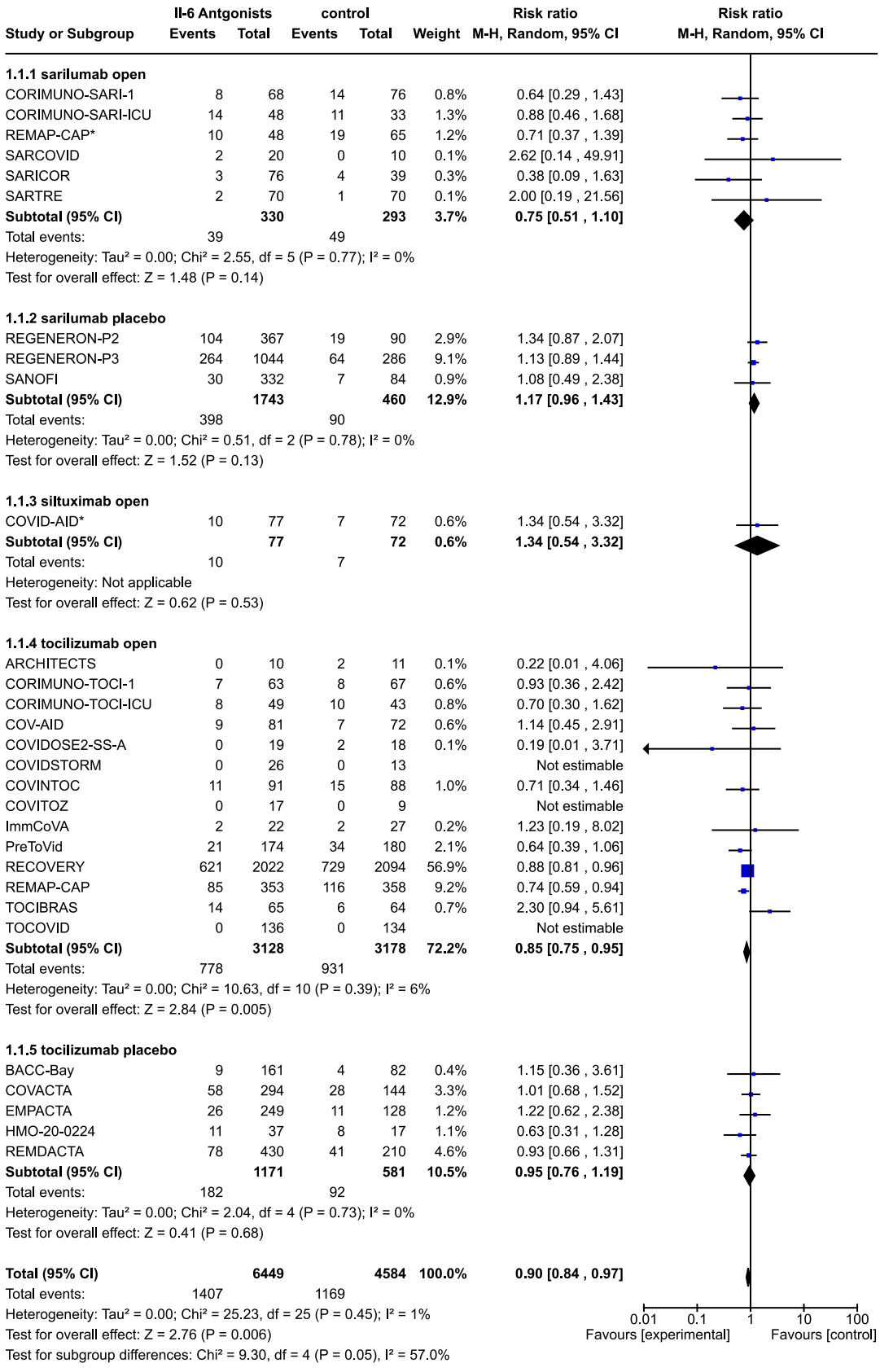

Fig. 2. Forest plot of RCTs testing the effect of IL-6 antagonist treatment on mortality of patients hospitalized for COVID-19. The trials are subdivided by agent and whether the trial employed either an open-label ("open") or placebo-controlled ("placebo") design.

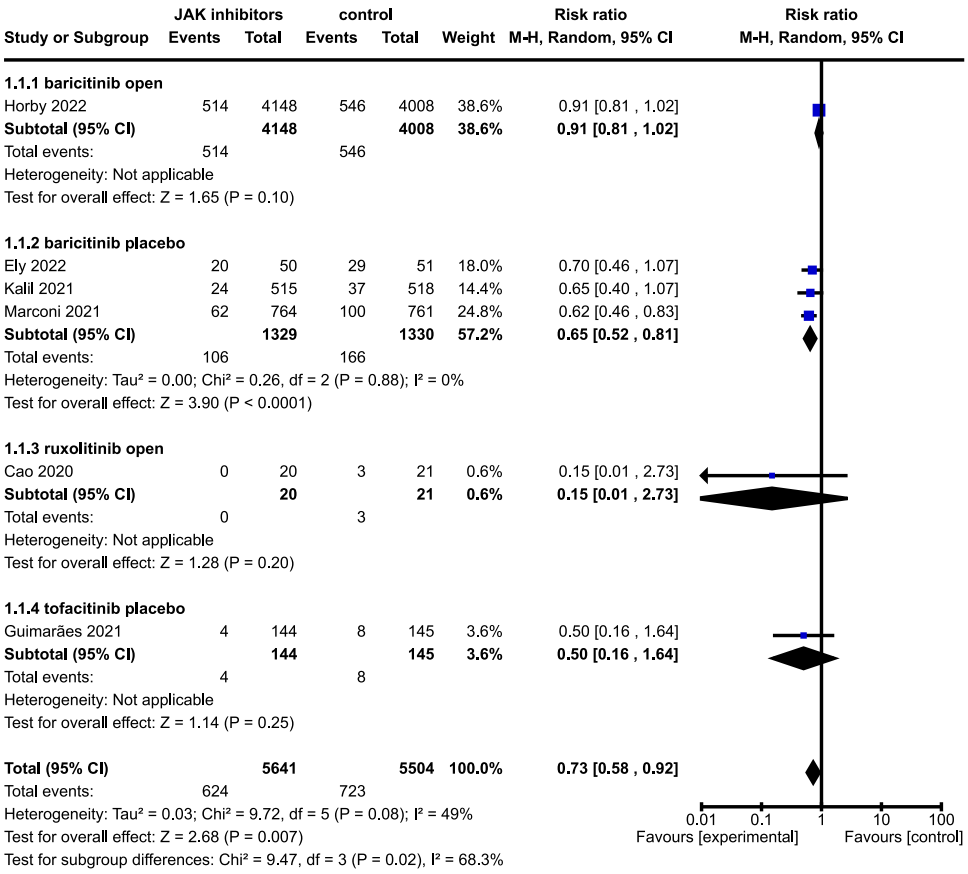

Fig. 3. Forest plot of RCTs testing the effect of JAK-inhibitor treatment on mortality of patients hospitalized for COVID-19. The trials are subdivided by agent and whether the trial employed either an open-label ("open") or placebo-controlled ("placebo") design.

The results of all the published reports investigating IL-6 pathway inhibitor therapy (tocilizumab, sarilumab, or siltuximab) for the treatment of patients with COVID-19 are similarly complicated and best understood with a meta-analysis using the most appropriate random-effects model and accounting for open-label and placebo-controlled studies (Fig. 2). The most cited meta-analysis conducted by a team from the WHO included 27 randomized trials and 10 930 participants utilized a fixed-effect model and concluded that IL-6 antagonist treatment compared with usual care or placebo was associated with a 28-day mortality benefit (OR 0.86 [95% CI, 0.79–0.95]) [6]. When meta-analysis of these same studies subdivided by specific IL-6 inhibitor is performed using a random-effects model, a more nuanced conclusion emerges (Fig. 2). Although there is an overall class benefit-associated IL-6 therapy, this benefit is limited to open-label studies involving tocilizumab. Sarilumab (whether studied using an open-label or placebo trial design), siltuximab (open-label design), or most importantly, tocilizumab when studied in placebo-controlled trials did not show a mortality benefit (RR 0.95 [95% CI, 0.76–1.19]).

JAK inhibitors

JAKs play a role in the mediation and amplification of extracellular signalling involving proinflammatory cytokines IL-2, IL-4, IL-7, IL-9, IL-15, and IL-21. JAK inhibitors have been developed for the treatment of various auto-immune diseases and three members of this class—baricitinib, ruxolitinib, and tofacitinib—have been repurposed and evaluated in RCTs for the treatment of hospitalized patients with COVID-19.

Of the JAK inhibitors, baricitinib is the most thoroughly studied. Three placebo-controlled double-blind RCTs have been completed, and all have consistently demonstrated benefits of baricitinib treatment: ACTT-2 trial showed a significant faster clinical improvement and lower progression to invasive ventilation or death (RR 0.60 [95% CI, 0.50–0.95]); COV-BARRIER trial showed a significant reduction in 28-day mortality (HR 0.57 [95% CI, 0.41–0.78]), COV-BARRIER-2 trial that evaluated only patients on invasive ventilation for COVID-19 also showed a significant mortality reduction (HR 0.54 [95% CI, 0.31–0.96]) [19–21]. A fourth RCT, RECOVERY, tested baricitinib versus control (open-label), similarly showed a significant mortality reduction (RR 0.87 [95% CI, 0.77–0.99]) [22]. Importantly, both COV-BARRIER and RECOVERY trials showed that there were no interactions between baricitinib and glucocorticoids regarding mortality, indicating that the baricitinib's survival benefits occurred independent of (with and without) glucocorticoids. Notably, side effects, including secondary infections, were significant less frequent with baricitinib compared with placebo [23]. And when baricitinib therapy was tested in the only randomized head-to-head trial comparing JAK inhibitor therapy with dexamethasone, the two immunotherapies resulted in similar mechanical ventilation-free survival by day 29; however, baricitinib was associated with significantly fewer adverse events including serious or life-threatening adverse events [21].

Meta-analysis of studies included in the Cochrane Review of JAK inhibitors for the treatment COVID-19 and using a random-effects model showed a significant survival benefit compared with either usual care or usual care and placebo (RR 0.73 [95% CI, 0.58–0.92])

(Fig. 3). Subgroup analysis shows that this survival benefit is mostly buoyed by the results of baricitinib therapy studied in three placebo-controlled trials that showed a large effect size (RR 0.65 [95% CI, 0.52–0.81]).

Complement C5a inhibitors

Inhibition of complement system activation has been identified as a possible therapeutic target in the treatment of patients with COVID-19. Complement can be activated directly by SARS-CoV-2, and elevated levels of C5a are associated with disease severity and mortality [24]. Several C5a inhibitors have been studied in the treatment of COVID-19 including ravulizumab, vilobelimab, and zilucoplan. Vilobelimab has been granted FDA Emergency Use Authorization for hospitalized adults with COVID-19 based on the results from the multi-centre Phase III PANAMO trial [25,26]. In this double-blind, placebo-controlled trial (n = 368) vilobelimab administered within 48 hours after intubation decreased overall mortality (HR 0.67 [95% CI, 0.48–0.96]). However, a statistically significant mortality benefit of vilobelimab treatment was not detected when the pre-specified primary site-stratified Cox model was applied (HR 0.73 [95% CI, 0.50–1.06]).

A recent meta-analysis of complement C5a inhibitors included four RCTs testing three different agents from this class [8]. Repeat meta-analyses of these studies using a random-effects model showed an overall mortality benefit for complement C5a inhibitor therapy (RR 0.72 [95% CI, 0.55–0.94]) (Fig. 4). Aside from the PANAMO placebo-controlled trial testing vilobelimab therapy (RR 0.76 [95% CI, 0.57–1.00]), neither ravulizumab nor zilucoplan studied in open-label trials showed a mortality benefit (RR 0.16 [95% CI, 0.01–2.64] and RR 0.44 [95% CI, 0.14–1.39], respectively). Although vilobelimab appears to potentially be an effective treatment for patients with critical COVID-19, confirmation in larger RCTs is needed in accordance with the US FDA and its precedent for requiring for favouring at least two controlled clinical trials [27].

Conclusion

When the clinical data for immunomodulation therapy for patients with COVID-19 are assessed based on the results of placebo-controlled trials, treatment recommendations emerge that differ from current guideline recommendations. Glucocorticoids and IL-6 inhibitors have not been shown in placebo-controlled trials to provide a survival benefit among patients hospitalized for COVID-19. Complement C5a inhibition with vilobelimab in a single placebo-controlled trial showed a mortality benefit albeit without accounting for site stratification. JAK inhibition, specifically baricitinib, is the immunomodulator with the most placebo-controlled trial data (3 trials, 2659 patients) consistently supporting its use with the largest survival benefit effect size and low risk of serious adverse events. Chiefly based on these findings, we recommend the use of baricitinib as the immunomodulator of first choice for all hospitalized patients because of COVID-19 who are receiving oxygen therapy, including low- and high-flow, non-invasive and invasive ventilation. We further advocate for an additional, larger placebo-controlled trial to measure the efficacy of vilobelimab that has shown promise in one placebo-controlled trial.

At its core, an RCT is designed to ensure that biases are minimized and there are multiple strategies that can be employed to not

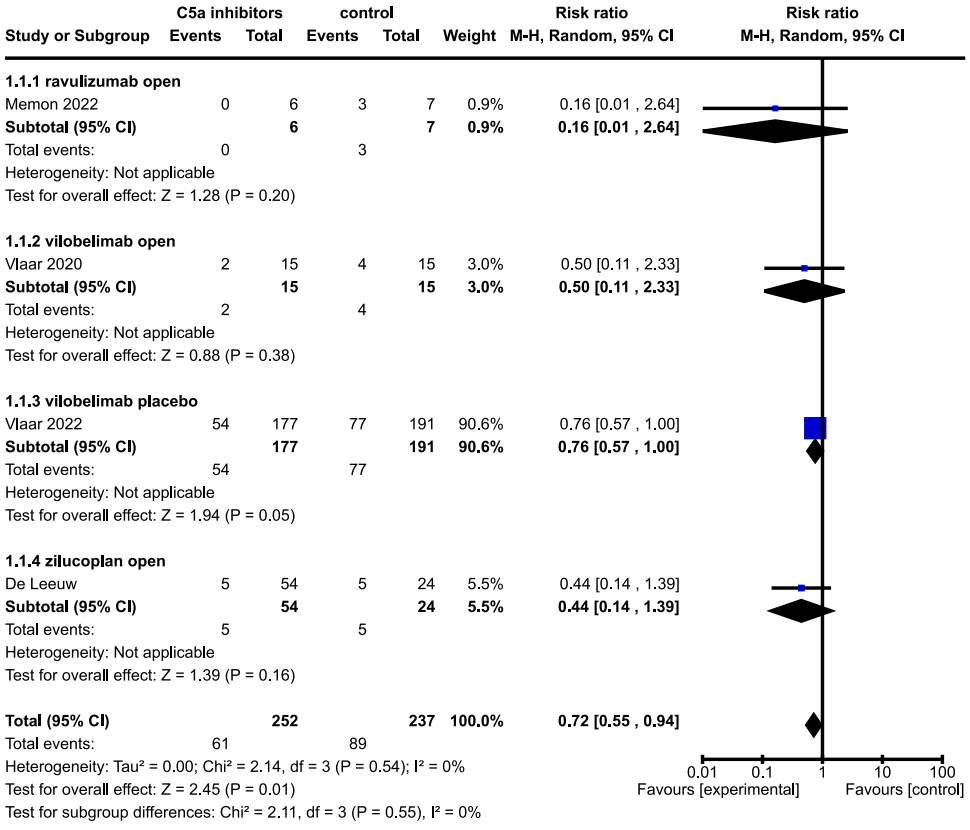

Fig. 4. Forest plot of RCTs testing the effect of complement C5a inhibitor treatment on mortality of patients hospitalized for COVID-19. The trials are subdivided by agent and whether the trial employed either an open-label ("open") or placebo-controlled ("placebo") design.

compromise the fidelity of the results. Implementation of a placebo-control design to a randomized trial is among the best approaches to avoid a multitude of biases, particularly ascertainment and performance biases that may be especially prevalent during a pandemic because well-intentioned clinicians urgently seek new treatments for critically ill patients. Indeed, the risk of open-label trial may lead to an overestimation of the benefits of a particular therapy. When blinded and unblinded studies involving the same intervention in critical care medicine have been compared, unblinded studies have demonstrated a 9% (95% CI, 1–16%) more favourable survival result compared with placebo-controlled trials [28]. More recently, a meta-analysis of convalescent plasma for the treatment of COVID-19 also showed a clinical benefit in open-label but not when studied in placebo-controlled trials [29]. This trend is precisely what we observed with the beneficial effect of glucocorticoids and IL-6 limited to open-label designed trials.

Despite these benefits, the value of the placebo-controlled randomized trial has been under siege in recent years [30]. During the pandemic, the placebo-controlled trial was viewed as impractical and inefficient, although it should be noted that the first trial to be completed during the pandemic enrolled 1062 patients from 60 sites in 10 countries in 58 days and released their preliminary results 10 days after completion of the study led by the NIH [10]. In place of placebo-controlled trials, large open-label trials such as the RECOVERY trial were constructed to rapidly identify potential new therapies. The release of the results from this trial led to the suspension of enrolment in other placebo-controlled trials investigating the role of glucocorticoids to treat COVID-19 [5]. Consequently, of the 1745 patients studied in the WHO-led meta-analysis, 571 were enrolled in placebo-controlled trials, and no other RCT in this meta-analysis, open label or placebo controlled, showed a mortality reduction with glucocorticoid therapy for the treatment of patients with COVID-19.

In much the same way that clinical trial design changed during the pandemic, some subsequent meta-analyses also diverged from established, conservative methodology. The random-effects model that allows for the realistically expected variable effect across studies is the recommended approach when performing a meta-analysis because it is more appropriate and better accounts for the clinical care and resource allocation variability between trials [31]. Yet the two meta-analyses authored by WHO investigators that addressed glucocorticoids and IL-6 inhibitor therapies based their conclusions on analyses that employed the fixed-effect model, which assumed an identical treatment effect among all different studies and distinct hospital sites in hundreds of countries.

We acknowledge limitations of this review. This study does not represent a de novo meta-analysis. We did not perform a literature search that would have identified if there were more recent RCTs addressing any of the immunomodulators we have discussed. Rather we re-analysed the studies included in prominent, published meta-analyses, which were referenced by the guidelines, or written by members of the guidelines' committees.

In conclusion, placebo-controlled randomized trials from the SARS-COV-2 pandemic unequivocally support the use of baricitinib immunomodulator therapy for the survival benefit of all hospitalized patients for COVID-19 who require oxygen therapy, including non-invasive and invasive ventilation. Guideline endorsement of both glucocorticoids and IL-6 inhibitors is based only on the results of open-label trials, whereas placebo-controlled trials consistently failed to show a mortality reduction of these two immunomodulators for the treatment of COVID-19. Finally, vilobelimab may represent the next class of immunomodulatory therapy for the treatment of patients with COVID-19, although an additional, large placebo-controlled trial showing the reproducibility of the original results is needed. These results strongly suggest that treatment guidelines for future pandemics should prioritize data from placebo-controlled trials over the results of open-label trials.

Author contributions

All authors contributed to the final version of the manuscript and approved it for publication.

Transparency declaration

DAS and ACK were investigators for the National Institutes of Health Adaptive COVID-19 Treatment Trial that was funded by the US federal government. SML was an investigator for the PANAMO study that was funded by the German Federal Government and InflaRx. PP has no conflicts of interest to declare. No funding was received for this study.

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