EXPERT REVIEW OF CLINICAL PHARMACOLOGY
https://doi.org/10.1080/17512433.2021.1949286

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REVIEW

Tocilizumab for the treatment of non-critical COVID-19 pneumonia: an overview of the rationale and clinical evidence to date

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ABSTRACT

Introduction: Tocilizumab is one of the main repurposed therapies investigated for COVID-19 pneumonia since the start of the pandemic, but there has been conflicting evidence for its use.

Areas covered: This review covers the physiology of interleukin-6 and its role in the pathophysiology of COVID-19. We discuss the use of tocilizumab in other diseases and the rationale for its use in COVID-19. We summarize the design, contrasting results, and implications of the clinical trials of tocilizumab in COVID-19 to date and discuss the current guidance for its use.

Expert opinion: The evidence to date suggests benefit with the use of tocilizumab in some but not all patients with COVID-19. Benefit seems to be greatest when given early after clinical deterioration with the presence of systemic inflammation. However, questions remain around the optimal timing, patient selection, and concomitant treatments.

ARTICLE HISTORY
Received 16 April 2021
Accepted 25 June 2021

KEYWORDS
Tocilizumab; COVID-19; interleukin-6; cytokine release syndrome; immunomodulatory therapy

1. Introduction

The COVID-19 pandemic has resulted in intense interest in drug repurposing to identify potentially effective therapies for this new disease. Tocilizumab, an interleukin six (IL-6) inhibitor licensed for use in some rheumatic diseases, has attracted significant attention as a repurposed drug and is the focus of many observational and randomized controlled trials. Over a year into the COVID-19 pandemic, the role of tocilizumab remains unclear, showing benefit in observational studies but mixed results in randomized clinical trials. This manuscript outlines the pathophysiology of IL-6, discusses the basis for the use of tocilizumab in COVID-19, and summarizes the clinical evidence to date.

2. Methods

Pubmed was searched with combinations of the terms COVID-19, IL-6 and tocilizumab from 1 December 2019 to 10 March 2021 to identify randomized controlled trials, observational trials, and original research articles published in English. Relevance was established based on content, and additional papers were retrieved from the reference list of selected papers. The final list of references was selected on basis of the relevance to this review to demonstrate the rationale and evidence for use of tocilizumab in COVID-19.

3. IL-6 pathophysiology

Tocilizumab is a humanized monoclonal antibody of the IgG1 subclass, which inhibits signaling of IL-6. A pleiotropic cytokine, IL-6, mediates inflammation, immune response, and hematopoiesis and has been implicated in a range of lymphoproliferative and autoimmune diseases. IL-6 has two signaling receptors, the membrane bound IL-6 receptor (mIL-6 R) and soluble IL-6 receptor (sIL-6 R). Binding of IL-6 to mIL-6 R induces homodimerization of glycoprotein 130 (gp130), a non ligand-binding signal transducing chain [1]. The mIL-6 R is expressed predominately on leucocytes and hepatocytes [2], but IL-6 can exert its biologic effects on cells through trans-signaling. This involves binding of IL6 to free sIL-6 R, and this complex can then interact with gp130, which is expressed on most cells [3]. The sIL-6 R is produced predominately by innate immune cells, such as neutrophils and macrophages [2]. A third signaling pathway, termed trans-presentation, involves IL-6 and mIL-6 R expressed on specialized dendritic cells interacting with gp130 on T cells, a pathway that is involved in priming pathogenic Th17 cells [4]. Downstream signaling of IL-6 R involves both a Janus Kinase (JAK) and signal transducer and activator of transcription (STAT) pathway and activation of mitogen-activated protein (MAP) kinase [5] (Figure 1). Activation of these pathways by IL-6 is involved in a number of varied cellular functions, including differentiation of plasma cells to facilitate antibody production, generation of acute phase proteins, such as C-reactive protein, bone homeostasis, and lipid metabolism.

3.1. Therapeutic uses for tocilizumab

Tocilizumab, as an inhibitor of IL-6 signaling, is approved for use in multiple inflammatory diseases. IL-6 is elevated in the synovial fluid and serum in patients with rheumatoid arthritis,

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and contributes to joint destruction by stimulating bone resorption and inducing vascular endothelial growth factor (VEGF), resulting in increased angiogenesis which contributes to the pathogenic inflammatory lesions in rheumatoid arthritis [5]. Tocilizumab has been shown to be effective as monotherapy or add-on therapy in patients resistant to first-line disease modifying agents, such as methotrexate [6]. Similarly, in systemic juvenile arthritis, an autoinflammatory condition in children, tocilizumab induces responses in patients with inadequate response to non-steroidal anti-inflammatory drugs or glucocorticoids [7]. IL-6 is increased in serum and tissue samples of patients with giant cell arteritis, a systemic vasculitis, and tocilizumab contributes to remission and serves as a steroid sparing agent [8].

Cytokine release syndrome (CRS) is a potentially life threatening complication of chimeric antigen receptor T (CAR T) cell therapy, a potent immunotherapy used primarily for B cell malignancies, and other immunotherapies. CRS is characterized by fever, arthralgia, headache, rash, and diarrhea in mild cases, and a systemic inflammatory response with multiple organ involvement in severe cases. The pathophysiology stems from the activation of lymphocytes and myeloid cells with the release of inflammatory cytokines including tumor necrosis factor alpha, interferon gamma (IFNγ), IL-1 beta (IL-1β), IL-2, IL-6, IL-8, and IL-10. IL-6 is thought to be a central mediator of toxicity in CRS [9]. Trans-signaling is particularly important in CRS, with high levels of IL-6 and sIL-6 R, leading to enhanced downstream signaling in many cells. For example, in vascular endothelial cells, IL-6 leads to the induction of VEGF and monocyte chemoattractant protein, and reduced E-cadherin expression, leading to vascular permeability, contributing to hypotension and pulmonary dysfunction [10]. Tocilizumab is effective for the treatment of CRS, often with rapid clinical improvement observed after treatment. In one trial of CAR T cell therapy for relapsed acute lymphoblastic leukemia, all patients with severe CRS treated with tocilizumab were weaned from vasopressor support and defervesced within 3 days [11].

3.2. Tocilizumab in COVID-19

While the majority of patients with COVID-19 never progress beyond mild disease, a significant proportion of those affected require hospitalization or intensive care treatment. Moderate-to-severe COVID-19 is characterized by pulmonary infiltrates and elevations in inflammatory markers, including fibrinogen, CRP, lactate dehydrogenase, and IL-6. Approximately 17% of hospitalized patients require treatment in an intensive care setting [12]. Progression to severe or critical disease typically occurs around day 10 post symptom onset, and deterioration can be rapid [13]. This phase of disease is mediated by a dysfunctional immune response with elevations of multiple cytokines, including IL-1β, IFNγ, and IL10 noted in early case series. In particular, IL-6 was noted to be associated with worse outcomes [14], including more severe pulmonary changes [15], a finding replicated in further phenotyping work [16]. This phase of early clinical deterioration is an attractive target for therapeutics, as the ability to dampen this immune response could prevent progression to critical disease. The similarities in clinical presentation and inflammatory profile between severe COVID-19 and CRS lead to the exploration of use of tocilizumab in these patients and its inclusion in early treatment guidelines from the Chinese Health Commission for

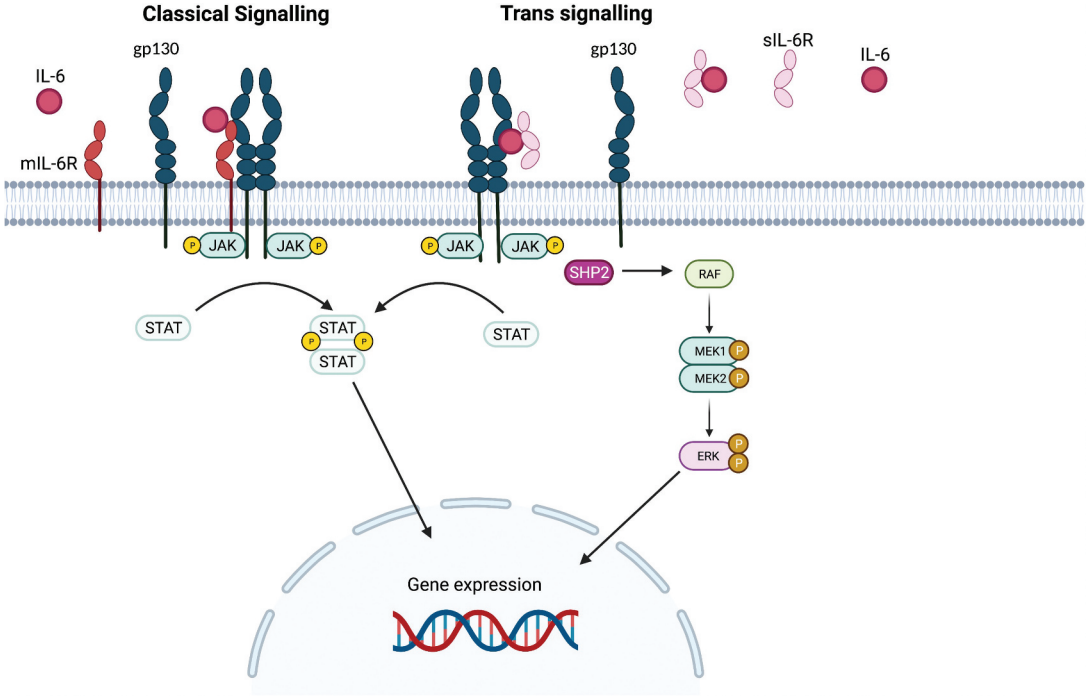

Figure 1. IL-6 signaling pathways. Classical signaling involves binding of IL-6 to membrane bound IL-6 receptor (mIL-6 R), forming a complex with glycoprotein 130 (gp130). Trans signaling involves IL-6 to soluble IL-6 receptor (sIL-6 R), which then interacts with gp130. Both pathways initiate signaling through the JAK-STAT and MAP kinase pathways.

patients with severe disease and elevated IL-6 [17], and subsequently other expert management guidelines [18].

3.3. Observational trials of tocilizumab in COVID-19

The potential clinical utility of tocilizumab for COVID-19 pneumonia was first demonstrated in a series of single centers experiences and retrospective reviews. Tonati et al. reported administration of tocilizumab to 100 patients admitted with COVID-19 pneumonia and acute respiratory distress syndrome requiring ventilatory support in a single center in Italy. Three quarters of these patients improved or stabilized in their clinical condition, with corresponding improvement in biochemical parameters, such as CRP, fibrinogen, and ferritin [19]. A case control study from a single center in New York found a statistically significant improvement in mortality in those given tocilizumab than those treated with standard of care. No difference was seen when intubated patients were included [20]. Multiple other case series and case control studies have demonstrated benefit in mortality or reducing progression to mechanical ventilation [21–26], particularly if used early in severe disease [27]. However, not all observational trials demonstrated benefit [28], and some suggested increased rates of infection in those treated with tocilizumab [29]. Ultimately, these studies serve best as a guide to the design of randomized controlled trials. To date, eight randomized controlled trials have released results, and others are ongoing [30], or have results not yet published [31].

4. Randomized controlled trials of tocilizumab in COVID-19

4.1. Boston Area COVID-19 Consortium Bay Tocilizumab Trial

The Boston Area COVID-19 Consortium (BACC) Bay Tocilizumab Trial was a randomized, double-blind, and placebo-controlled trial of patients with confirmed SARS-CoV-2 pneumonia and a hyperinflammatory state at seven hospitals in Boston, Massachusetts [32]. Eligible patients presented with clinical signs of inflammation defined as both fever and pulmonary involvement (either oxygen requirement or pulmonary infiltrates) and elevated ferritin, d dimer, lactate dehydrogenase or CRP. Patients were excluded if they required high flow oxygen. A total of 243 patients were randomized in a 2:1 ratio so that 161 received tocilizumab and 81 received placebo. The primary outcome was intubation or death, with secondary outcomes including change in clinical status based on a 7-point ordinal scale (Table 2) and time to cessation of supplemental oxygen therapy for patients receiving oxygen at randomization. The majority of patients (80%) were receiving supplemental oxygen at baseline but not high flow oxygen or noninvasive ventilation (NIV) (score 3 on the seven point ordinal scale). Sixteen percent were receiving no oxygen at baseline (score 2). Only 4% required high flow oxygen. Although no difference was found in the primary or secondary endpoints in this study, the primary outcome occurred less frequently than anticipated potentially leading to an underpowered study. The assumed rate of intubation or death in the placebo group was 30% at trial design, but only occurred in 12.5%. In addition, only 11% of patients received glucocorticoids in the tocilizumab group and 6% in the placebo group, as this study was performed before the results of the Randomized Evaluation of COVID-19 therapy (RECOVERY) trial demonstrated survival benefit with the use of dexamethasone in patients receiving supplemental oxygen [33]. Nevertheless, this was a multicentre, placebo-controlled trial that did not demonstrate benefit from tocilizumab in hospitalized patients with COVID-19.Table 1Table 3Table 4

4.2. COVACTA trial

The COVACTA trial [34] was a randomized, double-blind, and placebo controlled trial across 62 sites. Patients were eligible if they had confirmed SARS-CoV-2 infection, evidence of pulmonary involvement, and a blood oxygen saturation of 93% or less. Primary outcome was clinical status at day 28, assessed on a 7-point ordinal scale (Table 2). Secondary endpoints included clinical status at day 14, mortality at day 28, number of ventilator free days at day 28, time to improvement in clinical status of two points of the 7-point ordinal scale, time to hospital discharge, and time to clinical failure. The trial included 438 patients in the modified intention to treat population and three quarters were followed up to day 28. seventy percent of patients were male and mean age was 60.9 years in the tocilizumab group and 60.6 years in the placebo group. A smaller proportion of tocilizumab patients received glucocorticoids than the placebo group (19.4 vs 28.5%). Patients were at variable stages of disease, with time from symptom onset ranging from 1 to 50 days. Almost 40% of both groups were either mechanically ventilated or receiving extracorporeal membrane oxygenation at baseline. Like the BACC Bay trial, the COVACTA trial observed no difference in clinical status at day 28 between the two groups. However, within the secondary endpoints, the study identified a shorter time to hospital discharge in the tocilizumab group (20 days versus 28 days in the placebo group, Cox proportional hazard ratio, 1.35; 95% CI 1.02–1.79). Additionally, a subgroup analysis found that in patients, not in the ICU at baseline, transfer to the ICU occurred less frequently in the tocilizumab compared to the placebo groups (−14.8 percentage points). In a post hoc analysis of patients not receiving mechanical ventilation at baseline, clinical failure was significantly reduced in the tocilizumab group (hazard ratio 0.61, 95% CI 0.4–0.94). These analyses suggested a potential benefit for use of tocilizumab in those patients with COVID-19 who were pre-ICU.

4.3. CORIMUNO-TOCI-1

The CORIMUNO-TOCI-1 trial was an open-label, multicentre trial in nine hospitals across France [35]. The CORIMUNO-19 platform is used to examine multiple immunomodulatory

Table 1. Large observational trials of tocilizumab in COVID-19. Where two numbers are stated, figures refer to tocilizumab group; control group. HR-Hazard ratio.

	Biran et al.	Guaraldi et al.	STOP-COVID
Trial size	630	544	3924
Age (median)	62;65	67	62
Gender (% Male)	64;67	66	62.8
Trial groups	210 – at least one infusion of tocilizumab 420 propensity score matched controls	179 received tocilizumab 365 controls who did not receive tocilizumab	433 received tocilizumab within first 2 days of ICU admission 3491 controls who did not receive tocilizumab within 48 h of ICU admission
Clinical severity	ICU population 94;93% ventilated	Severe 17% required ventilation	ICU population 65;60% ventilated
Baseline steroids (%)	46;45	30;17	18.7;12.6
Follow-up (median)	22 days	9 days	27 days
Primary Outcome	Hospital-related mortality Multivariable Cox regression analysis with propensity score matching HR 0.64 95%CI 0.47–0.87	Invasive ventilation or death Multivariable Cox regression analysis HR 0.61 95% CI 0.4–0.92	Adjusted risk of death Cox regression model with inverse probability weighting HR 0.71 95% CI 0.56–0.92
Primary outcome met	Yes	Yes	Yes

therapies in moderate-to-severe COVID-19 pneumonia. The CORIMUNO cohort enrolled patients with confirmed or suspected SARS-CoV-2 infection requiring >3 liters per minute of supplemental oxygen (score 5 on the World Health Organization 10-point ordinal scale). Patients who were receiving oxygen but not NIV or mechanical ventilation were eligible for enrollment in CORIMUNO-TOCI-1. There were two primary outcomes: first, proportion of patients dead or needing NIV or mechanical ventilation on day 4; second, proportion of patients alive, not requiring NIV or mechanical ventilation at day 14. Secondary outcomes included time to oxygen independency and time to discharge. Unlike most of these randomized controlled trials, this study used Bayesian statistical methods to assess efficacy. A total of 131 patients were included in the trial. Median age was 64. Thirty-three percent of the tocilizumab group and 61% in the usual care group received glucocorticoids, with twice as many patients in the usual care group receiving steroids after randomization. One of the two predefined thresholds for treatment efficacy was met, 24% in the tocilizumab group and 36% in the usual care group required escalation of care, giving a 95% posterior probability of efficacy of tocilizumab for preventing NIV/MV death at 14 days. There was no difference in death at 28 days, although the authors comment that three deaths occurred in the usual care group after 28 days, and long-term outcomes will be reported later.

4.4. RCT-TCZ-COVID-19 trial

The RCT-TCZ-COVID-19 study [36] was an open-label, randomized clinical trial across 24 centers in Italy. They enrolled patients with mild acute respiratory distress syndrome, using the ratio of arterial oxygen to inhaled oxygen (PaO2/FiO2 ratio of 200 to 300 mmHg), not receiving NIV or MV at baseline, and systemic inflammation defined as fever 38 degrees Celsius or greater in the preceding 48 h and a CRP >100 mg/L or double the admission CRP. Patients were excluded if they were ineligible for ICU care or expressed preference to avoid intubation. Primary endpoint was clinical worsening in 14 days after randomization defined by any of: ICU admission with

Table 2. Randomized controlled trials – Trial size and patient characteristics Time from symptom onset is median and range or interquartile range (IQR). Two values indicate tocilizumab; control group; MV, mechanical ventilation; HFO, high flow oxygen; NIV, noninvasive ventilation.

	BACC	COVACTA	EMPACTA	CORIMUNO-TOCI	TOCIBRAS	RCT-TCZ-COVID-19	REMAP-CAP	RECOVERY
Trial size	243	438	377	131	129	126	778	4116
Age (mean)	59.3	60	55.9	64	57	60	61.4	63.6
Gender (%Male)	60	70	59.2	66;70	69	61	73	66;69
Time from symptom onset	9 (6–13)	11 (1–50)	8 (0–36)	10 (7–13) (IQR)	-	8 (6–11) (IQR)	1.2 days from admission	9(7–13);10(7–14)(IQR)
Respiratory support (%)								
None	16	3	9.3	-	-	-	-	-
Supplemental O2	80	26	64.2	100	60;44	NA	<1	46;45
HFO/NIV	4	30	26	-	23;44	NA	71	41
MV	-	38	-	-	17;16	-	29	13;14
Baseline steroids (%)	11;6	19;26.5	80.3;87.5	33;66	69;73	None	92;93	82

Table 3. Randomized controlled trials – Trial design and results. Two values indicate tocilizumab; control group. HR, Hazard ratio; CI, confidence interval; CrI, credible interval; ARD, median absolute risk difference; OR, odds ratio; RR, rate ratio. MV, mechanical ventilation; HFO, high flow oxygen; NIV, noninvasive ventilation.

	BACC	COVACTA	EMPACTA	CORIMUNO-TOCI	TOCIBRAS	RCT-TCZ-COVID-19	REMAP-CAP	RECOVERY
Study duration	28 days	60 days	60 days	28 days	29 days	30 days	21	28 days
Dose	8 mg/kg maximum 800 mg Single dose	8 mg/kg maximum 800 mg Single dose	8 mg/kg maximum 800 mg One or two doses	8 mg/kg Second dose of 400mg/kg at day 3 if notimproved	8mg/kg maximum 800 mg Single dose	8 mg/kg maximum 800 mg Two doses	8 mg/kg maximum 800 mg Second dose at physician discretion	400–800 mg (weight based) Second dose at physician discretion
Design	Double-blind placebo controlled	Double-blind placebo controlled	Double-blind placebocontrolled	Open label	Open label	Open label	Open label Platform	Open label Platform
Primary outcome	Progression to intubation/ death (HR 0.83, 95% CI 0.38–1.81)	Clinical status at day 28 (difference −1; 95% CI −2.5–0) Post hoc analysis-Clinical failure in those not in the ICU at baseline (HR 0.61, 95% CI 0.4–0.94)	MV or death at day 28 (HR 0.56, 95% CI 0.33–0.97)	Death/NIV/MV day 4 ARD −9%, 90% CrI; −21%-3% Survival without NIV/MV at day 14 (HR 0.58; 95% CrI 0.33–1)	Death/MV at day 15 OR 1.54 (95% CI 0.66–3.66)	Clinical worsening by day 14, RR 1.05; 95% CI 0.59–1.86	Number of organ support free days Adjusted OR 1.64, 95% CrI 1.25–2.14	Mortality RR 0.82, 95% CI 0.78–0.98
Primary outcome met	No	No	Yes	Yes (one of two)	No	No	Yes	Yes

Table 4. 7-point ordinal scale used in BACC, COVACTA, EMPACTA and TOCIBRAS trials.

1	Discharged or ready for discharge
2	In hospital, no supplemental oxygen
3	In hospital, receiving supplemental oxygen
4	In hospital receiving NIV or high flow oxygen (ICU or non ICU)
5	In ICU, mechanically ventilated
6	In ICU, mechanically ventilated with additional organ support, or ECMO
7	Dead

mechanical ventilation, death, or PaO2/FiO2 of <150 mmHg. Secondary endpoints included mortality and relative effect of early tocilizumab administration, given as per protocol, or late administration, given after oxygen requirements increased or after ICU admission, in preventing mortality. Although the target sample size was 398, the trial was discontinued early for futility. Of 126 patients that were included in the study, there was no difference between the two treatment groups in clinical worsening, with almost all events (33/34) being PaO2/FiO2 < 150, with only one being ICU admission. There were no between-group differences in ICU admission at 14 days, the proportion of patients discharged at 14 and 30 days or mortality. Of note, mortality in this trial was very low, at just 0.8% at 14 days and 2.4% at 30 days, and 14 patients in the standard of care group received tocilizumab after clinical worsening, which complicated the interpretation of results.

4.5. EMPACTA trial

The Evaluating Minority Patients with Actemra (EMPACTA) trial was a randomized, double blind, and placebo controlled trial evaluating tocilizumab in hospitalized COVID-19 patients in the USA, Peru, Brazil, Kenya, South Africa, and Mexico [37]. Patients were included if blood oxygen level on ambient air was less than 94% but excluded if requiring NIV or mechanical ventilation. This trial emphasized recruitment of patients from high risk racial and ethnic minority groups which made up 80% of the final study population. Mean age was 55.9 years and 59% of the study population were men. 26.5% of the study population were receiving high flow oxygen at baseline (ordinal scale 4). 80.3% of the tocilizumab group and 80.5% of the placebo group received concomitant glucocorticoids. A total of 377 patients were included in the modified intention to treat analysis. The primary composite outcome was mechanical ventilation or death by day 28. Secondary outcomes included time to hospital discharge and the time to an improvement in clinical outcome by two or more points on a 7-point clinical scale. Although the EMPACTA trial found a significant reduction in the composite endpoint of death and mechanical ventilation (HR, 0.56; 95% CI 0.33–0.97), death evaluated as its own secondary endpoint was not significantly reduced.

4.6. TOCIBRAS trial

The TOCIBRAS trial was a multicenter, randomized, and open-label trial of tocilizumab in moderate-to-severe COVID-19 across nine hospitals in Brazil [38]. Included patients had pulmonary involvement on imaging and required supplemental oxygen to maintain saturations >93%, and evidence of biochemical inflammation by elevation of two of D dimer, C reactive protein, ferritin, or lactate dehydrogenase. Primary outcome was clinical status based on a 7-point ordinal scale at day 15 (Table 2), secondary outcomes included clinical

status at day 8 and day 29, mortality at day 28, and time to independence from oxygen therapy. The trial was ceased prematurely due to an excess of deaths in the tocilizumab group at day 15 at the first interim analysis. The trial enrolled 129 instead of the planned 150 for this reason. Mean age was 57 and mean time from symptom onset was 10 days. Approximately 70% were receiving steroids at baseline. There was a higher proportion of patients receiving noninvasive respiratory support in the placebo than the tocilizumab group (41% vs 60%), but rate of mechanical ventilation was similar (17% vs 16%). The primary outcome was adjusted to a binary outcome (mechanical ventilation or death vs alive and not ventilated) due to an inappropriate distribution of clinical status on the ordinal scale at analysis. No difference was seen at day 15 in the primary outcome (OR 1.54; 95% CI 0.66–3.66), but there was a significant increase in death at day 15 in the tocilizumab group (11 vs 2 patients, 17% vs 3% odds ratio 1.54 95% CI 1.59–43.2). This increase in mortality was not observed at day 29. Tocilizumab was associated with a shorter hospital stay but no difference in any other endpoint.

4.7. REMAP-CAP trial

The Randomized, Embedded, Multifactorial Adaptive Platform Trial for Community-Acquired Pneumonia (REMAP-CAP) reported positive results for tocilizumab [39]. This trial is an international, adaptive platform trial designed to evaluate multiple therapies for severe pneumonia, which has adapted to respond to the COVID-19 pandemic. Patients were critically ill, defined as admission to an intensive care unit or receiving organ support in order be enrolled, and were enrolled within 24 h of receiving organ support. The REMAP-CAP trial evaluates therapies in multiple domains – such as antibiotics, antivirals, and therapeutic anticoagulation – and uses a Bayesian design. Tocilizumab was evaluated in the immunomodulatory domain alongside sarilumab, a second IL-6 receptor inhibitor. The primary outcome was the number of organ support free days up to day 21, so that higher scores indicate a better outcome. A total of 366 patients were randomized to receive tocilizumab and 412 to standard of care. In terms of organ support, 29% were mechanically ventilated at baseline, while 71% were receiving NIV or oxygen via high flow nasal cannula. Patients were treated early in their hospital course with a median time to enrollment of 1.2 days from admission. In terms of primary outcome, the median number of organ support-free days was 10 in the tocilizumab group and 0 in the control group, giving a median adjusted odds ratio of 1.64 (95% credible interval 1.25 to 2.14). Odds ratio for in-hospital survival was 1.64 (95% CI 1.14 to 2.35). Additionally, tocilizumab was found to be effective across all secondary outcomes, including time to ICU and hospital discharge, and time to improvement on a World Health Organization ordinal scale at day 14.

4.8. RECOVERY trial

Most recently, the RECOVERY trial reported preliminary results of the tocilizumab arm of their trial [40]. The RECOVERY trial is a randomized, controlled, open-label, platform trial of hospitalized patients with confirmed or suspected SARS-CoV-2. The initial main randomization consists of three parts. Part one no additional treatment, dexamethasone, hydroxychloroquine, lopinavir-ritonavir, azithromycin, or colchicine; part 2, no additional treatment, convalescent plasma or REGN-COV-2 (a combination of two monoclonal antibodies against the SARS-CoV-2 receptor binding domain) or part 3, no additional care or aspirin. Up to 21 days after the initial randomization in this trial, patients with progressive disease defined as oxygen saturation <92% on room air or receiving oxygen therapy and a CRP of 75 mg/L or greater were considered for randomization to tocilizumab. Follow up was completed to discharge, death or 28 days post randomization. Primary outcome was all-cause mortality, while secondary outcomes included time to discharge, escalation to mechanical ventilation in those not mechanically ventilated at baseline, and the use of renal replacement therapy. A total of 4116 patients were included in the study. Fourteen percent were mechanically ventilated at baseline and 41% were receiving noninvasive respiratory support. Eighty-two percent were receiving glucocorticoids at baseline. Mean age was 63.6 years and median CRP was 143 mg/L. Randomization was again relatively early in the course of the disease with a mean time from symptom onset of 9–10 days and mean time from hospitalization of 2 days. Tocilizumab was associated with a reduction in mortality at 28 days compared to usual care (rate ratio 0.86 95% CI 0.78–0.98), a greater probability of discharge at 28 days, and a reduction in the composite secondary outcome of progression to mechanical ventilation or death in patients not mechanically ventilated at baseline. Similar trends were observed in all subgroups including those only receiving supplemental oxygen but no higher respiratory support. A greater mortality benefit was seen in those receiving corticosteroids at baseline. Combining the results of the available studies to the time of publication of the RECOVERY, authors find that allocation to tocilizumab is associated with a 13% proportional reduction in a 28-day mortality (death rate ratio 0.87 95% CI 0.79–0.96, $p = 0.005$).

5. Safety considerations

The only major safety concern in any of the randomized controlled trials, to date, was the excess mortality in the tocilizumab group at day 15 in the TOCIBRAS trial. Reassuringly, this increase was no longer observed at day 29 and was not found in any of the other studies. However, adverse events have been observed with the use of tocilizumab in rheumatoid arthritis and other rheumatologic diseases. In treatment for rheumatoid arthritis, a small but significant increase in rate of infection has been observed with tocilizumab in addition to methotrexate compared to methotrexate alone [41]. Higher incidence of serious infections, including fungal infections associated with tocilizumab, has been reported in some observational studies [42]. None of the randomized controlled trials of tocilizumab in COVID-19 reported an increased rate of serious infections with tocilizumab, but most excluded those with current bacterial infection. Tocilizumab use is also associated with neutropenia or thrombocytopenia, which reverses on cessation of therapy, but

would not usually be considered in patients with a neutropenia or thrombocytopenia at baseline. Tocilizumab can cause elevations of transaminases and is generally contraindicated in those with baseline transaminases greater than five times the upper limit of normal, although does not seem to be associated with clinically significant liver injury [43]. Dyslipidaemia has been observed with tocilizumab treatment in rheumatoid arthritis, although without an increase in major adverse cardiac events [44]. There is a risk of intestinal perforation with tocilizumab, particularly in those with a history of diverticulitis [45], which again is a contraindication to therapy. These adverse events observed with the use of tocilizumab in rheumatologic conditions, where administration is prolonged for months to years, may be less likely in COVID-19 where only a single dose or two doses are given.

6. Expert opinion

On the basis of the REMAP CAP and RECOVERY data, the National Institute for Health updated its guidance on the 5 March 2021, to recommend the use of tocilizumab, in combination with dexamethasone in recently hospitalized patients who have been admitted to the ICU in the prior 24 h requiring MV/NIV/HFNC (high flow oxygen via nasal cannula), or recently hospitalized patients with rapidly increasing oxygen requirements requiring NIV/HFNC and who have evidence of systemic inflammation. However, results of trials of tocilizumab in COVID-19 have yielded mixed results. RCT-TCZ-COVID-19, BACC, and TOCIBRAS may have been underpowered to demonstrate their primary outcome. Similarly, EMPACTA, which demonstrated benefit in its composite endpoint but not in mortality alone, may have been underpowered to detect significant differences in mortality. One limitation of both REMAP-CAP and RECOVERY is their open label design, although the impact of tocilizumab on CRP risks unmasking even in placebo controlled trials. The platform design of these two trials has the potential to introduce bias through the use of non-contemporaneous controls and adaptive randomization strategy given the reduction in COVID-19 mortality over time [46] Other potential sources of the differential results include variable inclusion criteria and outcome measures, which in turn impact the applicability of these trials. Inconsistencies could also be explained by the heterogenous nature of clinical presentation of COVID-19 and associated patterns of immune dysfunction [47]. A number of characteristics have been associated with worse outcome in COVID-19, including male sex, advanced age, and elevated body mass index [48] . The pathophysiologic differences associated with these groups remain poorly understood, although sex differences have been identified in the immune response to COVID-19 with females showing higher levels of activated, terminally differentiated T cells and males showing higher levels of innate immune cytokines IL-8, IL-18, and CCL5 [49]. Whether age, sex, or body mass index modify response to tocilizumab has not yet been examined. In addition, the dosing regimen was similar in all the randomized controlled trials discussed here, with most using 8 mg/kg all to a maximum dose of 800 mg, with some studies allowing for a second dose at 24 h, but none examining impact of different dosing. It is feasible that this dose is too high for some patients [50] and too low for others, depending on the magnitude of the inflammatory responses and other characteristics. CRP has been shown to modify tocilizumab clearance, so an inflammation-based dosing strategy could be more effective [51]. A wide range of cytokines are elevated in severe COVID-19, and a greater understanding of the pathophysiologic changes associated with response to tocilizumab is needed to better guide the therapy.

The use of glucocorticoids, which has become standard of care, varied between the studies and may have impacted results, especially given that the synergistic effect of glucocorticoids and tocilizumab has been suggested in the RECOVERY trial. Similarly, EMPACTA and REMAP-CAP reported positive results in the setting of almost universal steroid use, supporting benefit of additional immunomodulation with tocilizumab above that provided by glucocorticoids. Other immunomodulatory therapies are under investigation for COVID-19, including the janus kinase inhibitor baricitinib which has shown benefit when added to remdesivir in a randomized controlled trial of hospitalized patients with COVID-19 [52] and anakinra, an IL-1 receptor antagonist. These agents could have an additive effect in COVID-19, or certain agents may perform better in different groups. Overall, these trials suggest that there is a benefit in some hospitalized patients with COVID-19, particularly deteriorating patients with systemic inflammation, when used relatively early. Further research is needed to define the optimal patient selection, timing, dosing schedule, and associated co-medications to use with tocilizumab for most effective use in preventing progression to severe disease and death in individuals affected by severe COVID-19.

Declaration of interest

The authors have no relevant affiliations or financial involvement with any organization or entity with a financial interest in or financial conflict with the subject matter or materials discussed in the manuscript. This includes employment, consultancies, honoraria, stock ownership or options, expert testimony, grants or patents received or pending, or royalties.

Reviewer disclosures

Peer reviewers on this manuscript have no relevant financial or other relationships to disclose.

Funding

This paper was not funded.

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Papers of special note have been highlighted as either of interest (•) or of considerable interest (••) to readers.

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